Ankle exercises via Mirror Therapy after stroke: co-design of the equipment, who might benefit, and dose-finding.

By

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Abstract

Mirror therapy (MT) has been applied successfully for upper limb motor rehabilitation following stroke. Lower limb mirror therapy (LLMT) is less understood but might also enhance motor recovery after stroke to improve walking ability. Robust studies are needed to fill the gaps in the current knowledge, develop evidence-based guidelines and ease implementation in clinical practice. In this thesis, multiple method research was used to investigate who might benefit from LLMT, the set-up of the device and what might be an appropriate dose of therapy.

A systematic review was conducted to elucidate current knowledge on the effect of LLMT motor recovery (Study I). The review examined the influence of time after stroke, level of paresis, and dose of therapy on recovery. The review revealed that LLMT enhances motor recovery and that it might be beneficial for people with severe paresis and who are less than six months post-stroke. The review highlighted a dearth of information about the effective dose.

A novel LLMT prototype device was constructed using an iterative co-design approach via focus groups involving 26 people including stroke survivors and physiotherapists (Study II). The main characteristics of the prototype are: the ability to produce MT ankle exercise from an upright sitting posture, an adjustable angle, and a lightweight device. The prototype can be used in clinical practice and subsequent research after clinical efficacy testing.

The prototype device was used in a subsequent study to determine the maximum tolerable dose (MTD) of ankle exercise using a 3+3 rule-based dose-finding (Study III). The study suggested an MTD of 35 min/day for ankle exercise via MT. Thus, to be used in subsequent dose-ranging studies to find the recommended Phase II dose. Then, Phase III clinical efficacy trial.

Therefore, LLMT is treatment worthy for future investigations to help stroke survivors return to walking.

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List of abbreviations

ADL= Activity of Daily Living

NHS= National Health Service

WHO= World Health Organization

CNS= Central Nervous System

MT= Mirror Therapy

PT= Physiotherapist

LLMT= Lower Limb Mirror Therapy

EEG= Electroencephalography

fMRI= Functional Magnetic Resonance Imaging

TMS= Transcranial Magnetic Stimulation

MEP= Motor Evoked Potential

MRI= Magnetic Resonance Imaging

UCSD= User Centred System Design

PAR= Participatory Action Research

MTD= Maximum Tolerable Dose

MRC= Medical Research Council

ROM= Range of Motion

RCT= Randomised Control Trial

PRISMA= Preferred Reporting Items for Systematic Review and Meta-Analyses

TIDieR= Template for Intervention Description and Replication checklist

ROB 2= Risk of Bias tool Version 2

MoveExLab= Movement and Exercise Laboratory

MI= Motricity Index

RPTD= Recommended Phase II Dose

mFBS= modified Fibonacci sequence

TA= Tibialis Anterior

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chapter 1. Introduction

1.1 Introduction to thesis

Stroke is considered the leading cause of serious long-term disability in adults worldwide (1). It often causes long-term physical, cognitive and visual impairments, limiting an individual's ability to perform daily life activities such as walking (2). Most stroke survivors have noticeable upper or lower limb motor impairment (3,4), and two thirds of stroke survivors are not able to walk independently after their stroke (3). Usually, the stroke survivors' main goal is to return to walking independently. Stroke rehabilitation is an important area that helps stroke survivors achieve this goal, enabling them to return to their pre-stroke function (5). There are many interventions to help stroke survivors regain walking activity (6)but for stroke survivors who have a severe impairment, interventions that involve practising walking will be too challenging. Mirror therapy is one of several new techniques that enhance motor recovery without the requirement to move the paretic limb (7–9). Practising key activities such as ankle exercise via mirror therapy could help lower limb motor recovery which might help stroke survivors return to walking.

This thesis compromises five chapters:

- Chapter one provides an overview of stroke and discusses lower limb motor impairment, motor recovery, stroke rehabilitations and in particular, lower limb mirror therapy as a rehabilitation intervention, its underlying mechanism and the quality of the available evidence about its effectiveness. The research questions are outlined, along with the overall thesis structure and methodology.

- Chapter two is a systematic up to date review of the available evidence regarding lower limb mirror therapy, including the influence of time after stroke, level of paresis and the dose on recovery.
- Chapter three presents the user perspective on the design and setup of lower limb mirror therapy equipment after stroke.
- Chapter four identifies the maximum tolerable dose of lower limb mirror therapy.
- Chapter five discusses the three empirical studies in the context of existing research. It then considers the strengths and the limitations of the thesis and proposes future directions for mirror therapy research before making concluding remarks.

1.2 Stroke definition and statistics

The World Health Organization (WHO) defined the stroke as “rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause apart that of vascular origin”(1). A stroke is considered a non-traumatic, focal vascular-induced injury of the central nervous system (CNS) which causes permanent damage in the form of cerebral infarction, subarachnoid, and/or intracerebral haemorrhage (10). The stroke happens as a result of the brain cells’ deaths because of lack of oxygen once the blood flow of an artery to the brain is lost because of blockages or rupture (2).

According to WHO, cerebrovascular accidents (strokes) are the second leading cause of death ,third for serious long-term disability in adults (2,11,12) and may cause dementia and depression (2). Every year, about 100,000 strokes occur in the United Kingdom (UK), accounting for 11% of all fatalities. (13–15). Each year, nearly 80,000 people in England and Wales are admitted to hospitals with acute stroke (11). Around one million stroke survivors across England, Wales, and North Ireland require further care after discharge from the hospital (16) while 84% of patients leave the hospital needing help with everyday tasks and, in many cases, will need long-term rehabilitation for the reminder of their life (17,18). Approximately, 33% of stroke survivors in the UK are moderately or seriously impaired (14) and half of them do not recover completely. This disability greatly impacts the economy (19), health system, families and patients (20), as in England alone it costs the National Health Service (NHS) over £3 billion a year (21). Therefore, reducing the stroke burden on the individual and helping them to live independently after a stroke is a vital goal for health systems.

1.3 Lower limb motor impairments

Most stroke survivors suffer from persistent neurological deficits that impair the activities of daily life (14). Stroke can lead to loss of motor function, weakness, aphasia, ataxia (impaired coordination), visual loss or deficit (22). The variety of signs and symptoms depend on the extent and site of the stroke's lesion in the brain but motor deficit is the most noticeable impairment (4). Motor deficits are defined as "a limitation or loss of function in muscle control or movement or a limitation of movement"(5,23,24). Motor impairment after a stroke usually affects the control of movement over one side of the body opposite to the brain that includes the face, arm and leg, and affects around 80% of patients. This weakness of one side of the body, referred to as "contra-lesion hemiparesis" (25), or "hemiparesis" if there is an ultimate loss of motor function (25), is caused by the interruption of descending signals from the motor cortex, pre-motor cortex, motor tracts or associated motor pathway in the cerebrum or cerebellum to the spinal motor neurons (26). This impairment limits the ability of stroke survivors to participate in daily life activities, as two thirds of stroke survivors have initial mobility deficits which affect their daily activities, balance and walking (3,15). More than 30 % of stroke survivors cannot walk independently six months post-stroke (3). Therefore, the ability for the stroke survivors to live independently is based on the recovery of the motor function (27,28).

1.4 Motor recovery after stroke

Recovery after stroke is heterogeneous across subjects with different factors influencing it (29,30). Langhorne *et al*. (2011) note that motor recovery after a stroke is complex, with many treatments designed to help recover motor impairment and function of the upper and lower body (5). Functional motor recovery refers to the improvement in mobility that allows the stroke survivor to manage daily activities. Motor recovery after stroke is connected to neuroplasticity (31) which is known as the capacity of the nervous system to adapt to internal or external stimuli by changing its structure, function, and connections (31,32). Neuroplasticity occurs through a lifetime (33) and may be improved following injury (34). Although explaining the mechanism of neuroplasticity is beyond the scope of this thesis, neuroplasticity concerns the fundamental principle (35,36) in the learning process of the intact brain and the relearning that can occur in the damaged brain through rehabilitation (36–38). The changes to the damaged brain after stroke can take from a few days to years and it can be both adaptive or maladaptive (31,39). For example, stroke survivors may develop "learned non-use" of a limb as an example of maladaptive behaviour (40).

Recovery of body functions and activities usually happens through spontaneous and learning dependent processes, including: restitution (restoring the functionality of the injured neural tissue); substitution (reorganisation of the partly injured or spared neural pathways to relearn lost functions); and compensation (enhancement in the adaptation between a patient's impaired skills and the environmental demands) (11,21,22). Spontaneous recovery after a stroke usually occurs in the first weeks after stroke onset, then plateaus three months after stroke (29,30) while training- induced recovery has been detected over a longer time period (29). Evidence for the critical role of rehabilitation in facilitating the neuroplasticity changes

associated with recovery, is growing (41,42). Therefore, stroke rehabilitation research has focused on training to induce beneficial neuroplasticity (43) and prevent maladaptive behaviour (40).

1.5 Stroke rehabilitation

Once stroke survivors no longer need the medical input because their condition is no longer life-threatening, they need to optimise their function to participate in daily activities and this stage will involve engagement in a rehabilitation programme (5). Stroke rehabilitation is a dynamic process with the primary goal of reducing disabilities (5). A stroke rehabilitation programme will usually involve a multidisciplinary team to ensure the effective delivery of stroke rehabilitation (44) by providing an organised package of care through a cyclical process involving assessment, goal setting, intervention and reassessment (5,45).

Most members of stroke rehabilitation teams, such as physiotherapists, are focused on recovering the impaired movements and associated function (5). Physiotherapists are considered a crucial part of the stroke rehabilitation teams, as they play a major role in addressing the recovery needs of the stroke survivors, especially with regards to re-educating motor function via movement experiences (5). According to current evidence, such behavioural experience is a driver for the functional reorganisation of the brain following a stroke (46). Neuroimaging studies have shown that physical therapy can induce beneficial neuroplasticity in the acute and chronic phases of recovery (42,47–49) that enhance motor recovery after a stroke (50–52). Indeed, beneficial cortical reorganisation has been established following lower limb interventions (53). Therefore, rehabilitation teams should aim for therapy that utilises neuroplasticity with afferent stimulation, via a variety of interventions (54). This may accelerate the recovery of motor function during spontaneous recovery (28) or even longer after that period (32). As result, physical therapy intervention is considered a high priority in stroke rehabilitation research (6).

The recent growth in stroke rehabilitation research has identified some key neuroplasticity principles that promote recovery (37). For example, performing a repetitive motor activity can produce beneficial change to the brain representation maps (55); goal directed activity can help in acquiring functional benefit (37); bilateral movement training of the required activity increases progress towards recovery (56) which may facilitate cortical neural plasticity. The period of time after stroke matters as different forms of plasticity occur at different times during training (57). To promote neuroplasticity and motor functional recovery, these principles should inform planning and delivery of interventions (58).

These principles help to understand how to drive recovery after stroke. However, in order to use current knowledge to inform the development of new rehabilitation interventions, it is important to know who might benefit, when and how much, in order to best use the intervention to achieve the required outcome (59). Given that, motor recovery after a stroke depends on other influential factors (29,30,60–62) such as time after stroke (57,63,64), the severity of paresis (64–66) and the dose of therapy (67,68), the following section reviews the evidence for the influence of these three factors that inform current practice.

Time after stroke

Awareness of the time window within which spontaneous recovery may be anticipated enables clinicians to concentrate their therapy either on the restitution of current deficits or on utilising adaptation techniques to achieve their functional objectives. Current evidence from stroke rehabilitation suggests that rehabilitation is most effective in the early stages: the highest percentage of recovery is likely to occur within the first three to six months. This is called the "critical window" after a stroke (30,69) although evidence suggests that patients in

later stages can also improve (47,70–72). Kwakkel *et al*. (2006) found that 16% of the improvement in body function and activities observed could be explained by time alone (57).

Clinical trials have investigated how the time after stroke affects motor recovery. For example, Paolucci *et al*. (2000) included 145 participants in inpatient rehabilitation in homogeneous subgroups that match the age and Barthel index score at the baseline of these groups, with different entrance timelines. The rehabilitation timeline began either in the first 20 days after the stroke, between 21 and 40 days, or between 41 to 60 days after the stroke. The study found that a better outcome was noticeable with the group that started the therapy earlier (73). A similar study conducted by Maulden *et al*. (2005), including 969 patients in observational cohorts, and counted the number of days from symptom onset to rehabilitation admission. The authors found that individuals who had fewer days between the start of their stroke and their admission to rehabilitation had better functional results and spent less time in hospital (74). Likewise, Horn *et al*. (2005) included 830 patients in a prospective observational cohort study and noted that earlier rehabilitation admission was associated with a better stroke rehabilitation outcome (75).

The effect of early rehabilitation on both brain changes and subsequent functional effects has been investigated through research using animal models. For example, Bierneskie *et al.* (2004), noted significant gain in the recovery of the forelimb reaching ability when the rats' rehabilitation started earlier on day 5 or day 14 following the middle cerebral artery occlusion, whereas outcomes in terms of improving recovery were less favourable when their rehabilitation started on day 30 after the stroke (76). Another study by Kozlowski *et al.* (1996) (77) used a cast to immobilise the rat's impaired forelimb, the unimpaired forelimb, or neither forelimbs, from day one to 15 after the inducement of a unilateral brain lesion. All

groups were then subjected to similar behavioural tests and observation. Lesion size dramatically increased in rats who were forced to use the impaired limb. The author suggests that excessive use of the impaired limb might cause damage as a rehabilitation technique: "use-it early-or-lose-it" may be used with the intact hemisphere but not the injured one (77). The author concludes from the study that for optimum restoration of forelimb function corresponding to the injured hemisphere, it is better to adopt the "use-it-but-do not-overuse-it" approach (77).

However, translating animal models to human rehabilitation remains a challenge (78) due to many factors such as the difference in structural and functional connectivity; the difference in lifespan of the rats, as five days in rat life might not be considered early intervention; also the time course of recovery in animals is more rapid than in humans. On the other hand, studies that investigate recovery after a stroke have suggested that even stroke patients in the chronic stage show some recovery. Teasell *et al*. (2012) and Ballester *et al.* (2019) synthesised the evidence from rehabilitation initiated at six months (71) or extended beyond one year after stroke (70) and found that participants in the chronic stage showed improvement in recovery (70,71). More evidence of when to start therapy and how early that might be, is still needed (79).

In summary, most stroke rehabilitation studies concur that therapy initiated soon after a stroke achieves better outcomes, although recovery is also possible long after the stroke occurrence. These findings highlight the uncertainty that persists in terms of the optimal time after a stroke for rehabilitation to begin, and that further investigation is therefore required.

Severity of paresis

In order to achieve the required recovery, identifying the responders to the therapeutic intervention is crucial, especially for the clinical therapist. Rehabilitation of stroke survivors who have had a severe stroke is associated with greater use of rehabilitation resources. Evidence has shown that people who survive severe strokes pose a greater health and economic burden than people with mild to moderate strokes (80) as stroke survivors with severe paresis usually need a longer medical treatment, leave with poorer functional results, face difficulties with discharge, and need more care (81,82). This might create bias toward choosing patients with less severity after a stroke, as more severe cases can be more challenging, outcomes might be less desirable and they are also less likely to show functional improvements during rehabilitation (65,74). Nevertheless, this is not always the case; some patients with severe paresis who received highly specialised rehabilitation care improved their functional outcomes (83).

Jorgensen *et al*. (1995) found a strong relationship between the time course of functional recovery and initial stroke severity. They found that the best ADL functions measured using Barthel Index, was reached as follows: in patients with initially mild strokes, the best ADL was reached within 8.5 weeks; in patients with moderate strokes best function was reached within 13 weeks; in patients with severe strokes within 17 weeks, and in patients with extremely severe strokes, within 20 weeks (84). Similarly, Duncan *et al.* (1992) found that improvements in motor function decreased according to the time period since the stroke occurred, along with severity of the stroke (64).

In summary, survivors with severe paresis have a greater impact on rehabilitation resources as recovery may take longer, which creates a significant burden on the physiotherapist.

However, more research is needed in terms of identifying the responder to interventions and the best time to begin such interventions. This will not only improve outcomes, but it will help use limited resources more effectively.

Dose of therapy

How much therapy should be given is a crucial question for the physiotherapist when designing the rehabilitation intervention as the reorganisation of the brain appears to be more affected by the amount of the received therapy than the type of intervention (85,86). The amount of dose in stroke rehabilitation is usually reported as the number of the sessions, minutes or repetitions for the intervention. However, reporting the exact "active" dose is not well stated in the current literature (59). The dose of the therapy has different components such as frequency, intensity and total length of the training period, which is often expressed in weeks (87). However, the influence of these factors on enhancing motor recovery after stroke and which aspects produce beneficial neuroplasticity, is still under investigation. Hornby *et al.*(2011) found that the specificity, amount, and intensity of walking practice play a significant role in improving motor recovery (88).

Recent systematic reviews recommend that by increasing the dose of the therapy, the better the functional improvement is noticed among stroke survivors (68,86). A recommendation from the Intercollegiate Stroke Working Group (11) proposes a minimum threshold of 45 minutes of stroke recovery treatment for the patient who is willing to maintain it for a minimum of five days per week (11). However, this recommendation was based on the general agreement of experts' meetings rather than scientific-based guidelines. How much

therapy needs to be provided or how high that should be to produce the preferable outcome remains under investigation in stroke rehabilitation (59,89).

The higher dose of the rehabilitation intervention has been investigated in animal models. Rats or primates were trained to do repetitive motor tasks after brain damage inducement. A significant neural change in cortical representation was observed in animals able to achieve between 300 to 400 repetitions, compared with those who received a lower dose (37,90–93). While a lower threshold below 240 repetitions might not produce the required recovery and intensive rehabilitation is needed (94). However, results based on animal models should be treated with caution when compared with human stroke survivors, as translating neural processes and recovery from animal models to human clinical studies is not straightforward (44).

Clinical trials do not always support the higher dose, however. Di Lauro *et al*. (2003) investigated the efficacy of intensive rehabilitation in sixty patients admitted to hospital compared to standard rehabilitation and found that high-intensity training was not always vital to produce positive motor changes, and therefore should be used judiciously due to time and cost implications (95). In addition, Cooke *et al.* (2010) conducted a systemic review to investigate the effect of increased dose using exercise-based therapy to enhance motor recovery, and concluded that there was limited evidence that the higher dose is the better. They concluded that, dose-finding studies of specific interventions were needed before efficacy trials (96).

Furthermore, although evidence suggests that the amount of therapy needed to maximise functional recovery is linked with the time since the brain injury, as earlier is generally better (97), there are risks early after the injury associated with the vulnerability of the brain

(79,97). The AVERT trial tested the hypothesis that a higher dose of therapy is always better, especially early after a stroke, finding that the higher dose with very early mobilisation caused a reduction in a favourable outcome (98,99). Therefore, more research is needed to establish the relative importance of the intensity (55,100), and dose-response relationship of the therapy (59,67) in stroke rehabilitation.

In summary, while dose is important in motor recovery, more research is needed on the optimal dose of interventions that is required to produce beneficial plasticity.

The previous sections have shown that stroke rehabilitation is vital in helping stroke survivors to improve their recovery and in particular, to regain functional motor recovery after a stroke. To enhance plasticity, stroke rehabilitation research has identified some key neuroplasticity principles that promote recovery, such as training tasks, repetition, intensity and specificity (5). Such principles should be implemented while designing the therapeutic intervention (58). Also, stroke rehabilitation research for new interventions should focus more on investigating the influence of time after stroke, level of paresis and the dose of the therapy on motor recovery.

1.6 Intervention targeting lower limb

When designing an intervention, stroke survivors' primary goals also need to be taken into account. Stroke survivors identify recovery of walking as a priority goal of rehabilitation (101). Existing evidence suggests that therapeutic interventions should focus on the patient practising functional activities to improve motor recovery and daily life activities (4,102). However, 20 to 30% of stroke survivors have difficulties in returning to walking after a stroke (3) and participants with substantial paresis cannot perform walking exercises. Interventions need to be developed carefully, therefore: on the one hand, they need to take into account such limitations and what stroke survivors feel is essential to achieve their goal on the other, they need to consider the time and resource implications for the health system.

Task-oriented lower limb movements that are associated with walking or practising the walking itself, require some degree of voluntary movement and are therefore not applicable for people with severe paresis, as they are too weak to adopt a standing posture without help (103). Some therapies, such as electromechanical training, robot assistive gait training, repetitive passive or assistive movement stimulation, have shown some evidence in improving motor recovery outcomes in people with severe deficits after stroke (104,105). However, these types of training require some assistance from a physiotherapist or carer to perform. Stroke survivors with severe paresis need therapeutic interventions that have good outcomes and can be carried out in the home independently.

Many rehabilitation interventions for people with severe paresis, utilise the principle of priming the brain (106,107). Currently, there are some techniques that help with the re-balance of M1 excitability that occurs after a stroke, with the aim of priming the motor

system for beneficial plasticity to be more responsive, thereby enhancing stroke recovery (108). Such priming techniques are defined by Stoykov and Madhavan (2015) "a change in behaviour based on previous stimuli" (109), and can occur after a single learning episode (109,110). One of the interventions that is utilised by the principle of priming the brain is mirror therapy (MT) (107). MT is considered one of the most cost-effective treatments as stroke survivors can use it in their own home without the need for extra assistance or presence of the PT (103). Mirror therapy is a treatment that does not require the patient to move the more paretic limb, as it involves watching the reflection in the mirror of the less paretic side.

Recent systematic reviews found that mirror therapy is useful for motor recovery of the lower limb after stroke (103). Participants with severe paresis who cannot perform walking training, can use mirror therapy to practise a key component of walking and other functional activity such as sit-to-stand. Key components such as ankle exercise can be performed in un upright sitting posture by people who cannot complete the whole training task.

The key component of walking and sit-to-stand is the ability to control ankle dorsiflexion and plantar flexion (111). Lack of dorsiflexion in the swing phase and at heel strike is a commonly reported kinematic deviation in people with a hemiplegic stroke and can lead to dragging the toe in the swing phase (112). Voluntary ankle dorsiflexion is considered a way of indicating the achievement of selective motor control (104), and ankle movement training is known to facilitate brain reorganisation (113). Ankle dorsiflexor strength training is also recommended in stroke rehabilitation programmes to improve sit-to-stand ability, walking endurance (111,114), which is thought to reflect functional mobility in relation to the hemiplegia (115). Practising ankle dorsiflexion in the closest position to that required for the

performance of sit-to-stand, in this case, upright sitting, has been shown to be effective in improving sit-to-stand function in stroke survivors (115). Therefore, performing an ankle exercise via mirror therapy is the focus of this thesis.

1.7 Mirror therapy

Mirror therapy (MT) was first introduced by Ramachandran and his colleagues in 1995 as a non-invasive technique to reduce phantom pain in people with amputation (7). He first used mirror visual feedback to induce kinaesthetic sensations in the phantom limbs of the amputee's arm by placing the mirror vertically in front of the subject, who was told to move the intact arm while looking at its reflection as if it was the phantom arm (7). The theory behind using MT was that visual feedback provided by a mirror image of the intact limb might produce positive cortical reorganisation to restore the efference -afference loop that had been interrupted (7). Several MT studies were carried out on pain-related syndromes such as phantom limb pain (116) and complex regional pain (117,118), which is a biological condition in which the pain is experienced as two different types: Type I is pain occurring after the injury, even when there is no obvious nerve damage; Type II is pain following nerve damage even without the loss of either limb. MT was again shown to "trick" the brain into believing that the painful limb was, in fact, not in pain and could move freely without restrictions (119). It has also been used in stroke rehabilitation (9,120), to improve recovery for upper extremity (9), lower extremity (121) or to improve neglect (122,123). In 1999, MT was first reported as being used positively with people after stroke and upper limb paresis (9). The mirror was placed in the sagittal plane between the upper limbs so that the unaffected side was reflected in the mirror and the affected side was hidden. The mirror therapy was provided for 15 minutes twice a day, six days a week, for four weeks (9).

1.8 Scientific Rationale for Using Mirror Therapy to Enhance Recovery After a Stroke

This section explores the evidence for the proposed underlying mechanism of motor impairment reduction in response to mirror therapy. Several studies have investigated changes in the brain that occur after mirror therapy in healthy participants as well as stroke survivors. In order to investigate the effect of mirror therapy on brain function, various methods have been used such as EEG (electroencephalography), fMRI (functional magnetic resonance imaging) and TMS (transcranial magnetic stimulation). Such studies focus on the activation of a different brain area in response to mirror therapy (124).

There are several proposed mechanisms for how mirror therapy might benefit the motor recovery of movement after a stroke (125). According to a review by Deconinck *et al.*(2015), these mechanisms can be classified into three general categories (126): a mirror neuron system mechanism (127,128); a recruitment of ipsilateral motor pathways-primary motor cortex mechanism (119); and a visual feedback mechanism which activates a broad neural network in the brain dedicated to attention and action monitoring (129).

The first hypothesis, the "mirror neuron system" is the underlying mechanism (128,130,131) in that the observation of the mirror illusion triggers the mirror neurons that fire when an individual observes another performing a motor action, known as "action observation" (126,127,132). The visual feedback is thought to enhance motor recovery, thereby activating the neural circuits involved in motor control (131). These "mirror neurons" are thought to be key in activating a neural network in the observer that is similar to when they actually perform the motor action and as a mental practice, is aimed to improve motor function (133).

Mirror neurons were initially discovered by Di Pellegrino in monkeys for goal-directed activity devoted to hand, mouth and foot actions such as manipulation of objects and mouth movement; this mirror neurone system is thought to be activated in brain area F5 (134). However, there is no direct evidence for the existence of mirror neurons in humans (133). Still, it is thought that Broca's area (Brodmann area 44 which is considered the equivalent to F5 in monkeys) is activated when observing hand action (133,135) or when preparing to imitate movement by imaging hand action (136). Bhasin *et al.* (2012) investigated the influence of MT on chronic stroke patients using fMRI. Their results supported the “action observation” hypothesis as they noted an increase in the activation of different primary motor, and pre-motor cortex areas after MT (137).

The second hypothesis is that mirror therapy might promote the recruitment of ipsilateral motor pathways (138) which are located in the unaffected hemisphere, projecting ipsilaterally to the paretic body-side. This is thought to play a significant role in improving the motor function (126,139–142). Also, it increases the excitability of the ipsilateral primary motor cortex (M1) that projects to the "untrained" hand (126,143–148). During MT, both the affected limb movement and the passive observation of the movement of the unaffected limb (hand) as reflected in the mirror, influence M1 excitability (149,150).

Two studies have measured the motor evoked potential (MEP) before and after applying mirror therapy for hand muscle. An increase in the MEP of the affected limb, and change in balance of M1 activity toward the affected hemisphere, have been observed in both healthy and stroke participants (149,150). In addition, mirror therapy recruits ipsilesional brain areas that are relevant for the control of the affected hand (148,151), as well as high order the visuomotor network in the lateral occipital area (148,152) and parietal, posterior temporal,

and occipital areas (149,153–156). It has also been noted that restricting vision among healthy participants enhances the visual illusion more than uncovering the condition, which might enhance the excitability of the ipsilateral motor cortex (157). Rossiter *et al*. (2014) used the MEG to measure the changes in the cortical activity comparing the mirror therapy group to the control group. Their results showed that during bilateral movement via MT, a better normalization of the asymmetrical pattern of movement-related beta desynchronization occurred in the primary motor cortices (158).

Guo *et al*. (2016) were the first to investigate the effect of producing mirror therapy ankle exercise in healthy and stroke participants (159). They used an MRI to evaluate the neural activation of mirror visual illusion of ankle movement in both groups (159). Significant activation of the ipsilateral sensorimotor cortex, the occipital gyrus, and the anterior prefrontal gyrus was found in stroke patients using MT as compared to the non-mirror group (159).

The third hypothesis is that the associated illusion of the mirror therapy increases an individual's (spatial) attention toward the unseen (affected) limb, which may activate motor networks (126,129). Studies that support this hypothesis show that mirror therapy increases neural activity in the brain that relates to attention and cognition. MT based activation of the motor cortex may be referred to as the engagement of a contralateral (contralesional) action observation network (126,153,160). Precuneus activation due to mirror visual illusion has been observed in various studies (126,154,161) as has the activation of the posterior cingulate cortex area; these areas are associated with self-awareness and spatial attention. Therefore, by increasing the stroke patient's awareness, there might be a decrease in learned non-use of the affected limb (120).

According to Deconinck *et al*. (2015) , mirror therapy is thought to increase neural activity in areas responsible for attention and cognitive control (hypothesis 3), and to increase ipsilateral M1 excitability reacting to the untrained limb (hypothesis 2), as the current literature supports these hypotheses (126). There is less evidence to support the mirror neuron system hypothesis when compared to other proposed hypotheses (126).

Even though the exact mechanism of how mirror therapy drives neuroplasticity remains unclear, the previous section established that MT is beneficial on enhancing motor recovery after stroke for both upper and lower limb (103).

The following section will discuss in detail the quality of evidence regarding the use of mirror therapy for lower limb motor impairment after stroke.

1.9 The quality of evidence regarding the use of mirror therapy for lower limb motor impairment after stroke

At the beginning of the PhD programme, a scoping review was conducted to identify the main gaps in lower limb mirror therapy research and to formulate the main research questions for the thesis. The terms “lower limb", "mirror therapy", and "stroke" were used to search for the key articles in this field.

Recently, a stroke recovery trial development framework was developed from the second stroke recovery and rehabilitation roundtable meeting (59). The framework was designed in order to guide the GO or NO-GO decision-making to improve the development of stroke rehabilitation trials. The framework was established to address the need for the interventions to refer to important areas for consideration in trial development, referred to as the “knowledge units”, such as: how much treatment should be offered; what are the active ingredients of the treatment; who should be treated, and when is the treatment best delivered. This framework has been followed to guide this section in order to synthesize and better understand the available evidence (59) for lower limb mirror therapy and to help guide the next phase of the research to be undertaken.

The quality of the available evidence, When and who might benefit

At the beginning of the PhD programme while conducting the scoping search, only one systematic review was found that focused on the effects of LLMT (162) or combined UL& LL mirror therapy (8). In the review that focused on the lower limb (162), only five studies with different studies designs were included in the former. The review concluded that MT in the acute stage might improve walking ability, in the subacute phase might improve ADL

function and gait, and in the chronic stage might be beneficial for gait speed and ankle passive range of motion (162). However, these findings could just reflect the characteristics and outcome measures of the primary trials included in the systematic review.

The review that combined upper and lower limb studies (8) included one study for the lower limb, and concluded that there is low evidence that lower limb mirror therapy improves lower limb motor recovery, due to small sample size. Moreover, due to the variation in the frequency and duration in previously limited number of included studies and lack of specific protocol for using MT in the lower extremity (163,164), the study recommended further investigation to identify the optimal use and specific treatment regimens at different stages of stroke.

Later in the PhD programme, a few systematic reviews investigating the effect of LLMT (165–167) and systematic reviews that combined UL & LL (103,168) were published. Li *et al*. (2018), who primarily investigated the effect of lower limb mirror therapy on walking and balance, concluded that while mirror therapy might improve lower limb function, there was insufficient evidence to suggest when and how to approach mirror therapy (167). Similarly, Broderick *et al.* (2018) suggested that mirror therapy might enhance motor function, walking velocity and step length (166).

In Yang *et al*. (2018) and Thieme *et al*. (2018), evidence for the effect of mirror therapy on both upper and lower limb was reviewed, with both concluding that mirror therapy has a positive effect on improving motor function and ADL after stroke (103,168). However, most of the synthesized evidence in these two reviews pertained to the upper limb. More recently, Louie *et al*. (2019) investigated the effect of mirror therapy on balance, gait and motor function. They found that mirror therapy has a large effect on gait speed improvement, and a

small effect on mobility and motor recovery, recommending further investigation regarding the dose of the therapy (165). The main conclusion from these studies is that mirror therapy has a positive effect on improving motor recovery, gait and balance after stroke. However, they provide insufficient detail with regards to who might benefit, when to apply it, and the optimum dose for recovery.

In mirror therapy, no studies or reviews identify who might benefit from the therapy, and how severity of paresis might influence recovery, particularly in terms of lower limb. The researcher is aware of only one study that promotes the use of mirror therapy with severe arm paresis (129). However, no studies have been conducted for the lower limb. Further investigation about the influence of severity of paresis on recovery is therefore required for lower limb mirror therapy.

In addition to who would benefit, the best time to apply the therapy is also uncertain. According to Thieme *et al*. (2018) in their updated Cochrane review about the effect of mirror therapy on both upper and lower limb, mirror therapy is effective in "acute", "subacute", and "chronic" stages after stroke (103). However, this could reflect the time applied in both upper and lower limb so further investigation is required to find out more about the influence of time after stroke on the recovery for lower limb mirror therapy.

In addition, while most of the published reviews emphasize the need to identify optimum dose of the therapy (103,165,168), the current literature on lower limb mirror therapy has so far not addressed this. Most empirical studies vary in terms of the dose provided and no has investigated the dose-response relationship in the current evidence. Further investigation of the influence of the dose on recovery for lower limb mirror therapy is therefore required. This

limitation in the current knowledge and the lack of protocols for the use of lower limb mirror therapy (163,165), hamper the use of lower limb mirror therapy in clinical practice as well as in research. In order to better apply the therapy, the "knowledge unit" must be known.

The set-up of tool

In clinical practice, MT is considered one of the latest treatments in stroke rehabilitation (9). The set-up of upper limb mirror therapy is easy as it is the more functional exercise for the upper limb, and the mirror can be set-up on the table. In contrast, lower limb mirror therapy, its apparatus set-up, the position of the mirror, and the position of the participant, make it more complex and the set-up varies across studies.

Figure 1-1 Illustration of mirror therapy set up for rehabilitation of upper limb motor function. The participant maintains a good upright posture, looking at the reflection of the less paretic limb while obscuring the view of the more paretic limb. Participants are instructed to focus on the mirror image of the less paretic limb whilst performing a series of movements, thus providing the visual illusion, and therefore visual feedback to the brain that the more paretic limb is moving normally.

Most studies place a mirror on a parasagittal plane between the lower limbs, and some provide the dimensions of the mirror as: 40×70 cm (121,169), 60×90 cm (170,171), and 50×70 cm (172). In some studies, participants adopt a half-lying position (169,173), while, in

others, they are in a sitting position (121,170). However, essential adaptations such as holding the mirror in place to see a good reflection, were missing from these studies. Also, most studies do not mention the importance of obscuring the more paretic lower limb so that the subject only sees the reflection of the less paretic side in the mirror. One issue is that the available commercial mirror therapy for use with the lower limb is difficult to use: the user either needs to lean back to see a clear reflection of the mirror or hold the mirror with their hand to see the reflection with an angle. All these adaptations are hard to manage by stroke survivors, especially if they use it in their own home where mirror therapy is meant to be used (163).

Consequently, current evidence presents challenges to adopting MT as an intervention for the lower limbs, and the unclear methods and the lack of protocol make replication difficult. However, despite user-centred design being considered crucial to the uptake and use of such technology (174,175), to the researcher's knowledge, there is no evidence of users of MT being engaged in the development of equipment in any of the published studies (175). These limitations hamper the use of evidence-based lower limb MT by stroke survivors and clinicians (174,176). Therefore, within lower limb MT, stakeholders need to be involved in designing and evaluating the tools to meet the users' requirements, including accessibility, usability and acceptability (177,178).

Several research approaches involve the user in tool design, such as user centred system design (UCSD) and participatory action research (PAR). The main difference between PAR and UCSD is that PAR seeks to deeply involve the users in the process, by authorising them to process and design the tool as part of the research group so that every time the team meets,

all the users need to be there (179,180); thus the PAR design approach is hard to use due to the limitation in time and transportation for both researchers and participants.

Norman and Draper first introduced user-centred system design (UCSD) research in 1986, emphasising the essential involvement of user feedback. Since then, many definitions have been used to describe the approach (181); but simply, it is an iterative process in which the primary goal is the development of a usable system, achieved through the involvement of the potential users of a system in the design process (181,182). This design process has been more widely used in technology and computer sciences but has started to be used in health sciences to improve rehabilitation tools (183–186). In addition to involving the main users, it is recommended that multi-disciplinary teams are also involved so as to move the research towards clinical practice (178).

In summary, due to the lack of protocols for the use of lower limb mirror therapy, and the varieties of the reported technical details in a limited body of evidence, there is a need to incorporate user voices in the development of the lower limb mirror therapy tool. Understanding the users' needs in terms of the set-up of the device will allow improvement of application of lower limb mirror therapy in both clinical and research settings.

How much

In addition to the missing technical details for lower limb mirror therapy tools, how much mirror therapy should be given, optimal frequency and duration, remain unknown (103). Although a higher dose of therapy is expected to produce better outcomes (187), this is not always the case in stroke rehabilitation (67,188), and specific investigation is required to

ascertain the best dose levels for mirror therapy (103,165). Particularly, more robust dose studies are needed in stroke rehabilitation (59,96,189,190).

To identify the dose, especially in pharmacology, two common methods are used: dose-finding or dose-ranging for medications (191). These two designs have pre-specified criteria to use. Dose ranging is used to identify the response to treatment by using safe quantities of pre-specified doses that have been identified through earlier phases of the research (192,193). However, such predefined doses are not available for mirror therapy, as current systematic reviews show that none of the doses in current clinical trials were derived from dose-finding evidence. This design would require a large sample size to test all the pre-specific doses (192), which would make the research both costly and time-consuming (192) .
Therefore, there is a definite need for robust, dose-finding studies to identify the dose (189). In pharmacological studies this is usually undertaken in early Phase I research (194), if there is uncertainty about the dose-response relationship, as is the case here in mirror therapy. Using this design helps to ascertain the maximum tolerable dose of mirror therapy (MTD), which can be defined as the highest dose at which adverse consequences are still acceptable for participants (195). After identifying the MTD, a progressive staging for the dose can be conducted. Therefore, dose-finding research is needed to investigate the maximum tolerable dose (MTD) per day of ankle dorsiflexion exercise delivered via mirror therapy.

In summary, there is a lack of critical information about the main units of knowledge pertaining to lower limb mirror therapy, with regards to when to apply the therapy, who might benefit, the design of the tool, and how much treatment should be given. The lack of these critical units of knowledge meant that it was not possible to proceed with a phase III

clinical trial. Therefore, the thesis was developed to answer some of these key questions, as discussed in the following section.

1.10 Research Questions

The introduction of the thesis has established that:

- Most available evidence about mirror therapy applies to the rehabilitation of the upper limb. There is a paucity of studies investigating potential benefits for the lower limb.
- Moreover, current evidence does not answer the questions of who might benefit from the therapy and when to apply it.
- Current studies do not provide sufficient technical details to enable a full understanding of the set-up of LLMT and the best equipment to use with stroke survivors. Thus, replicating lower limb MT in clinical practice or research is challenging.
- The lack of knowledge about the optimal dose of lower limb mirror therapy after a stroke makes the best dose-response relationship hard to predict.

In light of these research gaps, this thesis provides:

- A synthesis of the evidence about the efficacy of lower limb mirror therapy on motor recovery after stroke, and investigates the influence of time after stroke, severity of paresis and the dose of the therapy for recovery.
- Develops a piece of MT equipment and set-up, co-designed with end-users to produce user-friendly equipment.
- Identifies MTD as phase I dose for lower limb MT.

Research question one

Does provision of lower limb exercise via mirror therapy enhance motor recovery after stroke?

- Does time after stroke influence response to mirror therapy?
- Does the level of paresis influence response to mirror therapy?
- Does the amount of mirror therapy (dose) influence response to mirror therapy?

The question gives rise to the following aims:

Aim-1

- To update the synthesis of the available evidence on the effect of lower limb mirror therapy on motor recovery after stroke.
- To investigate if time after stroke influences the response to mirror therapy.
- To investigate if the severity of paresis influences the response to mirror therapy.
- To investigate if the dose of therapy influences the response to mirror therapy.

Secondary research questions

- **Does provision of lower limb exercise via mirror therapy enhance the improvement of functional capacity after stroke?**

- Does time after stroke influence response to mirror therapy?
- Does the level of paresis influence response to mirror therapy?
- Does the amount of mirror therapy (dose) influence response to mirror therapy?

Secondary aim

a) To update the synthesis of the available evidence on the effect of lower limb mirror therapy on functional capacity after stroke.
b) To investigate if time after stroke influences the response to mirror therapy.
c) To investigate if the severity of paresis influences the response to mirror therapy.

d) To investigate if the dose of therapy influences the response to mirror therapy.

Aim 1 (a,b,c,d) and the secondary aims were investigated using systematic review and meta-analysis.

Research question two

What is user-friendly, feasible equipment and set-up of the mirror therapy for lower limb rehabilitation after stroke?

This question gives rise to the following aim:

Aim 2

To co-design lower limb mirror therapy equipment and setup by working directly with stroke survivors and physiotherapists.

Aim 2 was investigated using a co-design approach through focus groups.

Research question three

What is the maximum tolerable dose (MTD) a day of mirror therapy for ankle dorsiflexion for use in a subsequent dose-ranging study?

This question was informed by the need to identify the maximum tolerable dose per day of mirror therapy for the lower limb, precisely, ankle exercise.

This question gives rise to the following aim:

Aim 3:

To identify the maximum tolerable dose per day to do ankle exercise mirror therapy.
This aim was investigated by using a 3+3 rule-based, dose-escalation/de-escalation design.

1.11 Thesis structure and methodology

The Medical Research Council (MRC) framework to develop complex intervention (196,197) was used to develop the thesis aims. This thesis concerns itself with the early stage of intervention development, and these are mapped on to the MRC framework. A recent update for the MRC (198) emphasizes the importance of the developmental phase of an intervention in terms of improving the performance and the design of the intervention before investigating its effectiveness. O'Cathain *et al.* (2019) propose key principles and actions to consider when developing complex intervention to improve health and healthcare (199), namely these key principles of the intervention development should be "*dynamic, iterative, creative, open to change and forward looking to future evaluation and implementation*" (199). Therefore, the researcher needs to plan the research framework carefully (199) to ensure the appropriate progression of the evidence pathway and the best approach to answering the research questions so as to develop an effective intervention to be used later on (198).

This thesis was also guided by the progressive staging of pilot studies to develop its methodology and improve the phase III trials for motor interventions (194). It is underpinned by the stroke recovery trial framework (59). Many approaches are considered in the developmental phase of a complex intervention (198,199) such as including the stakeholder in the development of the intervention, reviewing published evidence, understanding the context and undertaking primary data collection (199). In this thesis, the lack of evidence in extant LLMT literature regarding the main knowledge units (see section 1.8) made it difficult to proceed with the GO decision to conduct a randomised control trial (RCT). Therefore, in this trial development, identifying the main knowledge units was essential to help guide the Go/No-Go decision-making process (59), as was further investigation to fill the knowledge gaps, thereby contributing to the evidence base for LLMT.

According to the MRC recommendations regarding the development process of complex interventions, relevant research evidence should be considered using a systematic review (198). A few systematic reviews and meta-analyses have been conducted but their usefulness was limited due to knowledge gaps regarding the influence of time after stroke, severity of paresis and the dose of therapy on recovery. It was therefore difficult to know who might benefit from therapy, when to apply therapy and the dose of therapy.

Nonetheless, current evidence was investigated to understand the potential factors that influence recovery. These factors were considered when co-designing the tool and making decisions about the early phase I dose of the therapy. Using this type of approach also helped to fill some of the critical gaps in the knowledge units, without which these investigations could not have moved forward. For this reason, these investigations need to be considered as part of the developmental phase of the intervention.

Another crucial element in the developmental phase is intervention design (199) using prototypes and a series of iterative cycles to assess the acceptability and feasibility of the intervention design, prior to further testing. However, as outlined earlier in the introduction, technical information about the best equipment set-up and design to be used with stroke survivors with regards to LLMT is limited by the lack of a well-developed evidence base. When designing an intervention, the guidelines recommend the inclusion of stakeholders (199). Particularly given the knowledge gaps, it was crucial to incorporate user input in the development of the LLMT prototype device by involving them in the iterative development process. User involvement helped to define priorities, understand problems and propose solutions (199) and led to the production of a device that could be used by the target users prior to its implementation in clinical practice.

With regards to the current knowledge gaps in LLMT, therapy dose was the missing component that had to be identified prior to conducting any piloting or feasibility study. Establishing therapy dose as an "active ingredient" needs to follow certain steps in the knowledge pipeline to be able to be translated into clinical practice. In other words, therapy dose needed to be established before knowing who might benefit and when to apply the therapy (59). Therefore, a phase I investigation needs to be conducted prior to proceeding with RCT (194). In this study, identifying MTD as a phase I dose was considered to be a crucial investigation and was conducted in the developmental phase of the intervention. Once the set-up of the equipment had been co-designed and questions about who might benefit, when to apply the therapy and the dose of the therapy had been addressed, the further work of piloting, formal evaluation and implementation could be carried out in post-doctoral work.

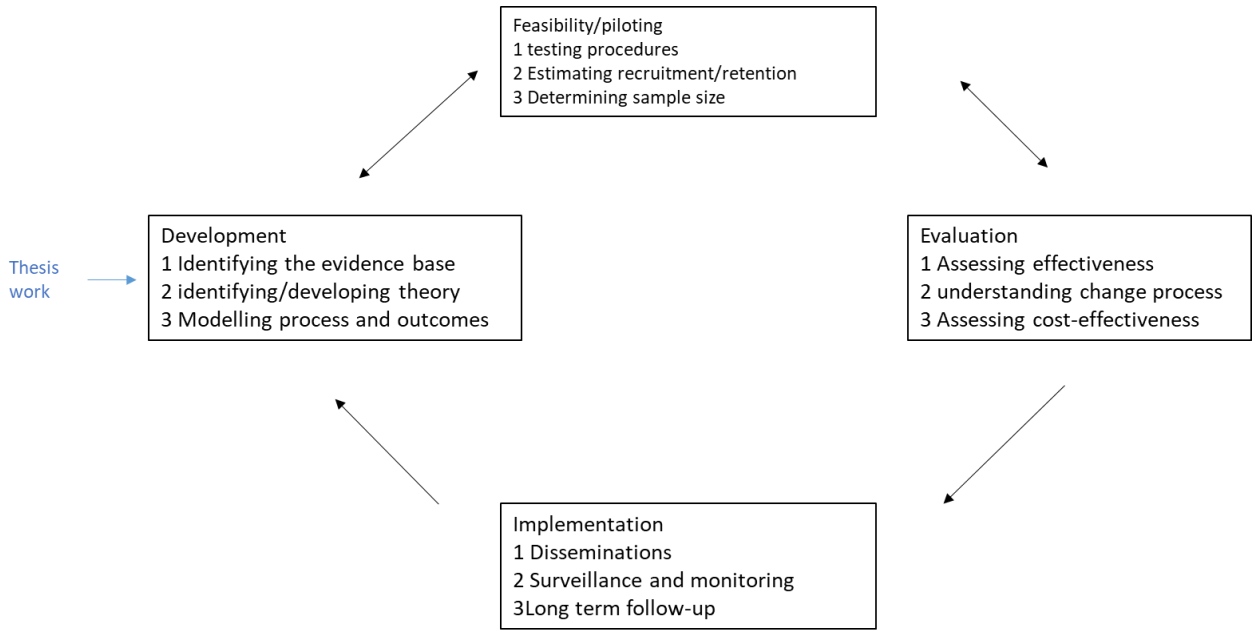


Figure 1-2 key elements of the MRC framework to develop complex intervention (197), and the stage of the thesis in the framework.

To allow an appropriate progression of the evidence-based pathway as recommended by Dobkin (2009) to improve motor interventions (194). A sequential multiphase multiple-method design was used (200–202) to address the aims of the thesis. Multiple method research is widely used in health research (203–206), helping researchers answer research questions using different designs that cannot be answered using one design only (207). This can draw on the strengths of both quantitative and qualitative data to support the thesis conclusion (208). A multiphase sequential approach was adopted which allows the use of quantitative and qualitative data based on a sequential order, wherein each study builds on the previous one, and together they aim to answer the thesis research questions (209). This PhD comprised three phases as follows: phase I which was a quantitative study (systematic review and meta-analysis) followed by phase II, a qualitative study (co-design via focus group) and lastly, phase III, a quantitative study (dose-finding). The rationale for using this approach was that the quantitative data from the meta-analysis and the subsequent analysis would provide a general understanding of the influence of lower limb mirror therapy on motor recovery and

whether time after stroke, severity of paresis and the dose of therapy might influence recovery. Then qualitative data from a co-design approach helped to identify and understand users' needs by iteratively involving them in the co-design of the equipment and improvement of the set-up for the use of ankle exercise via mirror therapy. Results from phase I and II informed the quantitative data which was needed to identify MTD of lower limb mirror therapy, specifically ankle exercise. More justification about the rationale used in each study can be found in the subsequent chapters of this thesis.

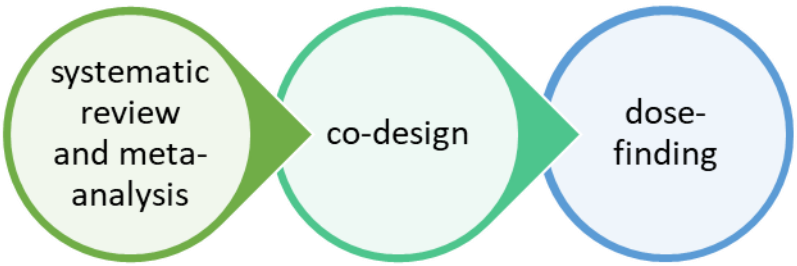


Figure 1-3 overall thesis component diagram

chapter 2. The influence of time after stroke, level of paresis and the dose of intervention on efficacy of lower limb mirror therapy after stroke: systematic review and meta-analysis.

2.1 Introduction

Recent systematic reviews on the efficacy of mirror therapy after stroke (103) have stated that MT has moderate evidence for improving motor function after stroke, especially on the upper limb (103) and the lower limb (165,166). In addition, a recent systematic review indicated that lower limb MT might improve the balance and gait of the lower limb (165). However, these reviews did not address the influence of time after stroke, level of paresis of the stroke survivors, and the dose of the therapy on recovery. In this review, two-term were used; motor recovery and improvement in functional capacity. The definition for theses are; motor recovery is the return of the foot or leg toward the normal pattern of motor control (210), while the improvement of functional capacity is the ability to perform a function such as the ability to walk independently (4).

Purpose

The main aim of this review was to update the evidence of the effect of mirror therapy on the lower limb motor recovery after stroke, and then to investigate whether time after stroke, the level of the paresis, and the dose of intervention have the potential to influence the response to mirror therapy. The secondary aim was to evaluate the effect of mirror therapy on improving the functional capacity of the lower limb after stroke. Then to investigate if whether time after stroke, the level of the paresis and the dose of intervention have the potential to influence the response to mirror therapy.

Research questions

The primary research questions:

- Dose provision of lower limb exercise via mirror therapy enhance motor recovery after stroke?
    - Does time after stroke influence response to mirror therapy?
    - Does the level of paresis influence response to mirror therapy?
    - Does the amount of mirror therapy (dose) influence response to mirror therapy?

The secondary research questions:

- Dose provision of lower limb exercise via mirror therapy enhance the improvement of functional capacity after stroke?
    - Does time after stroke influence response to mirror therapy?
    - Does the level of paresis influence response to mirror therapy?
    - Does the amount of mirror therapy (dose) influence response to mirror therapy?

2.2 Method

2.2.1Design

A systematic review following the recommendation of the Cochrane collaboration was conducted (211). Furthermore, the preferred reporting items for systematic review and meta-analyses: the PRISMA statement (212) to report the study findings was used (Appendix I-a). This review was carried out by the lead author (SB) and the primary supervisor (VP). A systematic review provides a means by which evidence can be systematically identified and synthesised in order to answer a research question or identify the gaps in the current knowledge (211). Given the previous points that been raised in the introduction, about the main gaps in current knowledge and the uncertainty about the time after stroke, level of

paresis, and the dose of the therapy, and how these might influence response to mirror therapy, the systematic review method was the best approach to synthesising the current evidence in the field and answering these questions.

2.2.2 Searching for studies

2.2.2.1 *Electronic search strategy*

In order to be systematic and to avoid any publication bias in searching the current evidence, the searching strategy needed to be inclusive, and the keywords had to be suitable for identifying the relevant papers (211). Therefore, this search strategy was developed in liaison with the Medical Liberian at UEA. The terms were adapted according to each database's specific requirements using Boolean logic and symbols (Table 2-1 and appendix I-b for further details). No funding was available for translation; therefore, the search was limited only to English or Arabic papers. An Excel template was used to report each database's findings with a search date to keep the record up to date.

The search strategy used mainly these terms with slight adaptation for each database in the following table:

Table 2-1.key terms used in searching the databases.

Concept 1		**Concept 2**		**Concept 3**
Stroke OR cerebrovascular accident OR (CVA) OR cerebral stroke OR hemipleg*	And	Mirror therapy OR Mirror box OR Mirror visual feedback OR graded motor imagery	And	Lower limb OR Lower extremity OR Ankle OR foot OR leg OR Walk OR balance OR gait

Study selection

Studies were included if they met the following criteria:

a) Participants were 18 years old or above and had a stroke with hemiparesis affecting lower limb function and/or performance;

b) Mirror therapy intervention targeted the lower limb after stroke. In this context, mirror therapy is defined as an intervention using a mirror that is physically present, to produce a visual illusion that the more paretic lower limb is moving identically to the less paretic limb which is observed in the mirror. In this review, interventions providing mirror therapy with video or virtual reality were excluded.

c) Study designs were clinical trials and controlled studies with or without randomization to the group.

d) An outcome measured the motor recovery and/or functional capacity for the lower limb.

1. Primary outcome measure

- The motor recovery or motor impartment of the more paretic lower limb, e.g., Fugl-Meyer Assessment, Motricity Index, ankle Range of Motion (ROM), spasticity.
- However, if these scales were not available, we accepted other measurements that evaluate motor recovery.

2. Secondary outcomes measure

- Functional capacity of the lower limb e.g. gait, walking speed, double support time, balance (e.g. Berg Balance Scale) , general mobility (e.g. modified Rivermead Mobility Index), walking ability (e.g. Functional Ambulation Categories),
- Neurophysiological characteristics e.g.: cortical excitation or inhibition.

Table 2-2 Explain the PICOS for inclusion/exclusion criteria for the studies in the review.

PICOS	Inclusion	Exclusion
Participants	• ≥ 18 years old.	• < 18 years old.
	•Clinical diagnosis of stroke with hemiparesis affecting lower limb function and/or performance.	• Clinical diagnosis of stroke with hemiparesis affecting upper limb
Intervention	Mirror therapy for lower limb after stroke.	Mirror therapy with upper limb
Comparison	Conventional rehabilitation therapy or comparator e.g.: electrical stimulation therapy or no therapy	When MT is combined with another therapy in such the effect of experimental mirror therapy cannot be distinguished
Outcome measure	Motor recovery and/or functional capacity for lower limb	Measure only participation and /or quality of life.
Study design	clinical trials, cotrolled studies with or without randomization to the group. crossover trials included up to the first crossover point.	Longitudinal single cohort studies and case reports.

2.2.2.2 *Searching databases*

The lead researcher (SB) worked independently to search the databases and uploaded the search results onto the reference manager (Mendeley), removed any duplicates, and exported them to Excel sheets, then shared it with the primary supervisor (VP). Two reviewers (SB & VP) then worked independently to identify eligible studies. The reviewers considered each reference separately; an Excel sheet was used to highlight the screened title with an exclusion and inclusion list. After the relevant articles were included from the title, the abstracts were screened, followed by full paper screening as needed, based on the pre-defined criteria using standardized proforma to identify eligible papers. If there were disagreements about form, a one-to-one discussion was used to resolve it by referring to the original paper. Any persistent

disagreements were referred to a third party and resolved by discussion and re-referral to the original article.

The following databases were searched:

1. National Library of Medicine Database (MEDLINE)
2. PubMed Central
3. Allied and Complementary Medicine Database (AMED)
4. European Medical Database (EMBASE)
5. Cochrane Central Register of Controlled Trials (CENTRAL)
6. Cumulative Index to Nursing and Allied Health Literature (CINHAL) complete
7. Physiotherapy Evidence Database (Pedro)

The initial search period was conducted to cover the period from the induction of the databases to August 2018, and this was updated in August 2019, and December 2020.

Grey literature

Was searched in:

1- E-theses Online library (ETHOS)

2- core.ac.uk

3- Stroke charity

4-Open Grey Europe

5- ACPIN (synapse journal)

6- Newsletter for PT in the UK (and other countries USA, AUS, KSA). Such as chartered society of physiotherapy, world confederation of physical therapy.

Searching for ongoing trials and research registers

- ISRCTN registry
- Clinicaltrials.gov
- International clinical trials registry platform (ICTRP)

Search other resources

- European stroke conferences

- World Congress of Physical Therapy
- World Stroke Congress
- Screen reference list of all relevant articles
- Search the REHABDATA database (NARIC)

Hand searching

This was conducted in the reference list of the key published studies, conference papers, and abstracts that were related to the topic. Unpublished studies were searched in all previous databases (forthcoming), UEA digital repository, ProQuest dissertation, and theses in UK and Ireland.

2.2.3 Data extraction

Two standardized forms to extract the data from the included study were used. The first form was for the participants' characteristics of the included studies on:

- side of stroke
- type of stroke
- time after stroke
- age
- gender
- severity of motor impairment
- functional capacity

The second form reported:

- study design
- sample size
- intervention in the control group

- intervention in the experimental group
- primary outcome of the included study
- secondary outcome of the included study

The lead researcher (SB) extracted all data and gave each study an ID to organise the files (Appendix I-c). The primary supervisor (VP) then checked these forms and amended it if needed. Then, the lead researcher compared the tables and checked them to clarify any issues raised during the process. If there was any disagreement, a meeting was held to check the issue by returning to the original paper; if no agreement was reached, a third reviewer was consulted.

2.2.4 Assessment of potential risk of bias

1- Two reviewers (SB& VP) worked independently to assess the potential risk of bias in the included studies (Appendix I-d). Criteria for assessing the risk of bias were derived from the revised Cochrane review risk of bias tool for randomized trials (ROB 2) (213). This tool considers five domains to assess the risk of bias in controlled trials which are; bias arising from randomisation process, bias due to deviations from intended interventions, bias due to missing outcome, bias in the measurement of the outcome, and bias in the selection of the reported results (for further details about main and sub-questions for this tool please refer to Appendix I-d).

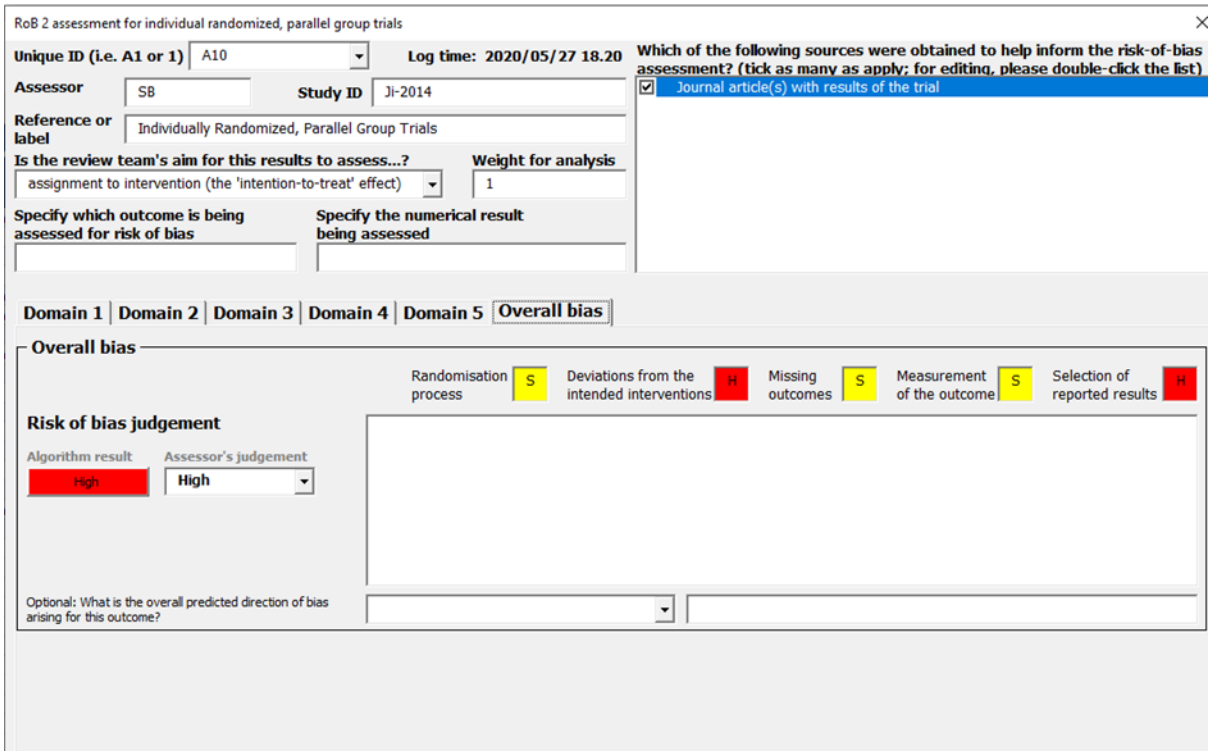


Figure 2-1 shows the revised tool with five domains and the risk of bias judgement for both assessor and algorithm (213).

Figure 2-2 shows the ability to combine the risk of bias judgment for the two assessors and the algorithm results. This would help to find any disagreement between the two authors (213).

Each of the domains contains questions that are answered using the algorithm method in which a particular answer lead to the next appropriate question. The answers to these questions are “yes”, “probably yes”, “probably no”, “no”, and “no information”. Each reviewer used the macro- Excel sheet that was provided with the tool, and each study was individually evaluated. Then the lead author compared the outcome from each reviewer about each study using the “discrepancy check” facility in ROB2. Any disagreements were resolved by a one to one meeting and or by referring to the tool guidance and the original paper. The assessment of risk of biases for all studies informed the interpretation of the review findings and future recommendations.

2.2.4.1 *Other Biases*

To avoid reporting bias that could arise with inclusion of the randomized controlled trials that used several outcome measures, in which the Researchers might tend to report the outcome measures with significant results or with the largest effect sizes (214). In this review, reporting bias was avoided by predefining the type of outcome measure that needed to be reported.

2.2.5 TIDier guideline to assess and describe the quality of reporting

In addition, the template for intervention description and replication (TIDieR) checklist and guide (215) was used to help assessing the quality of the reporting in the included studies and to highlight the common reporting gaps in the existing literature. This checklist included twelve main items as the following (215): brief name, why, what (materials), what (procedure), who provided, how (mode of delivery), where, when and how much, tailoring,

modifications, how well (planned), and how well (actual). (further information about the checklist is found in appendix I-e).

Both reviewers (SB & VP) completed the pre-defined excel form that included the twelve items. Any disagreements were solved by one-to one meeting, referring to the original study and the guideline.

2.2.6 Data synthesis and analysis

Descriptive statistics such as participants' age, the comparison group and data revealed from the TIDier reporting, were narratively synthesised. For quantitative data, a meta-analysis was conducted for the outcome measures between the control group and intervention group using Review Manager Software (Version 5.3.5) and Excel software for the sub-questions. Due to the similarity of the groups and intervention, these results could combine to increase their power and precision to answer the research question.

Meta-analysis was conducted into two main groups:

1. The primary meta-analysis was to investigate if the provision of lower limb exercise via mirror therapy enhances motor recovery after stroke.
2. The secondary meta-analysis was to investigate if the provision of lower limb exercise via mirror therapy enhances the improvement of functional capacity after stroke.

The outcome measures were chosen to report the primary outcome of the study. If not stated, then a common outcome measure between the studies was reported. If there were no common outcome measures, an outcome measure used for motor recovery and /or improvement of functional capacity was reported.

In this review, the focused was on the final value between groups rather than the change from the baseline score. This was due to insufficient information about the standard deviation of changes value among the included studies, and to ensure consistency in reporting. Also, in this review, no follow up points were analysed.

The meta-analysis was conducted according to the following steps in both primary and secondary analysis separately:

1- Summary of statistics for the included studies: most of the reported outcomes in the included studies were continuous outcomes that assessed the same outcome but used different scales to measure it. According to this, a standardized mean difference, and 95% of the confidence interval to standardise the continuous outcome scales before they can be combined were used (211). Effect sizes were considered as small, moderate, or large as the following: effect sizes of 0.20 as small, 0.50 as moderate, and 0.80 as large (211,216). The Random effect model was used as a clinical and methodological heterogeneity is expected to be between studies (211). For all outcome variables, two-tailed P-values of < 0.05 were considered statistically significant (211).

2- A summary (pooled) intervention effect estimate is calculated using inverse-variance method (211).

3- Examine heterogeneity:

   I. Examine the forest plot to identify whether there is substantial heterogeneity between studies “using the eyeballing approach.” to have an initial overview of the level of heterogeneity (216).

   II. Then, if heterogeneity is present, the degree of heterogeneity was calculated using I-squared. This is to describe the percentage of total variation across the

studies due to heterogeneity rather than chance. The values of heterogeneity are (211):

- 0% means no heterogeneity.
- 25% low heterogeneity
- 50% moderate heterogeneity
- 75% high heterogeneity.

III. For full heterogeneity investigation, a sensitivity analysis was used. After running the primary analysis, the sensitivity analysis was run by removing the outliers from the total effect size to investigate any differences in the total effect size and to assess the changes in heterogeneity level. Then as further step, studies with a high risk of bias in the randomization process were removed to allow us to understand the effect of that on the total effect size and the review's interpretation. This was only in primary and secondary analysis. However, in subgroup analysis the outliers did not remove due to insufficient data, and this is explained in detail in the discussion section.

IV. Subgroup analysis:

To enhance understanding about the influence of time afters stroke, level of paresis and the dose of intervention on response to mirror therapy, subgroup analysis used as follows:

a) time after stroke

Clinicians and researchers need to know when the best time after stroke to apply the therapy is (210). In this review, the baseline characteristics of the mirror therapy group among each of the included studies were examined. Then, checked

if that influenced the response to mirror therapy by grouping the time after stroke according to time reported in the studies, by using the same outcome measures in the main analysis, the following;

- one week or less after stroke
- more than a week and less than two months after stroke
- more than two months and less than six months after stroke
- more than six months after a stroke.

the standard grouping of time after stroke was avoided, which is acute, sub-acute, and chronic, as these terms are being used without adequate definition (210). If the included studies did not report the time after stroke, then it was excluded from this sub-group analysis.

b) Level of paresis

It was important to know the appropriate level of severity of the participants in order to understand if that influenced the response to mirror therapy, and to know who might respond more from the therapy. The included studies were divided among three groups according to the level of severity as following; severe paresis, moderate paresis, and mild paresis. The Brunnstrom Stages of recovery was used to classify these terms. However, if the included studies did not report the Brunnstrom stage of recovery, but they used the Fugl-Meyer assessment (FMA), that scale was accepted as it is based on Brunnstrom stage of recovery (217). If none of these scales was used at the baseline, then the study was excluded from this sub-group analysis. The severity of paresis was defined as the following:

- According to The Brunnstrom stages of recovery are:
  - Stage 1: flaccidity.

- Stage 2: synergy development (minimal voluntary movements)
- Stage 3: voluntary synergic movement (combined hip flexion, knee flexion and ankle dorsiflexion both sitting and standing)
- Stage 4: some movements deviating from synergy (knee flexion exceeding 90 degree and ankle dorsiflexion with the heel on the floor in the sitting position
- Stage 5: independence from basic synergies (isolated knee flexion with the hip extended and isolated ankle dorsiflexion with the knee extended in the standing positions
- Stage 6: isolated joint movements (hip abduction in the standing position and knee rotation with inversion and eversion if the ankle in the sitting position.

Stages were considered as the following: 1&2 severe, 3&4 moderate, and 5&6 mild. Therefore, a score of 0-2.9 = severe, 3 to 4.9 = moderate, 5 or above = mild (218). If BBS was not provided, then FMA-LL (total of 34 scores) was used as per the following classification; Severe= less than 19, Moderate= between 20 and 28, Mild= equal or more than 29 points (217,219).

The same method to subgroup participants for severity of paresis was used in the primary and secondary analysis (Appendix I-f). Then, after group participants the same reported outcome measure in the primary and secondary analysis was used subsequently.

c) Amount of intervention (dose).

One of the most critical factors that might influence the response to mirror therapy is the dose of the intervention. First, the included studies were grouped according to the amount of time (in weeks) over which the intervention was provided using

Revman software (Review Manger 5.3). Then if reported, the total number of minutes were added up, and plotted this against the effect size of the reported outcome using an Excel program to explore a pattern between the dose and the influence on recovery. If any study did not report enough details, then it was excluded from this subgroup analysis.

study ID	number of summed mintues	effect size
A6	360	1.77
A16	360	0.45
A1	600	0.65
A2	600	0.5
A8	600	0.89
A3	1740	0.37

Figure 2-3 shows the analysis used for the amount of intervention (dose in minutes). The study IDs were used for the studies reported the dose in minutes by summing the minutes of the whole intervention for the training program, then the effect size for each stud was reported. Then these data were plotted to investigate the relationship between the dose and the effect.

4- Additional sensitivity analysis:

To detect if the efficacy of mirror therapy was sensitive to changes by using different scales, all the scales used in the included studies were grouped into two main types: scales that measure motor recovery, then the scales that measure improvement in functional capacity. Then all the scales under these two sections.

5- Publication bias: refers to the problem that not all the studies conducted in a particular area are actually published. Authors, editors, and journals are inclined to publish studies that are significant and with large intervention effects. However, if research shows a small effect, then the chances of publication decrease (220), which is considered a big problem for meta-analysis. A visual detection of this bias by using a “funnel plot” for both primary and secondary meta-analysis was used.

2.3 Results

2.3.1Summary of the search result

A total of 282 studies were identified. Abstracts of 155 studies were screened, and 38 full papers assessed for eligibility. This process yielded 20 studies for inclusion.

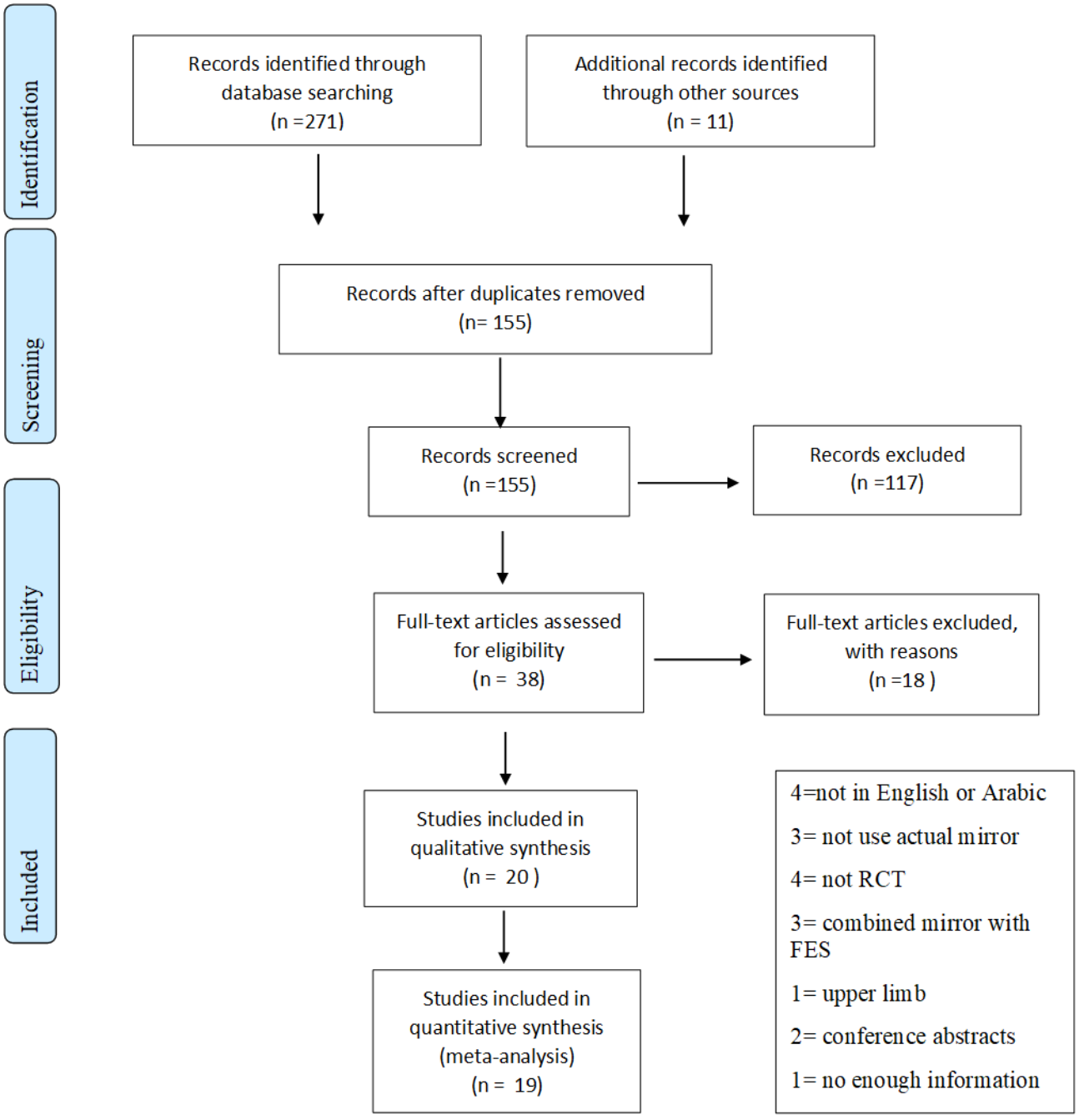


Figure 2-4 Prisma flow diagram of result of search strategy.

2.3.2Assessment of potential risk of bias

Among the twenty studies that were included in the review, eleven studies had an overall judgment of high risk of bias with 55.6% (170,221–230), seven studies had an overall judgment with some concerns 33.3% (121,172,173,231–234), and two studies had low risk of bias 11.1% (171,235) (table 2-3&2-4). In the randomisation process, six studies had a high risk of bias with 27.8 % among the included studies (170,222,229,230,234,236), five studies had some concerns with 29.4% (221,224–226,228), and nine studies had low risk of bias with 47.1% (121,171–173,223,231–233,235). In the deviation from intended intervention bias, seven studies had a high risk of bias 33.3%(221,224–226,228,230,231), while nine studies had some concerns about 50 % (170–173,222,223,227,229,235), and four studies had a low risk of bias 16.7% (121,232–234). In missing outcome domain, two studies had a high risk of bias 11.1% (223,232), eight studies had some concerns 44.4% (121,171,173,221,224,227,231,234),and ten studies had low risk of bias 38.9% (170,172,222,223,225,228–230,233,235). In the measurement of outcome domain, six studies had a high risk of bias about 33.3%(170,222,223,226,228,229), while six studies had some concerns with 22.2% (172,221,224,225,230,233), and eight studies had a low risk of bias about 44.4% (121,171,173,227,231,232,234,235). In the selection of reported results domain, three studies had a high risk of bias about 16.7 (225,226,228),twelve studies had some concerns about 55.6% (172,173,221,223,224,227,229–233,235), and five studies with low risk of bias about 27.8% (121,170,171,222,234).

Table 2-3 describe the percentage of each domain regarding the level of risk of bias as low, some concerns and high risk (from ROB2 tool).

	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Assignment to intervention (the 'intention-to-treat' effect)						
Total number of study = 20						
Low risk	44.4	16.7	38.9	44.4	27.8	11.1
Some concerns	27.8	50	44.4	22.2	55.6	33.3
High risk	27.8	33.3	11.1	33.3	16.7	55.6

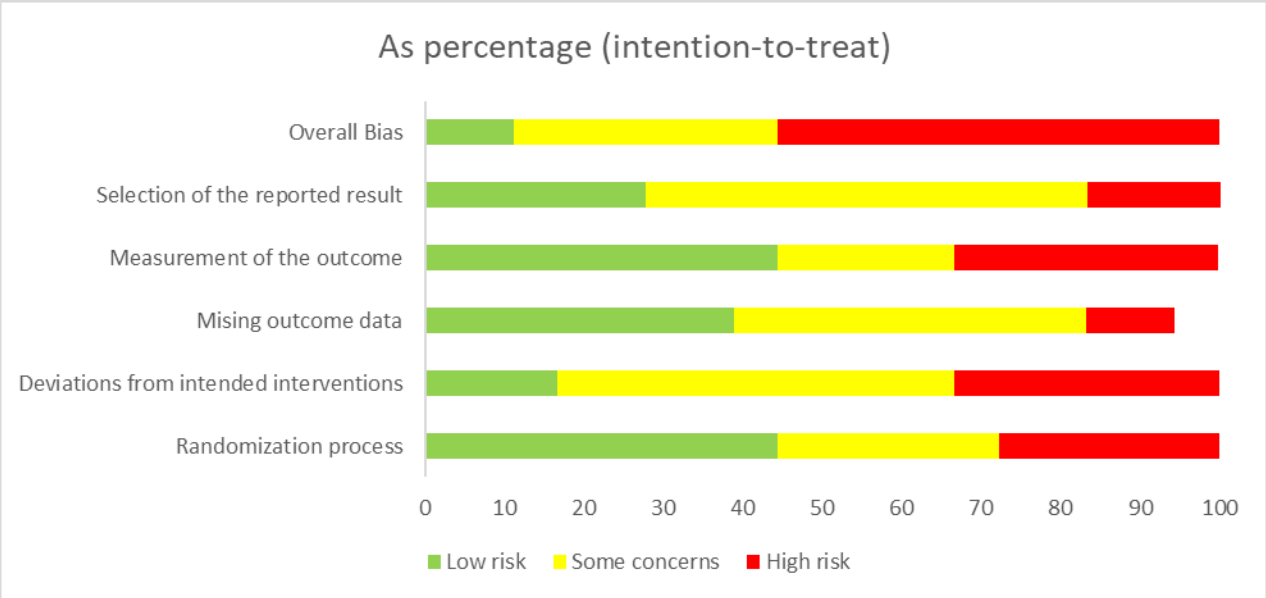
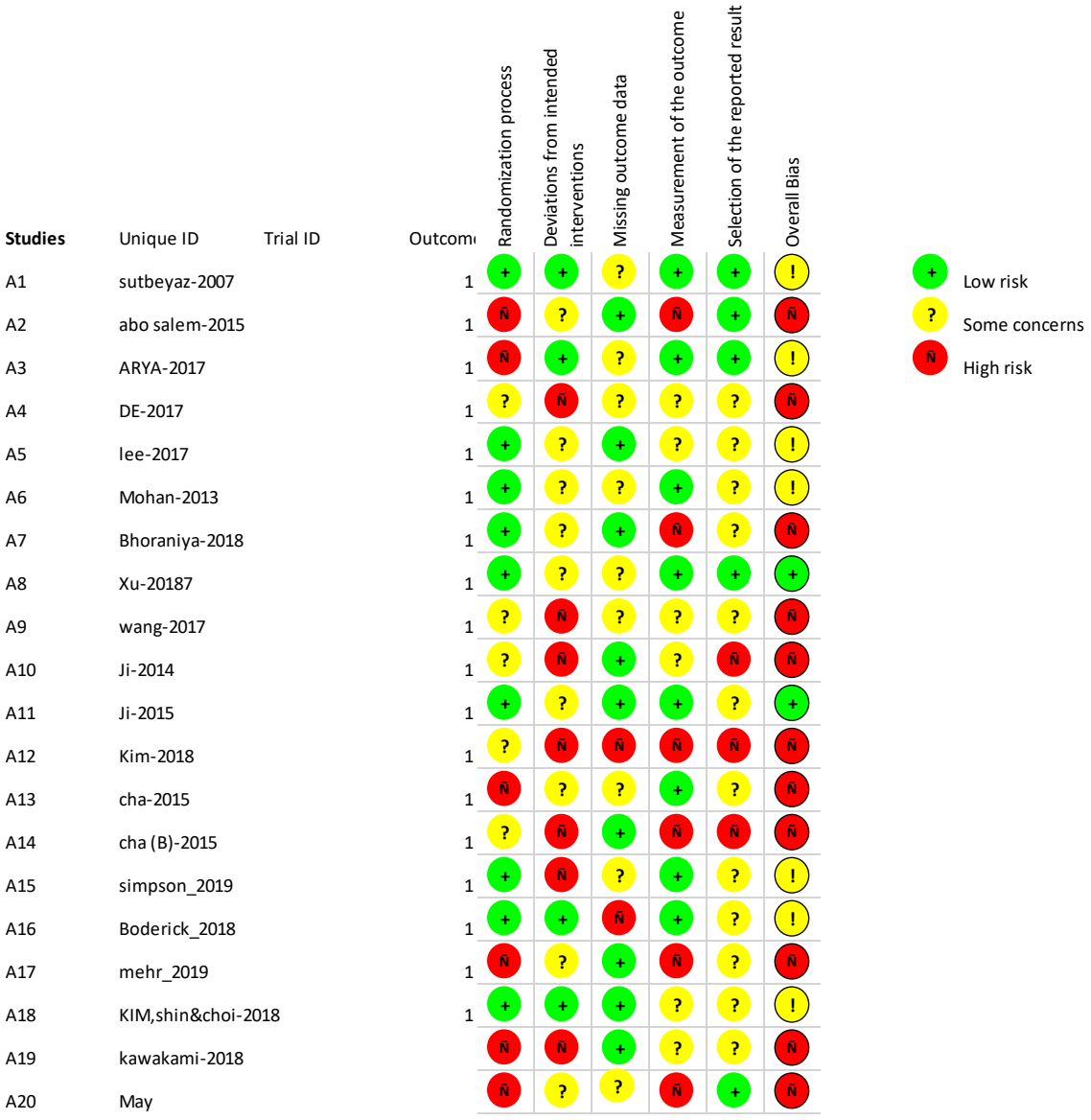


Table 2-4 shows the risk of bias level of the included studies. As noted, most of the studies have an overall high risk of bias, with only two studies have an overall low risk of bias



2.3.3Synthesis of results

2.3.3.1 *Narrative synthesis*

In this section, the qualitative data from the included studies was summarised as follows:

Characteristics of the included studies

The main characteristics of the included studies (Table 2-5) and the participants' characteristics (Table 2-6) are summarized below;

Study design

All of the studies included reported their design as randomized control trials.

Sample size

Altogether there were 791 participants included in this review. No studies included more than 93 participants (229) or less than 22 (173).

Participant age and gender

In most of the studies, the calculated mean age of the participants was between 59 to 69 years. In one study, only the mean age was between 44 and 48 (234), and one study from 50 to 59 (221), and one study mention range between 30-69 (229) (see table 2-6 for more details). All studies had male and female participants.

Time since stroke

Only one study included participants that were less than two weeks post-stroke (173), while five studies included participants that were less than three months post-stroke (171,222,224,227,230), three studies included participants that are more the three months but less than six months post-stroke (121,229,235). Only one study mentioned that participants were between 3 to 12 months post-stroke without mentioning any further exact details (221). Seven studies included participants that were more than 12 months post-stroke

(170,223,228,231–234), while three studies did not report any details about participants' time after stroke (172,225,226).

Type and site of stroke

Six studies mentioned that participants had their first-ever stroke (121,170,173,221,223,224), and most of them reported that participants had an ischemic stroke (for more details, see table 2-6). In comparison, three studies did not give any details about the participants' type of stroke (172,226,227). For the site of stroke, no studies mentioned the exact site of the stroke; most of them reported the location of the stroke on the right or left hemisphere. In addition, six studies did not mention the location or the side of the stroke of their participants (170,172,221,223,227,228).

Setting

Of those papers, six studies took place in inpatient hospitals (121,171–173,230,233), while only four studies conducted the therapy at outpatient clinics (224,229,234,235), and two university exercise labs (231,232). Eight studies did not make the setting of the study explicit (170,221–223,225–228).

The comparison groups

In eight studies, the control group received conventional rehabilitation, and the mirror therapy group received mirror therapy besides the conventional rehabilitation (121,170,223,224,229,234). While two studies compared mirror therapy to sham therapy besides the conventional rehabilitation for the control group and the experimental group (173,235). One study compared mirror therapy to the motor imagery besides the conventional rehabilitation for both groups (221).

One study (232) compared mirror therapy while walking on a treadmill with and without a mirror. Another study compared mirror therapy with a control group who received conventional rehabilitation in addition to other groups that received integrated volitional-

control electrical stimulation(IVES), or therapeutic electrical stimulation (TES), or repetitive facilitative exercises (RFEs) (230). Another study compared mirror therapy to mirror therapy in conjunction with neuromuscular stimulation (171).

One study (172) compared mirror therapy with action observation activity. The other study compared mirror therapy with neuromuscular electrical stimulation (171), while another study compared mirror therapy with functional electrical stimulation (225). Three studies compared the MT with strength exercise (226,231,233), and two studies combined the mirror therapy with TMS or rTMS, respectively and compared it with conventional rehabilitation (227,228).

Adverse event

None of the included studies reported any adverse event

Table 2-5 Characteristics of the included studies.

Study ID	Study design	Sample size	Experimental intervention	Control intervention	Primary outcome and secondary outcome measure
Sütbeyaz-2007 (A1)	▪ Randomised ▪ Placebo-controlled ▪ Observer blind	▪40 participants ▪20 experimental and 20 control ▪Post treatment were 20 experimental and 20 control – 1 month ▪Follow-up were 17 experimental and 16 control – 6 months	▪30 minutes of MT a day for 20 sessions ▪Less-paretic ankle dorsiflexion ▪Semi sitting on bed ▪Mirror board 40x70cm placed between legs in midline ▪Less paretic leg facing reflective surface watched that leg ▪Conventional stroke rehab programme 5 days a week, 2-5 hours a day for 4 weeks – neurodevelopmental facilitation techniques, PT, OT, SLT	▪ 30 minutes of placebo MT a day for 20 sessions ▪ Less-paretic ankle dorsiflexion ▪ Semi sitting on bed ▪ Mirror board 40x70cm placed between legs in midline ▪ Less paretic leg facing non-reflective surface – watched that leg ▪ Conventional stroke rehab programme 5 days a week, 2-5 hours a day for 4 weeks – neurodevelopmental facilitation techniques, PT, OT, SLT	Primary; not stated. Secondary: ▪ Brunnstrom stages ▪ Modified Ashworth scale ▪ Functional Ambulation Categories ▪ FIM - motor items
Abo Salem-2015 (A2)	▪ Randomised ▪Placebo-controlled	▪30 participants in total ▪15 in experimental ▪ 15 in control group.	▪ 30 minutes of MT ▪ Sitting position with mirror, 60x90cm, between legs in midline ▪ Less-paretic leg reflected in the mirror. Watched reflection of less-paretic leg and perform bilateral symmetrical movements as much as possible ▪ Hip-knee-ankle flexion; ankle dorsiflexion; and ankle eversion ▪ Conventional stroke rehabilitation 5 days a week 2-5 hours a day for 4 weeks – patient specific including OT, PT, electrotherapy, neurodevelopmental facilitation techniques and gait training	▪ 30 minutes of placebo MT ▪ Sitting position with mirror, 60x90cm, between legs in midline ▪ Less-paretic leg not reflected in the mirror ▪ Watched less-paretic leg and perform bilateral symmetrical movements as much as possible Conventional stroke rehabilitation 5 days a week 2-5 hours a day for 4 weeks – patient specific including OT, PT, electrotherapy, neurodevelopmental facilitation techniques and gait training	Primary: not stated Secondary: ▪ ROM ankle dorsiflexion – passive – goniometer ▪ Spasticity – Modified Ashworth scale – more paretic ankle plantar-flexors ▪ Brunnstrom stages ▪ Gait speed – 10m walk testing

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	Study design	Sample size	Experimental intervention	Control intervention	Primary outcome and secondary outcome measure
Arya-2017 (A3)	▪ Randomised controlled trial ▪ Observer-blind	▪ 36 participants enrolled and randomised ▪ 19 experimental & 17 control ▪ 3 participants lost to outcome assessment 1 experimental and 2 control participants ▪ Analysed 19 experimental and 17 control with last observation carried forward	▪ For sitting with knee, hip and ankle in 90 degrees- Mirror frame = 24x72 inches - Tilted in sagittal plane between 75 and 85 degrees ▪ For long-sitting with hip in 90 degrees knee at 0 degrees and ankle neutral - Mirror frame 36x48 inches ▪ Activity-based movements e.g. pedalling, wiping and shifting pillow for less-paretic side . Activities were progressed for individuals ▪ 30 x 30--minute sessions 3-4 times a week over 3 months ▪ Conventional intervention = motor therapy based on neurophysiological principles (Brunnstorm & Bobath) + hinged AFO + walking aids - 30 x 30--minute sessions 3-4 times a week over 3 months ▪ Total completed time mean of 29.04 (SD 1.09) hour	▪ Conventional intervention = motor therapy based on neurophysiological principles (Brunnstrom & Bobath) + hinged AFO + walking aids - 30 x 30--minute sessions 3-4 times a week over 3 months ▪ Total completed time mean of 29.15 (SD 1.47) hours	Primary: not stated Secondary: ▪ Brunnstrom recovery stages ▪ Fugl-Meyer assessment ▪ Rivermead Visual Gait Assessment ▪ 10-metre walk test
De-2017 (A4)	Randomised controlled	▪ 30 ▪ 15 =MT 15 = motor imagery	▪ MT 30 minutes a day 5 days a week for 4 weeks Conventional therapy, 30 minutes a day 5 days a week for 4 weeks: neurodevelopmental facilitation techniques, stretching, gait training	▪ Motor Imagery 30 minutes a day 5 days a week for 4 weeks Conventional therapy, 30 minutes a day 5 days a week for 4 weeks: neurodevelopmental facilitation techniques, stretching, gait training	Primary: not stated Secondary: ▪ Before and after intervention period ▪ Spasticity, Modified Ashworth scale ▪ Motor impairment, FMA lower limb Walk speed, 10 metre walk test

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	Study design	Sample size	Experimental intervention	Control intervention	Primary outcome and secondary outcome measure
Lee-2017 (A5)	Randomised controlled	▪ 35 in total ▪ 12 = action observation with activity (control) ▪ 11 = mirror therapy with activity (experimental) 12 = action observation	▪ mirror therapy with activity (experimental ▪ 3 times a week for 6 weeks ▪ Mirror therapy 15 minutes per day ▪ Mirror was 50 x 70cm & step board was 20x60x50cm ▪ Mirror reflected less paretic side ▪ Step board in front of the non-paretic limb ▪ Sitting in chair with knees flexed at 90degrees ▪ Dorsi-flexor training ▪ Physical training of same actions for 15 minutes a day ▪ General physiotherapy 30 minutes a day twice a week	▪ action observation with activity (control) ▪ Dorsi-flexor training ▪ 3 times a week for 6 weeks ▪ Action observation with video 15 minutes a day with a physiotherapist ▪ Physical activity of video tasks observed for 15 minutes a day ▪ General physiotherapy 30 minutes a day twice a week	Primary: not stated Secondary: ▪ Balance = Biodex balance system + postural stability + fall risk ▪ Walking ability =modified functional ambulation profile
Mohan-2013 (A6)	Randomised sham-controlled Observer blinded	▪22 in total ▪Experimental= 11 ▪control=11	▪MT for 30 minutes 6 days a week for 2 weeks.Reflective tilted surface facing the less paretic limb ▪Half-lying position: hip-knee-ankle flexion, hip & knee in flexion then moving knee inward and outward, and hip abduction + external rotation then hip adduction with + internal rotation. Each in 2 sets of 10 repetitions. ▪Sitting position: hip-knee-ankle flexion, knee extension with ankle dorsiflexion, and knee flection beyond 90 degrees. Each in 2 sets of 10 repetitions. No movement of more paretic limb Conventional stroke rehabilitation programme for 1 hour a day 6 days a week for 2 weeks: neurodevelopmental techniques, sensory motor re-education, active exercise, mobility training, balance and gait training	▪ Sham = MT with the no-reflecting side of the mirror facing the less paretic limb ▪ Half-lying position: hip-knee-ankle flexion, hip & knee in flexion then moving knee inward and outward, and hip abduction + external rotation then hip adduction with + internal rotation. Each in 2 sets of 10 repetitions. Sitting position: hip-knee-ankle flexion, knee extension with ankle dorsiflexion, and knee flection beyond 90 degrees. Each in 2 sets of 10 repetitions. ▪ No movement of more paretic limb Conventional stroke rehabilitation programme for 1 hour a day 6 days a week for 2 weeks: neurodevelopmental techniques, sensory motor re-education, active exercise, mobility training, balance and gait training.	Primary: not stated Secondary: ▪ Spasticity with modified composite spasticity index ▪ FMA ▪ Balance with Berg Balance Assessment ▪ Mobility with FAC ▪ Brunnstrom stage of recovery

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	Study design	Sample size	Experimental intervention	Control intervention	Primary outcome and secondary outcome measure
Bhoraniya-2018 (A7)	Randomised controlled	▪ 26 in total ▪ 13 experimental 13 control	▪ MT 15 minutes 5 times a week for 4 weeks	▪ Conventional therapy 30 minutes: custom-made programme 5 times a week for 4 weeks	Primary: not stated Secondary: ▪ Walk velocity ▪ Step length ▪ Stride length ▪ cadence
Xu-2017(A8)	▪ randomised controlled observer-blind	▪ 46 in total ▪ experimental = 23 ▪ control = 23	▪ MT 30 minutes a day ▪ Sitting position with mirror (60x90cm) between legs in the midline ▪ The reflective side facing less paretic leg ▪ Flex and extend ankle whilst observing in mirror A conventional rehabilitation programme for 4 hours a day 5 days a week for 4 weeks. PT, OT and neurodevelopmental facilitation.	▪ MT 30 minutes a day ▪ Sitting position with mirror (60x90cm) between legs in the midline ▪ The non-reflective side facing less paretic leg ▪ Flex and extend ankle whilst observing in the mirror. A conventional rehabilitation programme for 4 hours a day 5 days a week for 4 weeks. PT, OT and neurodevelopmental facilitation.	Primary: ▪ Brunnstrom stages of recovery Walk speed – 10m walk test Secondary: ▪ Spasticity – modified Ashworth Passive ankle joint dorsiflexion range of motion
Wang 2017-(A9)	▪ Randomised controlled ▪ Evaluated before treatment and 6 weeks after treatment	▪ 36 in total ▪ Experimental=18 ▪ Control= 18	▪ MT – assisted 40 minutes a day 5 days a week ▪ Long seat or a sitting position mirror, 45x70cm, along median sagittal plane ▪ Upper body inclined towards the less paretic side to observe the reflection of the less paretic limb ▪ Less paretic leg reflected in the mirror ▪ Asked to try to make both limbs do the same action and complete action with the aid of therapist if necessary ▪ Flexion/extension of hip, internal-external rotation of hip, flexion/extension knee, dorsi/plantar flexion of ankle , circumduction of ankle and composite movement S-shaped or ring map.	▪ Same training as mirror therapy with avoidance of visual feedback 40 minutes a day 5 days a week Conventional rehabilitation :2-3 hours a day 5 days a week: therapy of normal limb position put and lower limb-facilitation technique, training of balance function, gait and activities of daily living, training of play instruments like power bicycle and other physical factors	Primary: not stated Secondary: ▪ Brunnstrom recovery stage ▪ Berg Balance scale ▪ FAC FIM-walking

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	Study design	Sample size	Experimental intervention	Control intervention	Primary outcome and secondary outcome measure
Ji—2014 (A10)	▪ Randomised controlled ▪ Outcome points not stated specifically other that pre and post	▪ 30 in total (3 groups) ▪ Experimental= 10 ▪ Sham=10	▪ MT - intensity, frequency and duration not provided ▪ Sit on a table ▪ 60x90cm mirror placed between legs with less-paretic leg reflected and mirror angle adjusted so that movement of less-paretic limb could be seen in the mirror ▪ Simultaneous bilateral dorsiflexion ▪ Additional exercise for 20 minutes ▪ PNF neurodevelopmental technique 30 minutes a day 5 times a week for 6 weeks	▪ Sham MT - intensity, frequency and duration not provided ▪ Mirror covered with a white cloth ▪ 60x90cm mirror placed between legs with less-paretic leg reflected and mirror angle adjusted so that movement of less-paretic limb could be seen in the mirror ▪ Simultaneous bilateral dorsiflexion ▪ Additional exercise for 20 minutes ▪ PNF neurodevelopmental technique 30 minutes a day 5 times a week for 6 weeks	Primary: not stated Secondary: ▪ Gait analysis – not kinematics or kinetics specified ▪ Gait velocity ▪ Cadence ▪ Step length ▪ Stride length
Ji-2015 (A11)	▪ Randomised ▪ sham-controlled ▪ Observer-blind	▪ 34 ▪ Experimental = 17 Control = 17	▪ MT for 15 minutes a day 5 days a week for 4 weeks ▪ Mirror on a stand and titled toward the more paretic side of body ▪ The reflective surface facing less paretic leg ▪ Sitting position ▪ Less paretic movements only ▪ Hip-knee-ankle flexion, knee extension with ankle dorsiflexion, knee flexion beyond 90 degrees ▪ Conventional rehabilitation 30 minutes per day 5 days a week for 4 weeks: neurodevelopmental facilitation techniques	▪ Sham MT for 15 minutes a day 5 days a week for 4 weeks ▪ Mirror on a stand and titled toward the more paretic side of the body ▪ Reflective surface facing less paretic leg and covered in white fabric ▪ Sitting position ▪ Less paretic movements only ▪ Hip-knee-ankle flexion, knee extension with ankle dorsiflexion, knee flexion beyond 90 degrees ▪ Conventional rehabilitation 30 minutes per day 5 days a week for 4 weeks: neurodevelopmental facilitation technique.	Primary: not stated Secondary: Temporospatial gait characteristics, such as single stance, stance phase, step length, stride, swing phase, velocity, and cadence, were assessed before and after the four weeks therapy period.

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	▪ Study design	▪ Sample size	▪ Experimental intervention	▪ Control intervention	Primary outcome and secondary outcome measure
Kim-2018 (A12)	▪ Randomised controlled ▪Measures before and after the intervention	▪ 30 – 3 groups ▪ Experimental = 10 Control = 10	▪ MT - 150 repetitions of the exercise 5 time a week for four weeks ▪ Lower limb exercise using a mirror reflecting less paretic leg with mirror in the midline between legs ▪ Sit in a chair Flex hip and knee 90 degrees and maintain ankle dorsiflexion, then fully extend knee and flex to 90 degrees	▪ Exercise without a mirror – 150 repetitions of the exercise 5 time a week for four weeks ▪ Lower limb exercise using a mirror ▪ Sit in a chair Flex hip and knee 90 degrees and maintain ankle dorsiflexion then fully extend knee and flex to 90 degrees	Primary: not stated Secondary: Muscle strength (quadriceps, hamstring)
Cha-2015 (13)	▪ Randomised controlled ▪ Observer-blind Outcome measures before and after treatment	▪ 36 ▪ Experimental = 19 Control = 17	▪ MT + rTMS – 20 minutes MT & 20 minutes rTMS a day 5 days a week for 4 weeks ▪ Semi-seated on a bed with mirror board, 60x90cm, between legs in the midline ▪ Less-paretic leg reflected ▪ Flex-extend hip, knee, and ankle	▪ Sham MT + rTMS – 20 minutes MT & 20 minutes rTMS a day 5 days a week for 4 weeks ▪ Semi-seated on a bed with mirror board, 60x90cm, between legs in the midline ▪ Mirror covered in white fabric ▪ Flex-extend hip, knee, and ankle	Primary: not stated Secondary: ▪ Balance Index – Biodex Balance Master ▪ Dynamic limits of Stability – Biodex Balance Master ▪ Berg Balance Scale ▪ TUG
Cha(b)-2015 (14)	Randomised controlled	▪ 30 ▪ Experimental = 15 Control = 15	▪ MT & rTMs for 40 minutes per day 5 days a week for four weeks ▪ Mirror on stand tilted toward the more paretic side of body to prevent participant from viewing the more paretic limb ▪ Reflective surface facing less-paretic lower limb ▪ Semi-seated position ▪ Hip-knee-ankle flexion, knee extension with ankle dorsiflexion, knee extension beyond 90 degrees ▪ Did not move the more paretic lower limb	▪ Sham MT & rTMs for 40 minutes per day 5 days a week for four weeks ▪ Reflective surface covered with white fabric ▪ Semi-seated position ▪ Hip-knee-ankle flexion, knee extension with ankle dorsiflexion, knee extension beyond 90 degrees ▪ Did not move the more paretic lower limb	Primary: not stated Secondary: Temoporspatial gait data including step length, stride length, rate of swing phase, rate of stance phase, velocity, cadence and step length

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	▪ Study design	▪ Sample size	▪ Experimental intervention	▪ Control intervention	Primary outcome and secondary outcome measure
Simpson-2019 (A 15)	Randomized study	31 chronic stroke participants 15- unilateral strength training exercise 16- unilateral strength training with mirror therapy	▪ The MST group performed the same unilateral strengthening protocol as the ST group (see control intervention for further details). Besides that, the mirror was placed in the midsagittal plane of the participant while observing the training limb in the mirror. ▪ This protocol was conducted 3 time per week for 4 weeks for both group. No further details about the dose of the therapy, participant position or mirror design used.	▪ For strength training interventions, it was involving of isometric unilateral strength training which only applied for less affect leg.at the beginning, Warm up for one minute of dynamic dorsiflexion exercises was applied. Then, 5 unilateral submaximal isometric contractions of the less-affected limb. Participant was in seated position with back support, the less affected ankle was strapped with ankle brace at 10-degree plantar flexion angle. ▪ The training protocol was consisted of 4 set of 5 maximal isometric contraction for ankle dorsiflexion. The contraction held for five seconds with five second rest between repetition. Also, three minutes rest between sets were applied	Primary: Feasibility outcome (asses the feasibility of conducting cross- education with mirror therapy, patient eligibility, treatment reliability and feasibility of outcome measure were assessed). Secondary: Modified Ashworth Scale for spasticity ,10 MWT ,timed up and go; TUG ,London Handicap Scale LHS
Broderick-2019 (A 16)	single-blind pilot randomized controlled	30 in total Experimental= 15 Control=15	▪ Participant instructed to walk on treadmill at comfortable velocity ▪ The mirror therapy group watched the reflection of their non-paretic limb in an acrylic mirror. Mirror was adjustable to be tilted to right or left. The mirror was positioned in the mid-sagittal plane between the legs while walking on the treadmill. ▪ Mirror therapy treadmill training was conducted for 30 minutes per day, 3 days Per week, for 4 weeks.	▪ For the control group, same training protocol was followed with the mirror therapy group but the didn't receive MFV as the reflective side of the mirror was altered. ▪ treadmill for 30 minutes per day, 3 days per week, for 4 weeks.	Primary : 10 MWT 6MWT Secondary: MAS was used to assess lower limb muscle tone. - FMA-LE assessed lower limb motor impairment

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	▪ **Study design**	**Sample size**	▪ **Experimental intervention**	▪ **Control intervention**	**Primary outcome and secondary outcome measure**
Mehr-2019 (A17)	▪ Randomised controlled	93 in total MT (n=31), Non-reflective group (n=31),	▪ Mirror therapy group perform additional 15 minutes to the one-hour conventional rehab. ▪ Participant was on the bed with a semi-sitting position. the more paretic leg was put inside the mirror box (70×40cm). ▪ Participants were asked to perform ankle and knee exercise with less practice leg while watching the reflection on the mirror ▪ Number of sessions reported only	▪ While the non-reflective group performed similar exercise to the mirror therapy group for 15 minutes with facing the non-reflective wooden material has the same size as the mirror. This was in addition to the one hour conventional rehabilitation program. ▪ All groups were evaluated before and at the end of sessions five, ten, 15, and 20.	Primary: no stated Secondary: FAC
Kim,shin& Hong-2018 (A18)	Randomised controlled	30 in total Control=10 Experimental I= 10	Experimental I= performed the exercise whilst watching the reflection of the non-paretic limb in the mirror tilted towards the paretic side to prevent participant from viewing the paretic limb. No additional information about the mirror. Exercise performed in semi-seating position which are; hip-knee-ankle flexion, knee extension with ankle dorsiflexion, knee flexion beyond 90 degree Exercise conducted for 5 sets of 30 reps 5 x per week for 4 weeks	Control group performed the exercises without mirror for 5 sets of 30 reps 5 x per week for 4 weeks	Primary: Not stated Secondary: ▪ Berg balance scale ▪ Time up and go test ▪ temporal-spatial parameters of gait

(cont.) Table 2-5 Characteristics of the included studies.

Study ID	Study design	▪ Sample size	▪ Experimental intervention	▪ Control intervention	Primary outcome and secondary outcome measure
Kwa wkam i-20 (A19)	Randomised controlled	▪ 81 in total among 5 groups ▪ experimental MT =16 control =8	▪ MT for 20 minutes ▪ In sitting, mirror placed between legs in midline reflecting the less paretic lower limb.Dorsiflexion of ankle joint, stepping over and abd/add of hip joint. ▪ In ankle dorsi flexion; patient instructed to perform the movement on the less paretic side and simultaneously moving the paretic side, patients performed 4 sets of 50 repetitions ▪ less paretic movement for stepping over, on and off a wooden block, and imagine moving the paretic leg and performed 2 sets of 50 repetition ▪ less paretic movement and simultaneously motor imagery of the paretic side during hip abd/add. 2 sets of 50 repetitions	▪ Passive range of motion and active assisted movement gait training, standing training, balance training and ADL training. Training ration has not be determined	Primary: Not stated Secondary: ▪ SIAS Hip flexion ▪ SIAS Knee extension SIAS Foot pat
May (A20)	Randomised controlled trial	▪ N = 42 ▪ 21 Mirror therapy 21 control	▪ Intervention for 4 weeks on 5 days a week ▪ MT for 30 minutes ▪ Participants seated. The Mirror 40x70cm placed vertically between lower limbs. Reflective side of mirror faced non-paretic LL. Participants repeated ankle dorsiflexion & plantarflexion whilst watching reflection of non-paretic LL. Did not move paretic LL. Plus, conventional rehab for 30-120 minutes a day for 5 days a week. Included neurofacilitation techniques, sensorimotor re-education, balance training and walking training	▪ Intervention for 4 weeks on 5 days a week conventional rehab for 30-120 minutes a day for 5 days a week. Included neurofacilitation techniques, sensorimotor re-education, balance training and walking training	Primary: not stated Secondary: ▪ Motricity Index ▪ Modified Ashworth Scale for ankle plantarflexion spasticity ▪ FIM ▪ Berg Balance Scale ▪ Walk speed – 6 minute walking test

Table 2-6 participants characteristics of the included studies which highlight the main features of the participants such as side of stroke, type of stroke, time after stroke, age, gender, severity of motor impairment and functional capacity at the baseline level.

Study name (ID)	Side of stroke	Type of stroke	Time after stroke	Age	Gender	Severity of motor impairment	Functional capacity
Sütbey az-2007 (A1)	Experimental group = 30 % right Control group =35% right	▪ First-ever stroke	Mean 3.5 (SD 1.3) months for experimental and 3.9 (SD 1.9) for control	Mean 62.7 (SD 9.7) years for experimental and 64.7 (SD 7.7) for control	50% male for experimental and 65% for control	Modified Ashworth was 2.6 (SD 0.5) for experimental and 2.3 (SD 0.7) for control ▪ Mean Brunnstrom was 2.4 (SD 0.7) for experimental and 2.5 (SD 1.0) for control	▪ Mean FAC was 1.9 (SD).5 for experimental and 2.0 (SD 0.7) for control ▪ Mean FIM motor was 48.3 (SD 5.5) for experimental and 50.2 (SD 11.6 for control) ▪
Abo Salem-2015 (A2)	Unclear as use term 'rigidity'. (experimental group=60% right hemiplegia Control group=53%	▪ First-ever stroke ▪ 66.7% ischemic for experimental and 73.3% for control	Mean 14.9 (SD 1.83) months for experimental and 15.4 (SD 1.28) for control	Mean 60 (SD 8.97) years in experimental and 59.1 (SD 9.1) in control	53% male in experimental and 47% in control	▪Passive ankle dorsiflexion was mean 15.9 (SD2.33) degrees for experimental and 15.0 (SD 1.49) for control ▪MAS mean was 2.75 (SD 0.72) for experimental and 2.9 (SD 0.79) for control ▪Mean Brunnstrom was 3.1 (SD 1.21) for experimental and 2.8 (SD 1.15) for control.	▪Mean gait speed was 0.64 (SD 0.34) m/sec for experimental and 0.61 (SD 0.32) for control
Arya-2017 (A3)	53% right side paresis for experimental and 59% for control	▪ 79% ischemic stroke for experimental and 71% for control	13.74 (SD9.45) months for experimental and 18.29 (SD 8.08) for control	Mean 48.16 (SD 8.36) years for experimental and 44.53 (SD 6.09) for control	79% male for experimental and 88% male for control	FMA-LE mean 19.13 (SD 6.03) for experimental and 22.06 (7.38) for control	▪ FAC median = 3 for experimental and 2 for control (no IQR provided) ▪10m comfortable walk speed 0.50 (SD 0.31) m/sec for experimental and 0.53 (SD 0.87) for control

(cont.) Table 2-6 participants characteristics

Study name (ID)	**Side of stroke**	▪ **Type of stroke**	**Time after stroke**	**Age**	**Gender**	**Severity of motor impairment**	▪**Functional capacity**
DE - 2017 (A4)	No information provided	▪ First-ever stroke ▪ Middle cerebral artery territory	3-12 months after stroke	50-65 years	Male & female but not detail of %s	No baseline values provided ▪ Brunnstrom recovery stage 2 and above but no further detail provided	▪Able to walk more than 10 metres with supervision or aids
Lee-2017 (A5)	No detail in paper	▪ No detail in paper	No detail in paper	▪ Control = action observation with activity = 62.8 (7.4) years ▪ Experimental = mirror therapy with activity = 57.27 (5.7) years ▪ action observation = 59.8 (6.7) year	No detail in paper	No detail in paper	▪ Overall Balance: for experimental group = 1.2 (0.5) for control group = 2.3 (2.0) ▪ Fall risk: for experimental group = 2.6 (0.6) for control group = 2.8 (1.4) ▪ Functional ambulation: for experimental group = 74.0 (35.0 for control group = 102.2 (45.5)
Mohan -2013 (A6)	▪ Experimental =82% right side Control = 100% right side	▪ First-ever stroke ▪ Experimental = 64% ischemic ▪ Control = 64% ischemic.	▪ Experimental = 7.09 (3.18) days ▪ Control = 5.73 (3.47) days	▪ Experimental = 62.64 (17.30) years ▪ Control = 63.27 (7.63) years	▪ Experimental = 36% male Control = 73% male	▪ FMA for experimental = 19.36 (4.11) and for control = 11.36 (6.73) ▪ Spasticity for experimental = 4.64 (1.5) and for control = 4.0 (1.84)	Berg balance for experimental = 3.45 (1.37) and for control = 2.55 (1.37) FAC for experimental = 36.4 % score 0, 54.5% score 1 and 9.1% score 2 and for control = 45.5 % score 0, 36.4% score 1 and 18.2% score 2

(cont.) Table 2-6 participants characteristics

Study name (ID)	**Side of stroke**	▪ **Type of stroke**	▪ **Time after stroke**	▪ **Age**	▪ **Gender**	**Severity of motor impairment**	**Functional capacity**
Bhoraniya-2018 (A7)	Not stated	▪ First-ever stroke ▪ Experimental = 62% ischemic Control = 62% ischemic	▪ Experimental = 29.39 months Control = 31.69 months	▪ Experimental = mean 60.61 years Control = mean 61.30 years	▪ Experimental = 69% male Control = 92% male	No impairment measure	step length (cm) Paretic side experimental group 25.07±7.21 control group= 28.23±8.66 Non-paretic side experimental group= 28.15±7.78 control group=27.62±6.39 Stride length (cm) Paretic side experimental group= 44.23±14.34 control group=49.69±17.60 Non-paretic side experimental group=46.92±15.11 Control group=50.00±14.31 Cadence (steps/min) experimental group= 75.15±13.99 control group=71.77±8.69 Velocity (meter/min) experimental group= 19.06±11.59 control group=21.32±10.26
XU-2017(A8)	▪ Experimental =65% right side Control = 57% right side	▪ Experimental = 78% ischemic Control = 74% ischemic	▪ Experimental = 42.76 (5.65) days Control = 45.78 (6.50) months	▪ Experimental = mean 53.7 (8.98) years Control = mean 56.09 (8.12) years	▪ Experimental = 69% male Control = 65% male	▪ Mod Ashworth for experimental = 2.96 (0.64) and for control = 2.83 (0.78) Passive ROM for experimental = 10.35 (12.57) and for control = 9.61 (1.80) Brunnstrom stage for experimental = 2.35 (0.57) and for control = 2.35 (0.57)	▪ Walk speed (10mWT) for experimental = 25.81 (5.36) and for control = 24.62 (3.71)

(cont.) Table 2-6 participants characteristics

Study name (ID)	▪ Side of stroke	▪ Type of stroke	Time after stroke	▪ Age	▪ Gender	▪ Severity of motor impairment	▪ Functional capacity
Wang-2017 (A9)	▪ Experimental =44% right side ▪ Control = 50% right side	▪ First-ever stroke ▪ MCA territory stroke	Less than 2 months (from inclusion criteria)	▪ Experimental = 52.45 (2.91) years ▪ Control = mean 53.00 (SD 2.79) years	▪ Experimental = 78% male ▪ Control = 67% male	▪ Brunnstrom stage for experimental = 2.50 (1.10) and for control = 2.61 (1.14)	▪ FAC for experimental = 1.28 (0.96) and for control = 1.39 (1.04) ▪ FIM-walk for experimental = 11.22 (6.34) and for control = 10.89 (6.41) ▪ Berg Balance not reported
JI-2014 (A10)	▪ Experimental =60%right side Control = 60% right side	▪ Experimental = 70% ischemic Control = 70% ischemic	Experimental group= 7.3(2.9) month Control group= 6.7 (2.3) month	▪ Experimental = mean 48.6(8.5)(SD 9.9) years Control = mean 54.6 (SD 9.2) years	▪ Experimental = 70 male Control = 60% male	Not measured	Did not report gait analysis i.e. kinematics (& kinetics).Gait velocity for experimental = mean 45.3(SD 6.2) and for control = mean 46.6 (SD 5.3) ▪ cadence for experimental = mean 70.5(SD10.1) and for control = mean 69.2 (SD 10.3) ▪ step length for experimental = mean 30.1 (SD 6.1) and for control = mean 30.4 (SD 2.8) ▪ stride length for experimental = mean 60.3(SD7.9) and for control = mean 57.4 (SD 5.0)
Ji-2015(A11)	▪ Experimental = 35% right side ▪ Control = 47% right side	▪ Experimental = 59% ischemic ▪ Control = 47% ischemic	▪ Experimental = mean 4.3 (SD 1.5) months ▪ Control = mean 4.5 (SD 1.3) months	▪ Experimental = mean 55.2 (SD 7.5) years ▪ Control = mean 54.3 (SD 8.7) years	Experimental=53 % male Control=59% male	Not measured	▪ Single stance for experimental = mean 27.3 (SD 9.4) and for control = mean 28.7 (SD 8.2) ▪ Stance phase for experimental = mean 66.7(SD 6.3) and for control = mean 66.8 (SD 6.2) ▪ step length for experimental = mean 32.6 (SD 7.3) and for control = mean 32.7 (SD 6.1) ▪ stride length for experimental = mean 61.4 (SD 18.3) and for control = mean 62.5 (SD 18.7) ▪ swing phase for experimental = mean 33.5 (SD 6.3) and for control = mean 33.7 (SD 5.8) ▪ Gait velocity for experimental = mean 48.9 (SD 21.3) and for control = mean 47.5 (SD 19.7). cadence for experimental = mean 67.8 (SD 16.5) and for control = mean 69.2 (16.4). step width for experimental = mean 17.4 (SD 4.7) and for control = mean 17.2 (SD 4.1)

(cont.) Table 2-6 participants characteristics

Study name (ID)	▪ Side of stroke	Type of stroke	Time after stroke	▪ Age	Gender	▪ Severity of motor impairment	Functional capacity
KIM-2018 (A12)	Experimental = 20% right side Control = 60% right side	Not reported	Not reported	▪ Experimental = 69.6 (12.24) years Control = 62.1 (9.52) years	Not reported per experimental and control groups	▪ Muscle strength more paretic knee extensors for experimental = 36.3 (8.6) and for control = 37.3 (7.5) Muscle strength more paretic knee flexors for experimental = 26.5 (4.6) and for control = 28.3 (5.2) ▪ Brunnstrom stage for experimental = mean 3.3 (SD 0.48) and for control = mean 3.1 (SD 0.73)	NA
Cha (A13)	Not reported	Not reported	▪ Experimental = mean 1.95 (SD 0.62) months ▪ Control = mean 1.65 (SD 0.86) months	▪ Experimental = mean 60.0 (SD 7.8) years ▪ Control = mean 57.4 (SD 9.4) years	▪ Experimental = 53% male ▪ Control = 53% male	▪ Not reported	▪ Balance Index for experimental = mean 6.14 (SD 1.25) and for control = mean 5.49 (SD 0.66) ▪ Dynamic limit of stability for experimental = mean 10.08 (SD 2.73) and for control = mean 10.56 (SD 4.38) ▪ Berg balance for experimental = mean 40.74 (SD 10.61) and for control = mean 42.53 (SD 11.64) ▪ TUG for experimental = mean 30.95 (SD 4.27) and for control = mean 32.18 (SD 3.75)

(cont.) Table 2-6 participants characteristics

Study name (ID)	Side of stroke	▪ Type of stroke	▪ Time after stroke	▪ Age	▪ Gender	▪ Severity of motor impairment	▪ Functional capacity
Cha (A14)	Not reported	Experimental = 73% ischemic Control = 60% ischemic	Experimental = mean 14.45 (SD 3.14) months Control = mean 14.13 (SD 1.55) months	Experimental = mean 59.43 (SD 13.00) years Control = mean 62.00 (SD 12.00) years	Experimental = 47% male Control = 40% male	▪ Not reported	▪ Single support phase for experimental = mean 25.38 (SD 9.68) and for control = mean 24.66 (SD 8.69) ▪ Double support phase for experimental = mean 71.35 (SD 5.83) and for control = mean 70.61 (SD 6.39) ▪ Step length for experimental = mean 29.52 (SD 9.96) and for control = mean 28.52 (SD 7.34) ▪ Stride length for experimental = mean 58.31 (SD 16.36) and for control = mean 60.52 (SD 23.57) ▪ Swing phase for experimental = mean 29.33 (SD 6.23) and for control = mean 30.73 (SD 5.47) ▪ Walk velocity for experimental = mean 36.39 (SD 16.82) and for control = mean 36.38 (SD 18.67) ▪ cadence for experimental = mean 51.91 (SD 11.52) and for control = mean 54.45 (SD 13.74) ▪ step width for experimental = mean 17.38 (SD 2.45) and for control = mean 18.56 (SD 3.62)
Simpson A(15)	experimental =40% right side control= 53% right side	Experimental group = 69% ischemic control group= 60%	Experimental = mean 78.7 ± (SD75.2) MONTHS CONTROL= mean 90.1 (SD ± 83.3)	Experimental= mean 60.0 (SD14.7) years Control = mean 63.5 (SD12.0)	Experimental = 56% male Control= 73% male	▪ control group =MAS ankle mean 1.83 (SD 0.65), experimental group= MEAN 1.80 (SD 0.80) ▪ peak torque trained ankle MVC control group= mean 30.01SD(7.91), experimental group=24.63 SD(10.57).	▪10 MWT CONTROL =mean 0.78 (SD 0.45) (*n* = 14) Experimental =mean0.82 (SD 0.50) ▪TUG experimental group=28.05 SD(43.95) control group=18.68 SD(15.02)

(cont.) Table 2-6 participants characteristics

Study name (ID)	Side of stroke	Type of stroke	Time after stroke	Age	Gender	▪ Severity of motor impairment	▪ Functional capacity
Broderick A16	Experimental group =47% Right side control group= 53% right side	experimental=53 % ischemic CONTROL=67% ischemic	Experimental =mean 75.13 (SD 87.97) month Control=mean 34.26 (SD 30.61)	Experimental= Mean 61.2 (SD 9.50) YEARS CONTROL=mean 67.06 (SD 19.47) years	Experimental =69% male CONTROL= 93% male	▪ FMA MT=mean 23.53(SD 6.12) CONTROL=mean 22.53 (SD 7.58) -Hip flexion MT= Mean 1.66 (SD 1.04) control= mean 1.73 (SD 1.03) -hip extension MT=mean 1.46 (SD 0.92).Control=mean 1.26 (SD 0.88) -hip abduction MT=mean 2.13 (SD 1.06).Control=mean2.06 (SD 1.27) -hip adduction MT=mean 1.13 (SD 0.63).CONTROL=mean 1.4 (SD 0.82) -Knee flexion MT= mean 1.33 (SD 1.04) CONTROL= mean 1.33(SD 1.04) Knee extension MT=mean 1.46 (SD 0.92) CONTROL=1.33 (SD 0.89) Dorsiflexion MT= mean 2.46 (SD 1.30).CONTROL= mean 2.06 (SD 1.53) Plantarflexion MT= mean 1.93 (SD 1.43) CONTROL= mean 1.6 (SD 1.4)	▪ 10MWT for MT=mean 0.87 (SD 0.41) For control= mean 0.74 (SD 0.46) ▪6MWT MT= mean 315.12 (SD 164.26) CONTROL= mean 268.11 (SD 184.80)

(cont.) Table 2-6 participants characteristics

Study name (ID)	Side of stroke	Type of stroke	Time after stroke	Age	Gender	▪ Severity of motor impairment	Functional capacity
Mehr A 17	Non-reflective =77.4% right Experimental = 71.0% right Control=67.6% right	Non-reflective =93.5% ischemic Experimental = 87.1% ischemic Control=83.9% ischemic	Non-reflective = mean 5 (SD 5 MONTH MT= Mean 4 (SD 5) Control= mean 5 (SD 6)	30-65 YEARS	Not reported	▪ Muscular strength score of lower limbs (0-5) non reflective 1=(0.0%) 2= (32.3% 3=(58.1%) 4=(9.7%) MT 1=(0.0%) 2= (29.0% 3=(54.8%) 4=(16.1%) Control 1=(16.1%) 2= (32.2% 3=(41.9%) 4=(9.7%)	FAC Non-reflective 1=(12.9%) 2= (51.6% 3=(35.5%) 4=(0.0%) MT 1=(0.0%) 2= (54.8% 3=(41.9%) 4=(3.2%) Control 1=(9.7%) 2= (54.8% 3=(35.5%) 4=(0.0%)
Kim,2018 (A18)	Right side Control= 60% Experimental I=20% Experimental II= 50%	Ischemic Control=60% Experimental I=60% Experimental II=10%	Month Control=29.1(SD 25.03) Experimental I=31.9(SD 22.82) Experimental II=30.6(SD 22.29)	Control= 62.1(SD 9.52) years Experimental I=69.6(SD 12.34) Experimental II=72.3(SD 11.35)	Control= 60% male Experimental I=30% male Experimental II=40% male	Brunnstrom stage of recovery Stage 2 Control=20% Experimental I=0% Stage 3 Control=50% Experimental I=70% Stage 4 Control=30% Experimental I=30%	▪Berg balance scale Control= 36.70 (SD 6.48) Experimental I=37.10 (SD 4.86) Experimental II=34.3 (SD 4.88) ▪Timed up &go Control=25.89 (SD 8.39) Experimental I=24.70 (SD 11.40) Experimental II=26.62 (SD 11.67)

(cont.) Table 2-6 participants characteristics

Study name (ID)	Side of stroke	Type of stroke	Time after stroke	Age	Gender	▪ Severity of motor impairment	Functional capacity
Kawakami - A19	Paretic side -right MT=38% CoN=63%	Ischemic stroke MT= 38% Con=50%	In days MT=37.9(SD 11.8) Con=38.9(SD 14.8)	MT= 61.6(SD 12.7) years Con= 65.6(SD 15.9)	MT= 69%male Con=63%	▪ Hip-flexion mean MT=3.3 Con=3.9 ▪Knee extension MT= 3.3 Con=3.6 ▪Foot pat MT= 3.1 Con=3.2	NA
May-A20	Right MT=61.9 % Control= 57.1%	Ischemic MT=90.5% CONTROL=76. 2%	Median MT=60 (min 15.0, max 365.0) Control=30 (min 15.0, max 300.0)	MT= 57.2 (SD 7.6) years Control = 58.8 (SD 9.8)	Male MT=71.4 % Control= 47.6%	▪ BBS MT=2.4(SD 1.1) Control= 2.4(SD 1.1) ▪ Motricity index MT= 22.2(SD 16.8) Control= 22.8(SD19.5) ▪ MAS MT= 1.2(SD1.2) Control=1.1(SD1.2)	▪ FIM motor MT= 37.4(SD16.2) Control= 31.3(SD 18.1) ▪ FIM total MT= 70.1(SD 19.7) Control= 58.6(SD 21.6) ▪ Berg balance scale MT=12(SD 9.3) Control=8.6(SD 12.3) ▪ 6-minutes walking MT=33.3(SD 41.1) Control= 19.3(SD 38.4) ▪ FAC MT=0.4(SD 0.7) Control= 0.4(SD 1.0)

Abbreviations used in table (2-5&2-6). MT: mirror therapy, PT: physiotherapy, OT: occupational therapy, SLT: speech& language therapy, FIM: functional independence measure, ROM: range of motion, AFO: ankle foot orthosis, FMA-LL: Fugl Meyer assessment for lower limb, MAS: modified ashworth scale, FAC: Functional Ambulation Categories, rTMS: repetitive transcranial magnetic stimulation, 10-MWT:10 meter walking test,6-MWT: six meter walking test, SIAS: stroke impairment assessment set, TUG: time up & go, ST: strengthening training , MST: mirror therapy with unilateral strengthening training.

2.3.3.2 TIDIER guideline to describe the quality of reporting in the included studies

After using the template for intervention description and replication (TIDieR) checklist and guide. It showed the lack of reporting in the existing literature, which made the replication of these studies hardly possible (table 2-7). The results of the twelve items in the checklist are:

1) Brief name

All the included studies reported the study's brief name that described the intervention (121,170–173,221–228,230–235).

2) Why

Only nine studies described the rationale behind using the mirror therapy (121,172,173,223,225,228,231,235), while four had partials explaining of their rationale (222,226,229,233), and six studies did not make the rationale of the study explicit (170,171,221,224,227,234).

3) What (material)

Eleven studies provided information about the material used in the intervention (121,170–172,222,224,225,229,232,234,235), while no studies reported where the material could be accessed during the intervention.

4) What (Procedure): all the studies partially reported the procedure of the intervention or activities given. However, none of the studies explained in details the conventional rehabilitation received by the participant or any enabling or supportive activity.

5) Who provided:

Twelve studies partially reported who provided the therapy(121,170,171,173,222,227,229,231–235). However, no details were mentioned about their expertise, background or if they received any specific training. The remaining studies did not mention any details about the provider of the therapy or any related information(172,221,223–226,228,230).

6) How

Ten studies did not describe the modes of delivery (such as face to face or by some other mechanism) of the intervention and whether it was provided individually or in a group (170,172,173,221,223,225,226,228,231,234). Three studies had reported that partially(222,227,229), and only seven studies reported it fully (121,171,224,230,232,233,235).

7) Where

Only seven studies described the location where the intervention occurred (121,229–234). Four studies made a partial explanation of the location of the intervention (171,224,225,235). Nine studies did not report where the intervention occurred (170,172,173,221–223,226–228).

8) When and how much

All of the included studies partially described the planned number of times the intervention was delivered and over what period of time, including the number of sessions, duration or repetition. However, some studies did not report the planned number of the interventions, and no studies mentioned the actual time of the

intervention. Further details were discussed in the meta-analysis section (dose of the intervention).

9) Tailoring

No studies mentioned if the intervention was planned to be personalised, titrated or adapted.

10) Modification

None of the studies in this review explained or provided any information about whether the intervention was modified during the course of the study or described the changes (what, why, when and how).

11) How well (planned): no information in the included studies mentioned if interventions adherence or fidelity were assessed, or described how and by whom, and if any strategies were used to maintain or improve fidelity.

12) How well (actual): no information in the included studies mentioned if intervention adherence or fidelity was assessed or described the extent to which the intervention was delivered as planned.

Table 2-7 TIDIER guideline to describe the quality of reporting in the included studies

study ID	item 1: Brief name	Item 2: Why.	Item 3: What (materials)		Item4: what (procedure)	item 5: who	Item 6: How	Item 7: Where	Item 8: When and how much	Item 9: Tailoring	Item 10: Modifications	Item 11: How well (planned)	Item 12: How well (actual)
A1	Yes	Yes	Yes	NO	partial	partial	Yes	yes	partial	Not appropriate	No information	No information	No information
A2	Yes	no	yes	NO	partial	partial	no	No	partial	not appropriate	No information	No information	No information
A3	Yes	no	Yes	NO	yes	partial	no	yes	partial	Not appropriate	no information	no information	no information
A4	Yes	no	partly	NO	no	no	no	No	partial	Not appropriate	No information	No information	No information
A5	Yes	Yes	Yes	NO	partial	no	no	No	partial	Not appropriate	partly	No information	No information
A6	Yes	yes	partly	NO	partial	partial	no	no	partial	Not appropriate	No information	No information	No information
A7	Yes	yes	no	NO	partial	no	no	No	partial	Not appropriate	No information	No information	No information
A8	Yes	no	YES	NO	partial	partial	Yes	partly	partial	Not appropriate	No information	No information	No information
A9	Yes	no	yes	NO	partial	no	yes	partly	partial	Not appropriate	No information	No information	No information

study ID	item 1: Brief name	Item 2: Why.	Item 3: What (materials)		Item4: what (procedure)	item 5: who	Item 6: How	Item 7: Where	Item 8: When and how much	Item 9: Tailoring	Item 10: Modifications	Item 11: How well (planned)	Item 12: How well (actual)
A10	yes	yes	yes	NO	partial	no	NO	partly	partial	Not appropriate	No information	No information	No information
A11	yes	yes	yes	NO	partial	partial	yes	partly	partial	Not appropriate	No information	No information	No information
A12	yes	partly	partly	NO	partial	no	no	No	partial	Not appropriate	No information	No information	No information
A13	yes	no	no	NO	partial	partial	partly	no	partial	Not appropriate	No information	No information	No information
A14	Yes	yes	partly	NO	partial	no	no	no	partial	Not appropriate	No information	No information	No information
A15	yes	Yes	partly	NO	partial	partial	no	yes	partial	Not appropriate	No information	partly	yes
A16	Yes	Yes	Yes	NO	partial	partial	Yes	yes	partial	not applicable	No information	No information	No information
A17	Yes	partly	Yes	NO	partial	partial	partly	yes	partial	Not appropriate	No information	No information	No information
A18	Yes	partly	yes/partly	no	partial	partial	yes	yes	partial	not applicable	partly	No information	No information
A19	Yes	no	partly	NO	partial	no	yes	yes	partial	Not appropriate	no information	No information	No information
A20	Yes	partly	partly	NO	partial	partial	partial	no	partial	Not appropriate	no information	No information	No information

2.3.3.3 *Meta-analysis*

According to the Prisma flow chart, 20 studies were included in the systematic review narrative synthesis of the available evidence, and 19 studies were included in the meta-analysis. One study was excluded from the meta-analysis because of insufficient reporting details, and no contact information for the author was found in the paper or online (De *et al*, 2017). Meta-analysis was provided in two main sections: for the primary outcome then for the secondary outcome. Under each section, the influence of time after stroke, level of paresis, and the dose of intervention in response to mirror therapy were investigated.

2.3.3.3.I. Primary analysis: to investigate if the provision of lower limb exercise via mirror therapy enhance motor recovery after stroke

Eleven studies measured the effect of mirror therapy on motor recovery. In Mohan *et al*. (2013) (173), Broderick *et al*.(2019) (232) , the Fugel Meyer outcome measure was used. In Wang *et al*. (2017) (224), Xu *et al*. (2017) (171), Sutbeyaz *et al*. (2007) (121), Arya *et al*. (2017) (234) and Abo Salem *et al*. (2015) (170), May *et al.(*2020) (222) the Brunnstrom stage of recovery was the common outcome measure between these studies. In Simpson *et al*.(2019) (231), the peak torque in the untrained ankle was the outcome measure. In Kawakami *et al*. (2015) (230), the foot pat scale was used, and in Kim *et al*.(2018) (226), the quadriceps strength of the paretic side was the outcome measure used. These studies reported a moderate significant between-group difference showing a greater improvement in favour of mirror therapy (SMD =0.57 [95% CI=0.32, 0.83], I^2 =25% and p<.00001; fig 2-5).

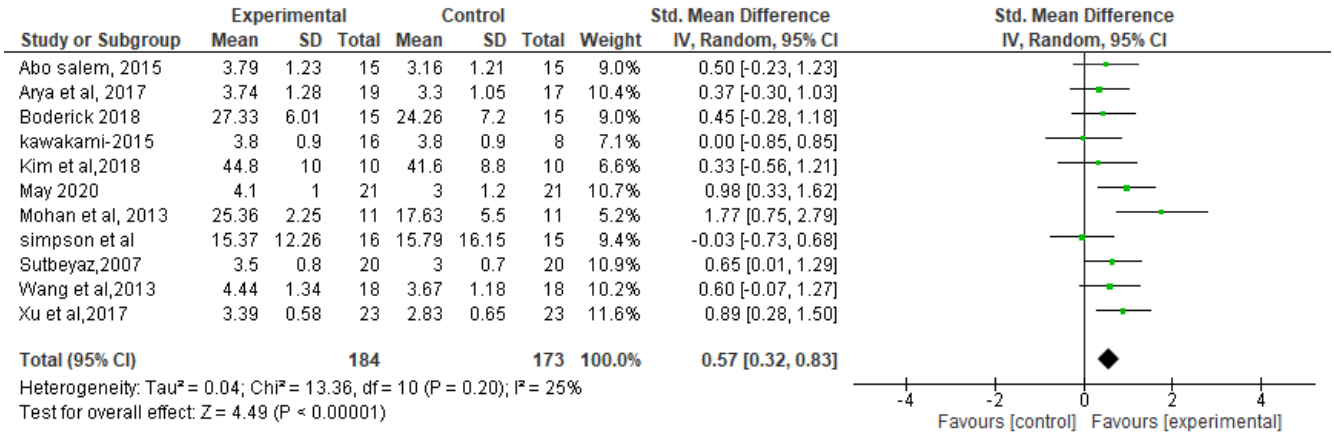


Figure 2-5 Forest plot shows the effect of lower limb mirror therapy on motor recovery after stroke.

Sensitivity analysis:

a- Remove the outliers to investigate if the results are sensitive to the occurrence of the outliers.

As it appeared in (fig. 2-5), Mohan *et al*.(2013) (173) was an outlier, and this could be due to the difference in baseline characteristics of groups, and this is the only study to perform the therapy for two weeks only and/or included participant after one week following a stroke.

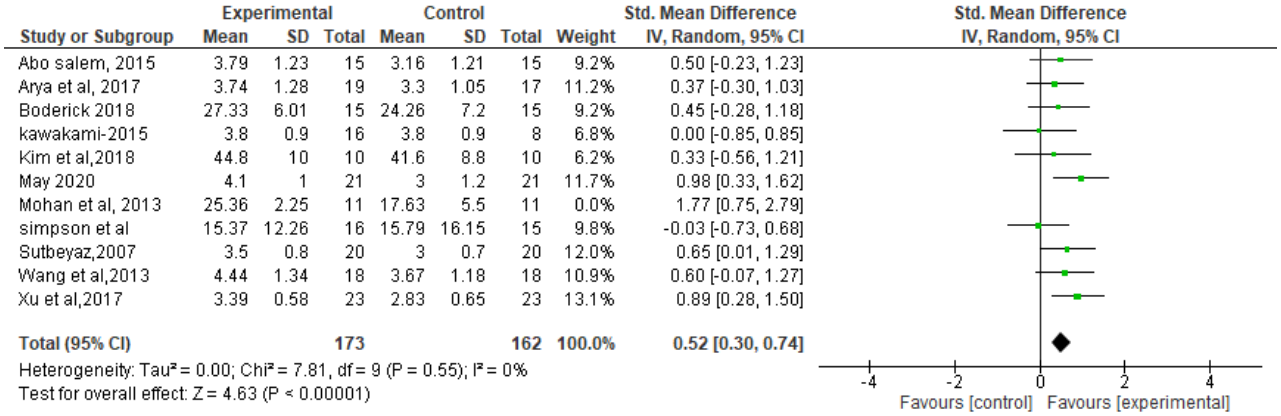


Figure 2-6 forest plot shows the influence of lower limb mirror therapy on motor recovery after stroke after removing the outlier with zero heterogeneity.

After removing the outlier, the effect size was reduced from 0.57 to 0.52, and I2 decreased from 25% to 0% as in fig 2-6.

b- To investigate if the results are sensitive to the studies with a high risk of bias

To investigate more about the included studies, four studies with a high risk of bias in the randomization were removed from the main meta-analysis to check if the bias would affect the pooled effect size. After removing these studies, the effect size changed from 0.57 to 0.62 and the I2 increased from 25% to 38%.

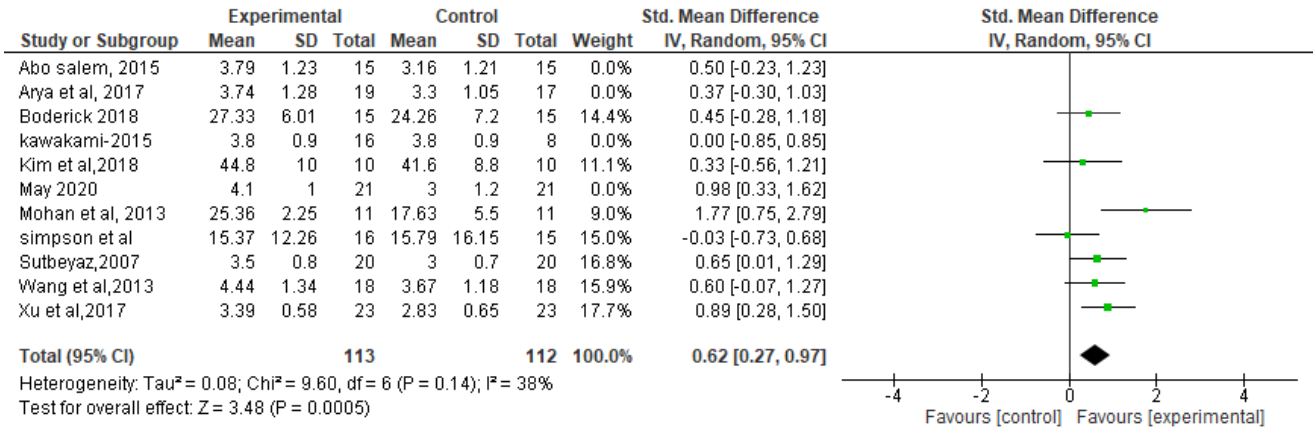


Figure 2-7 forest plot shows the influence of lower limb mirror therapy on motor recovery after stroke after removing the studies with high risk of bias in the randomization process.

Subgroup analysis for motor recovery

A subgroup analysis was conducted to understand if time after stroke, level of paresis, and the dose of intervention might influence the recovery while using mirror therapy. In all the following subgroup analysis, the same outcome measures that were included in the main primary analysis was reported. This was demonstrated in subgroup analysis as follows:

a. time after a stroke

Among the eleven studies included in the motor recovery analysis, ten studies (121,170,171,173,222,224,230–232,234) had mentioned the time after the stroke of participants at baseline. Here, the influence of time after a stroke was explored on the motor recovery of the lower limb in response to mirror therapy. The time has been grouped as:

- up to one week after stroke,
- more than one week and less than two months,
- two months to six months after stroke
- more than six months after stroke.

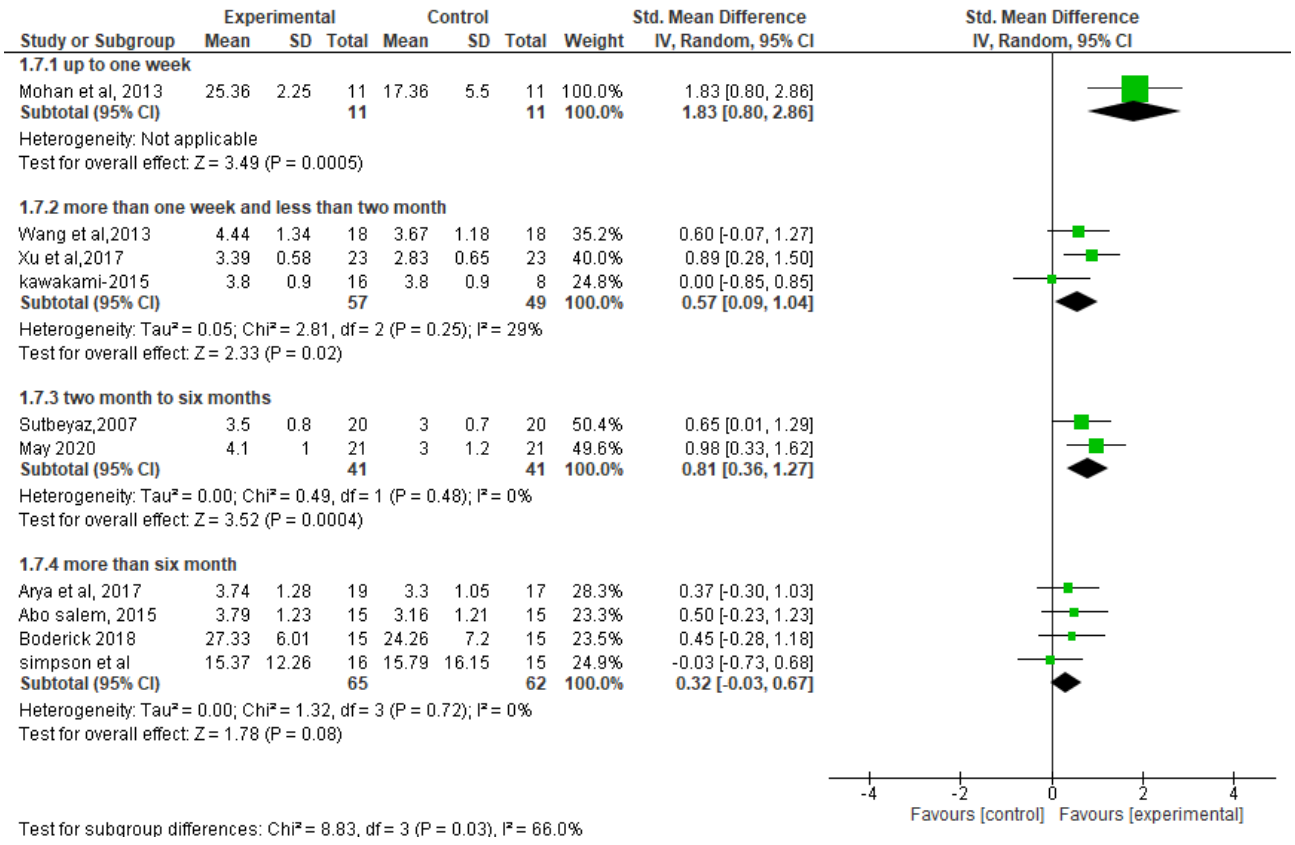


Figure 2-8 Forest plot shows the influence of time after a stroke on motor recovery of the lower limb after mirror therapy.

As shown in the forest plot, the included studies varied in terms of the participants' time after stroke. Only one study (173) included participants after a week following a stroke, which showed a significant difference favouring mirror therapy. Three studies (171,224,230) had participants for more than one week and less than two months after stroke. Two showed no significant difference, and one showed a difference with overall moderate significance difference (SMD =0.57 [95% CI=-0.09, 1.04], I^2 =29% and p=0.02; Fig 2-8). Two studies (121,222) had participants two months to six months after stroke and showed a significance difference toward mirror therapy (SMD =0.81 [95% CI=0.36, 1.27], I^2 =0% and p=0.0004; Fig 2-8). Four of the included studies (170,231,232,234) had participants more than six months after stroke with no significant difference among these studies (SMD =0.32 [95% CI= - 0.03, 0.67], I^2 =0% and P=0.08; Fig 2-8).

b. The level of paresis

Nine out of the eleven studies that have been included in the motor recovery analysis reported the level of severity at the baseline characteristics of their participants according to BRS or FMA of LL.

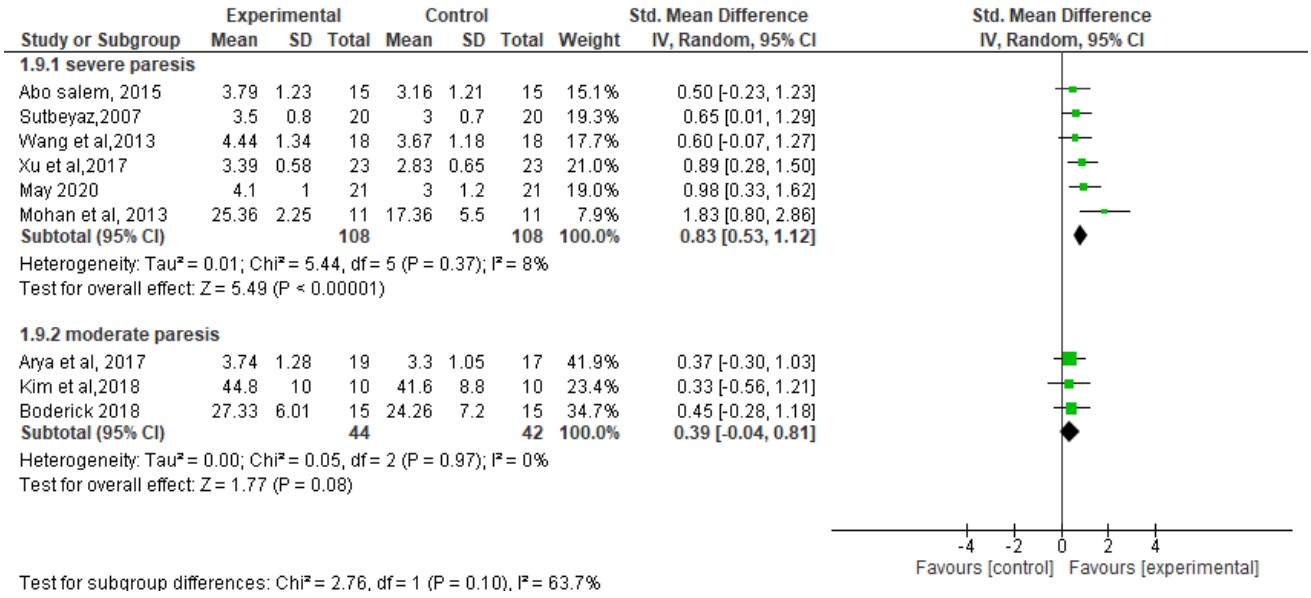


Figure 2-9 Forest plot shows the influence of the severity of paresis on motor recovery of the lower limb after mirror therapy.

From the forest plot, six studies included participants with severe paresis after stroke(121,170,171,173,224), and these had a significant between-group difference in favouring the mirror therapy (SMD =0.83 [95% CI=0.53, 1.12], I^2 =8% and P < 0.00001; fig 2-9). Three studies (226,232,234) had participants with moderate paresis with no significant difference among the group (SMD =0.39 [95% CI= - 0.04, 0.81], I^2 =0% and P = 0.08). No studies included participants with mild paresis after stroke.

c. Amount of intervention (dose)

Ten of the included studies reported the planned time of intervention. However, they did not report the actual time of intervention that was performed by the participants. Here the reported time (weeks) of intervention for each study was examined and the influence of that in motor recovery as a response to mirror therapy.

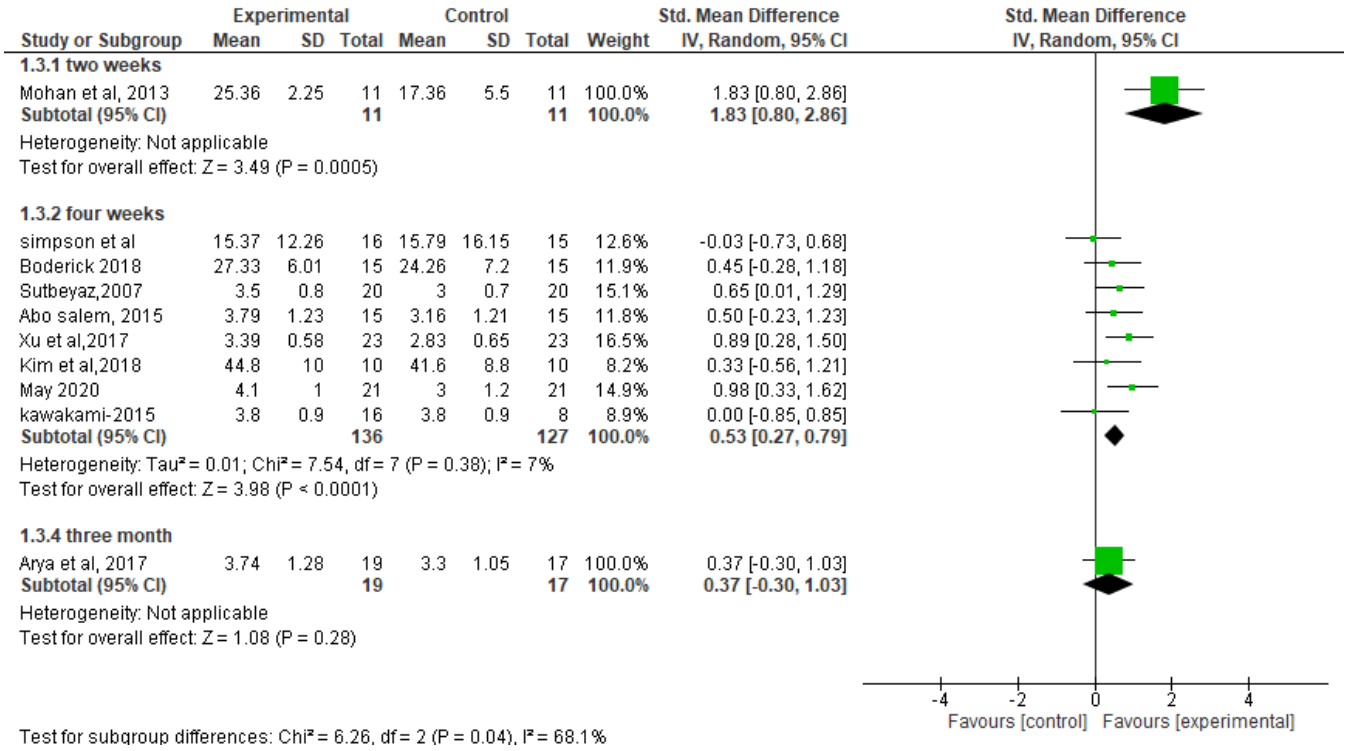


Figure 2-10 Forest plot shows the influence of the amount of mirror therapy (dose) on the lower limb's motor recovery.

One study only performed mirror therapy for two weeks, and it favoured the experimental group, while eight studies performed four weeks of intervention with overall small effect size favouring the mirror therapy (SMD =0.53 [95% CI=0.27, 0.79], I^2 =7% and p < 0.0001, fig 2-10). One study delivered three months of intervention and showed no significant difference. To investigate more about the influence of the dose of the intervention of the motor recovery, further analysis was conducted by plotting the dose in minutes against the effect size of the reported outcome. Four out of the eleven studies were excluded from the graph as they reported the number of repetitions (226) (230), the number of sessions only (231)**,** or the lack of clarity of reporting in term of the weeks of therapy whether it was one week or six weeks as in Wang *et al.* (2017) (224).

Seven studies only reported the time of the planned minutes (121,170,171,173,222,232,234). The curve suggested that with an increase in dose, there was less influence on motor

recovery. However, the number of the included studies in this analysis made the data insufficient to be certain about the results.

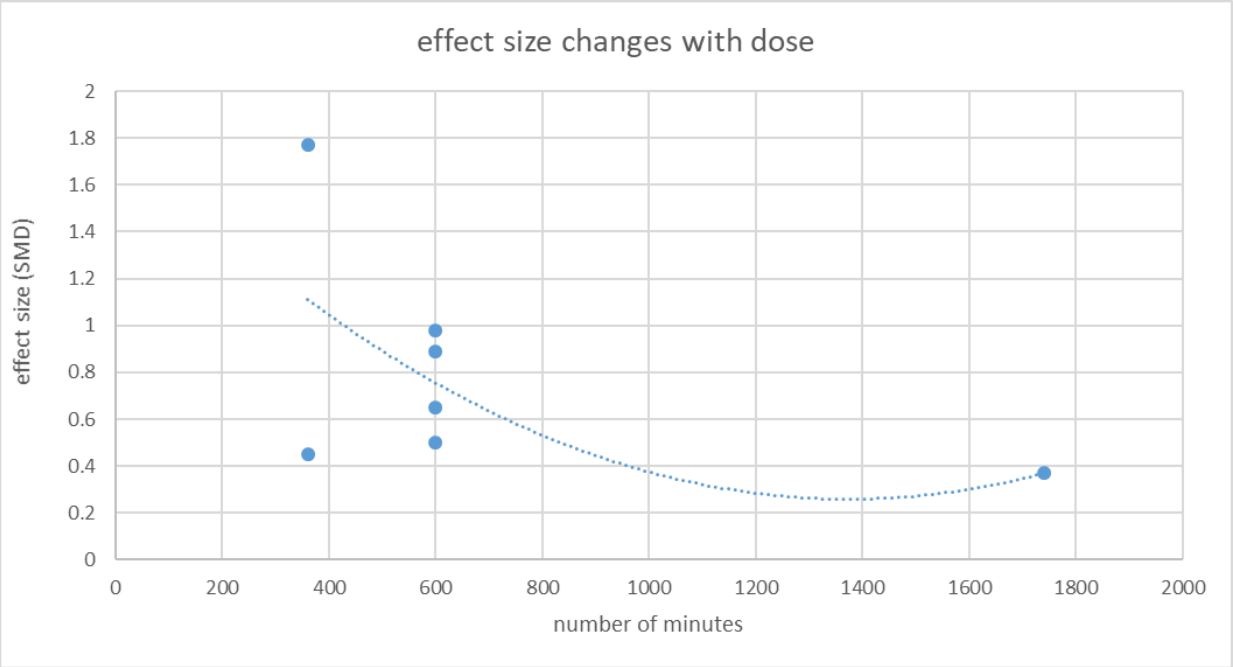


Figure 2-11 the influence of the amount of mirror therapy (dose in minutes) on the improvement of the motor recovery of the lower limb after mirror therapy.

Reporting all the motor recovery outcome measures among the included studies

To detect if mirror therapy's efficacy was sensitive to changes by using different scales, we grouped the available outcome measures that evaluated the motor recovery among the included studies.

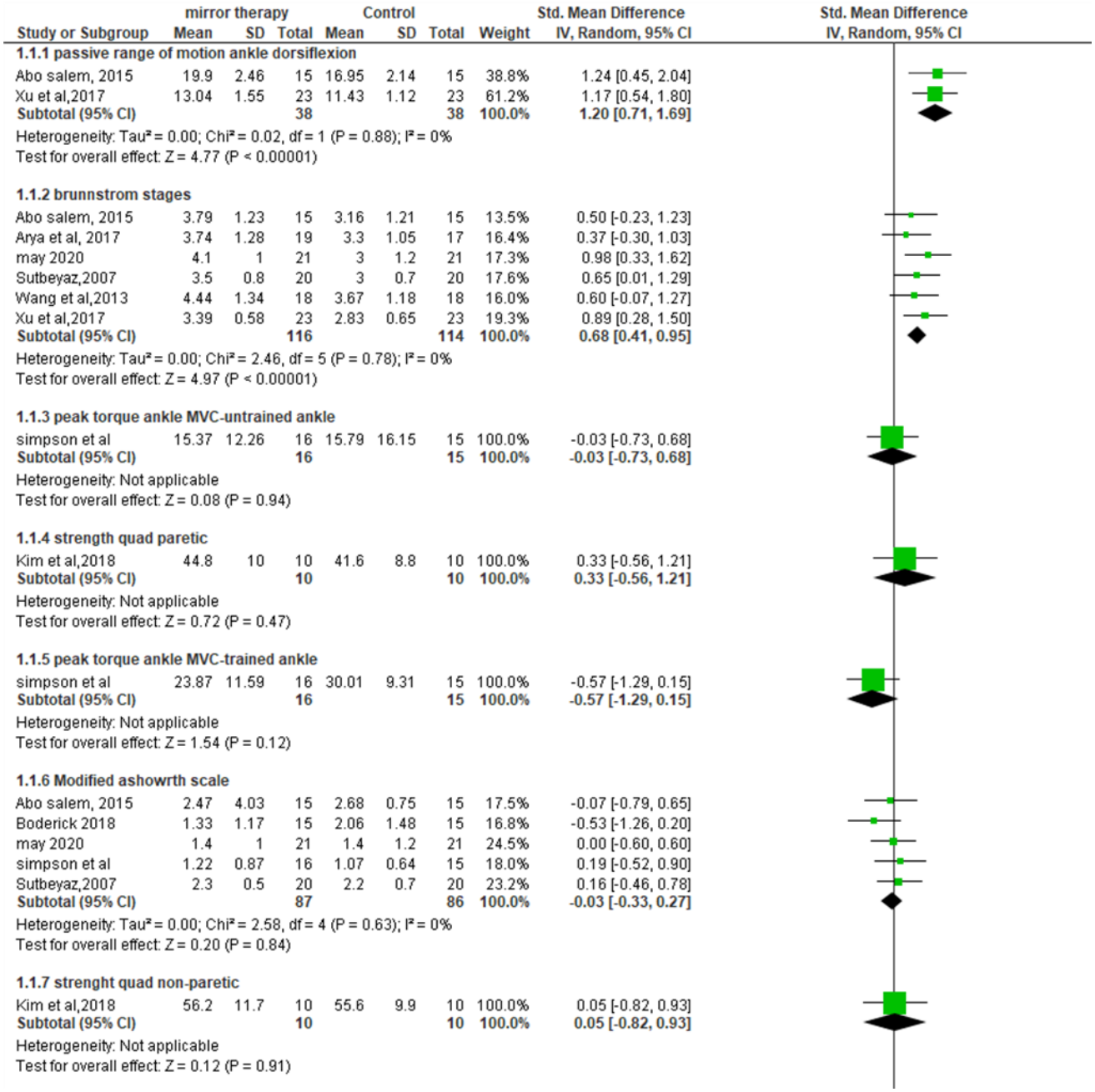


Figure 2-12 The Forest plot shows sensitivity analysis on using different scales of motor recovery on the effect of LLMT.

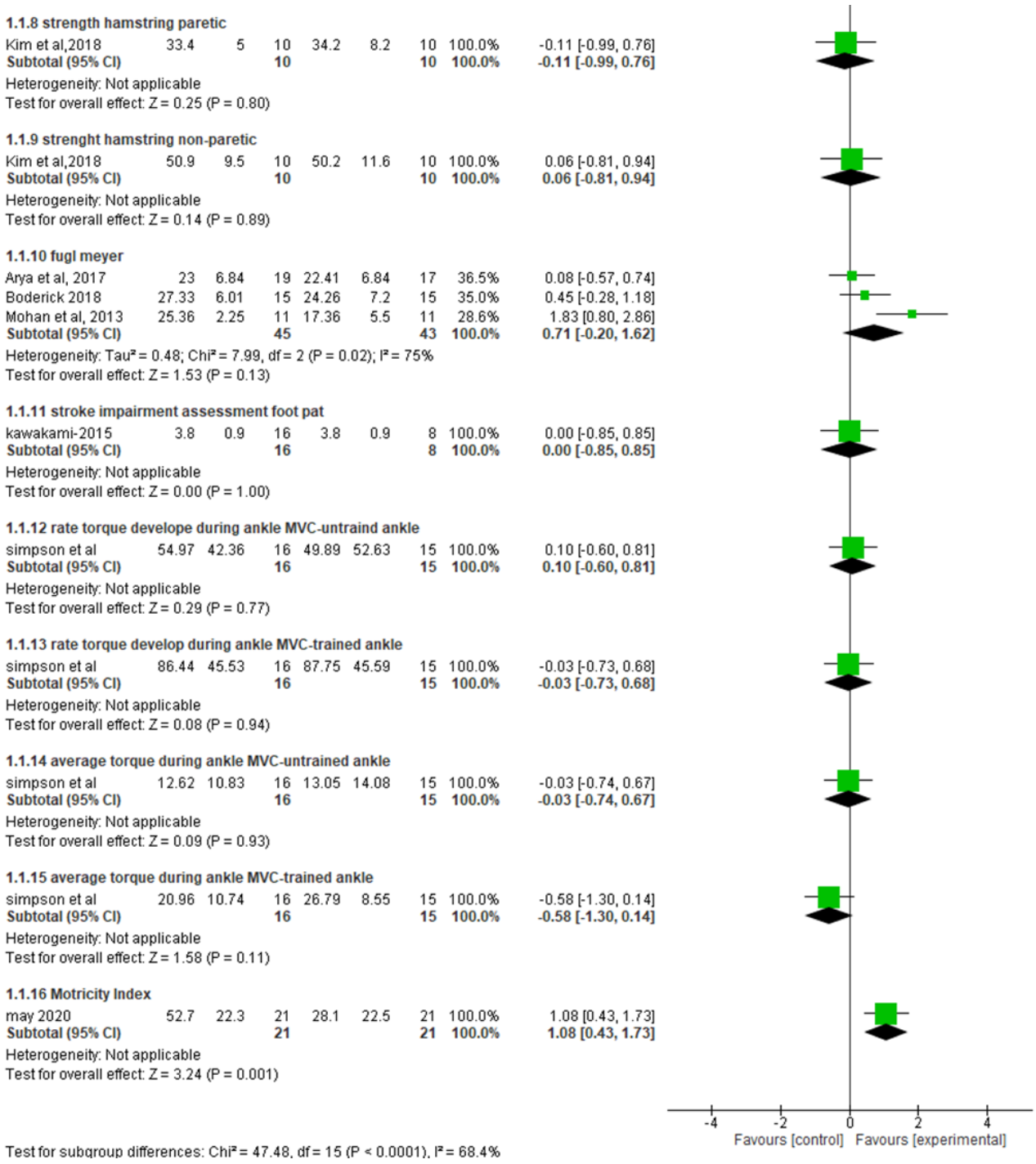


Figure 2-12 *(continuous) The Forest plot shows sensitivity analysis on using different scales of motor recovery on the effect of LLMT.*

From the forest plot, it can be seen that the included studies used different scales to measure the effect of mirror therapy on motor recovery. These scales showed different effects. Moreover, the scales that favour the mirror therapy as follows: passive range of motion for

ankle dorsi-flexion were performed by two studies (170,171) which favoured the mirror therapy (SMD =1.20 [95% CI=0.71, 1.69], I^2 =0% and p<0.00001). Six studies (121,170,171,222,224,234) used the Brunnstrom stages of recovery, and showed a moderate significant effect favouring the mirror therapy (SMD =0.68 [95% CI=0.41, 0.95], I^2 =0% and p<0.0001), while, five studies (121,170,222,231,232) used the Modified Ashworth scale, and showed non-significant difference (SMD = - 0.03 [95% CI= - 0.33, 0.27], I^2 =0% and p=0.84). Also, three studies (173,232,234) used the Fugl Meyer and showed no significant difference (SMD =0.71 [95% CI= - 0.20, 1.62], I^2 =75% and P=0.13). Individual studies used different scales such as peak torque ankle, rate torque ankle and average torque ankle in both trained and untrained ankle and showed no difference among these scales (231). Also, strength quadriceps and hamstring for both sides (226), stroke impairment assessment foot pat (230), and all these scale showed no differences. In contrast, the Motricity index showed a significant difference favouring mirror therapy (222).

2.3.3.3.II. Secondary analysis: to investigate if the provision of lower limb exercise via mirror therapy enhances functional capacity after stroke.

Among the included studies in the meta-analysis, 17 studies did report functional capacity measures such as Functional Ambulation Category (FAC), 10- meter walking, and gait parameters (121,170–173,223–225,227–229,231–235). These measures were as follows: FAC outcome measure were reported for (Mohan *et al*. (2013) (173), Wang *et al*. (2017) (224), Meher *et al.* (2019) (229), and Sutbeyaz *et al.(*2007) (121), May *et al*. (2020) (222)). The 10 m walk (Xu *et al*.(2017) (171), and Abo Salem *et al*.(2015) (170) & Arya *et al*. (2017) (234), Simpson et al. (2019) (231), Boderick *et al.* (2019) (232)). The velocity (Ji *et al.(*2015) (235), Kim &shin (2018) (233), Ji *et al*. (2014) (225), Borhaniya *et al*. (2018) (223), Cha&Kim (2015-b) (228)). The Time Up and Go as in Cha&Kim,(2015)(227). The gait (Lee *et al*.(2017) (172)). These studies reported a significant between-group difference favouring the mirror therapy (SMD =0.45 [95% CI=0.17, 0.72], I2 =60% and p =0.001; fig 2-13). In this analysis and the subgroup analysis, the same outcomes that were mentioned above were reported.

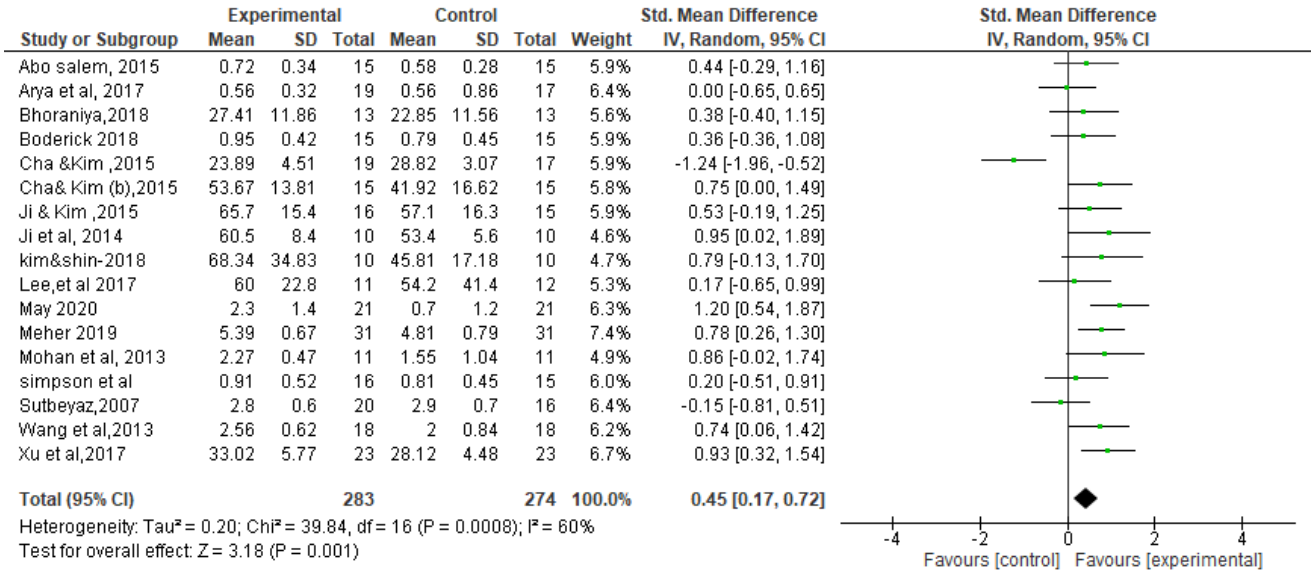


Figure 2-13 Forest plot shows the effect of lower limb mirror therapy on functional capacity.

Sensitivity analysis:

a- Remove outlier

To investigate if the results are sensitive to the occurrence of the outliers.

As it appeared in (fig2-14), Cha& Kim (2015) (227), was an outlier. To explore more, the outlier was removed, and the effect size changed from 0.45 to 0.55, and the I2 decrease from 60% to 14%.

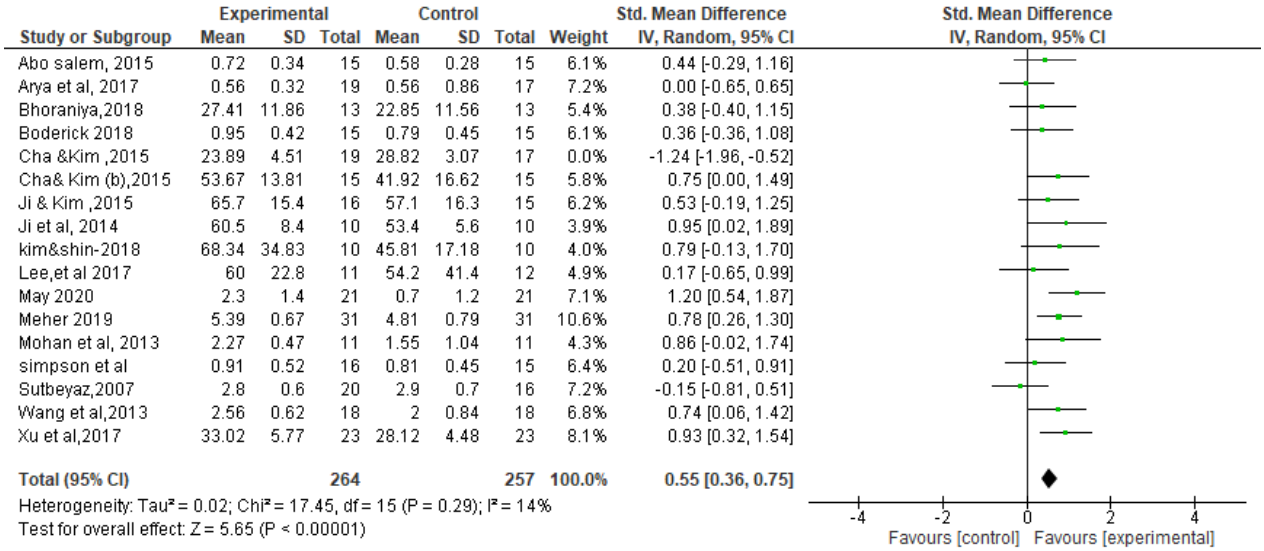


Figure 2-14 Forest plot shows the effect of lower limb mirror therapy on functional capacity after removing the outliers.

b- To investigate if the results are sensitive to the choice of the included studies, studies with a high risk of bias were removed.

To investigate more about the included studies, five studies with a high risk of bias in the randomization were removed from the meta-analysis to check if the bias would affect the pooled effect size (170,222,227,229,234). After removing these studies, the effect size changed from 0.45 to 0.52, and the I2 decreased from 60 % to 0%.

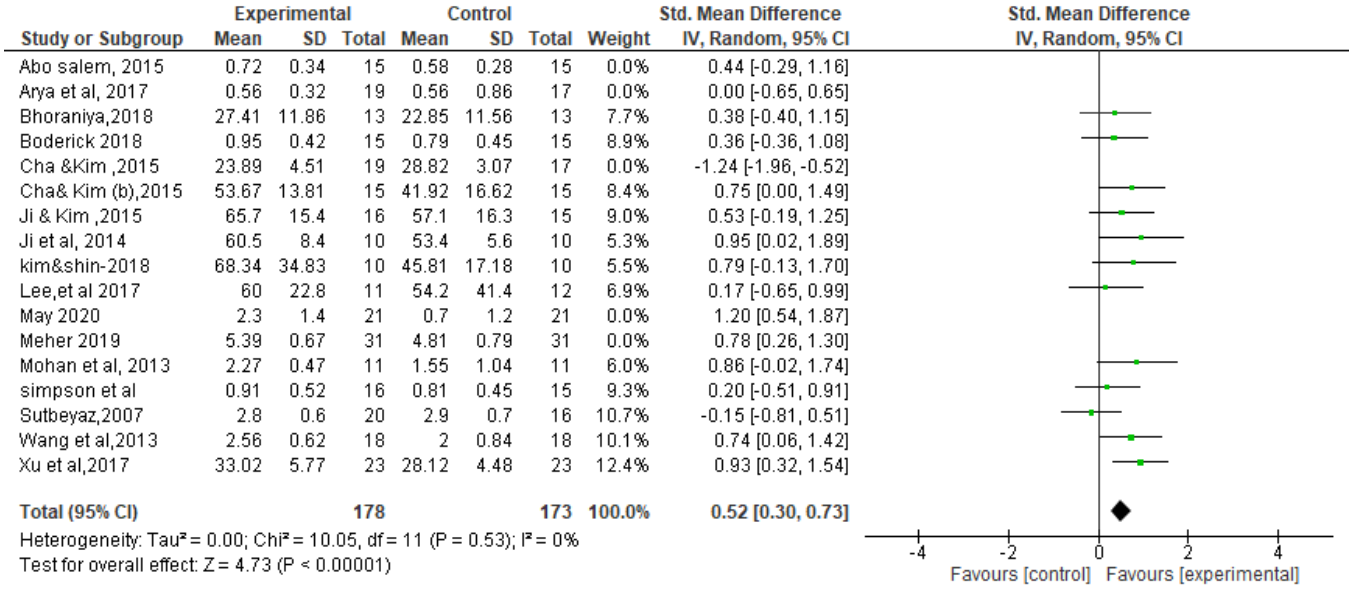


Figure 2-15 Forest plot shows the influence of lower limb mirror therapy on functional capacity after removing the studies with a high risk of bias in randomisation.

Subgroup analysis:

a- time after a stroke

Among the seventeen studies that were included in the functional capacity analysis, sixteen studies (121,170,171,173,222–225,227–229,231–235) described the time after the stroke of their participants in their baseline characteristics. Here, the influence of time

after a stroke on the improvement of functional capacity of the lower limb after mirror therapy was explored. The same outcome measures were used in the main analysis of the functional capacity. The time has been grouped as:

- up to one week after stroke,
- more than one week and less than two months,
- two months to six months after stroke
- more than six months after stroke.

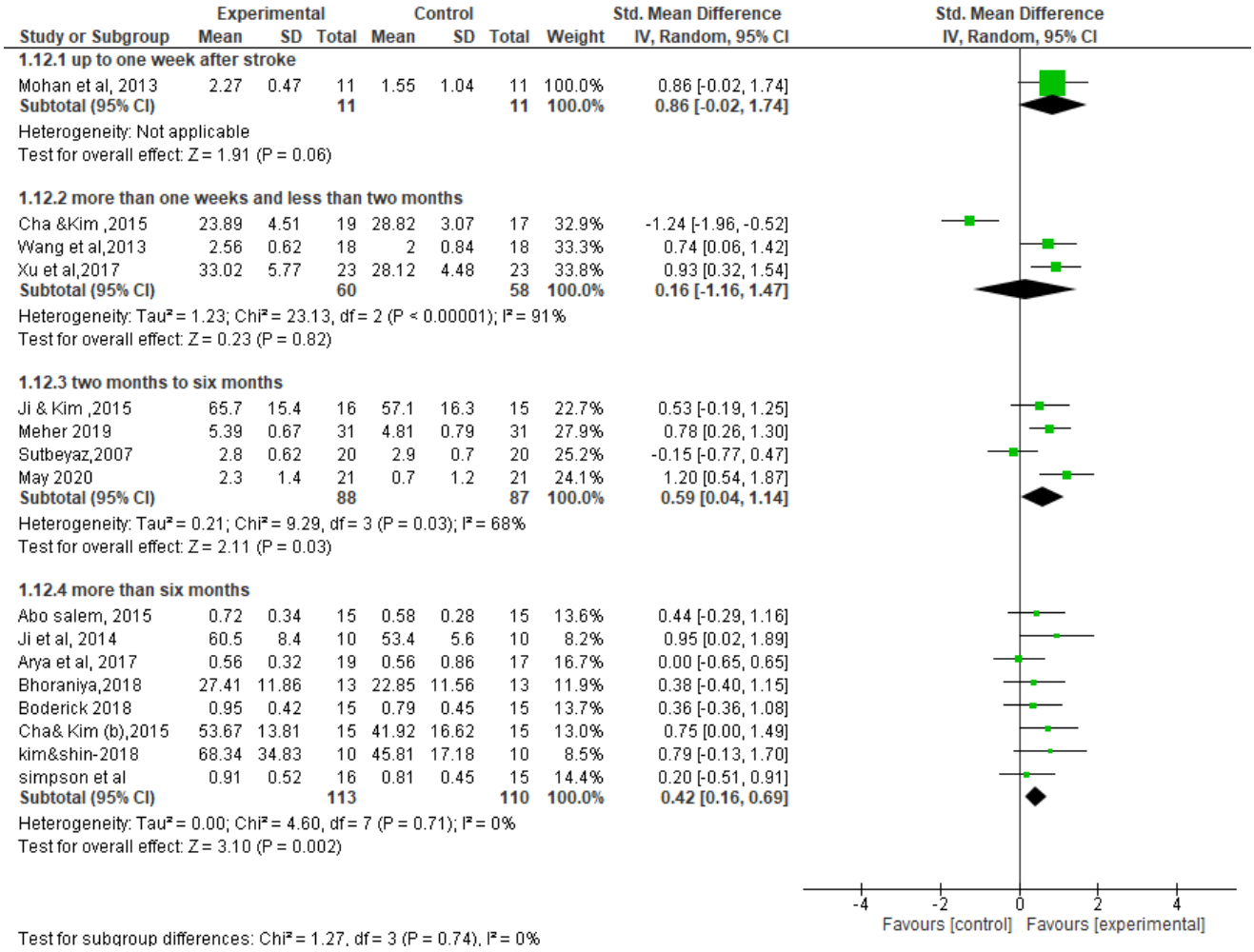


Figure 2-16 Forest plot shows the influence of time after a stroke on the improvement of the functional capacity of the lower limb after mirror therapy.

As shown in the forest plot, the included studies varied in terms of the participants' time after stroke; only one study included participants after a week following a stroke (173), favouring the mirror therapy.

Three studies had participants more than one week and less than two months after the stroke (171,224,227), with two studies showing a significant difference, and one with no difference with overall no significant difference (SMD =0.16 [95% CI= - 1.16, 1.47], I^2 =91% and p =0.82; fig 2-16). Besides, four studies included participants for more than two months and less than six months (121,222,229,235) with a significant difference (SMD =0.59 [95% CI= 0.04, 1.14], I^2 =68% and P =0.03; Fig 2-16). Eight studies included participants more than six months after a stroke (170,223,225,228,231–234). Of these, two studies showed a significant difference, and four were insignificantly different with overall moderate size effect showed a significant difference toward mirror therapy group (SMD =0.42 [95% CI=0.16, 0.69], I^2 =0% and P=0.002; Fig 2-16).

b- the level of paresis

Among the 17 studies, ten studies reported the severity of paresis of their participants' baseline characteristics (121,170,171,173,222–224,229,232–234). the severity of paresis was determined according to Brunnstrom stage of recovery or Fugl Meyer, if available (Appendix I). The same functional capacity measures in the main analysis to detect its influence were reported.

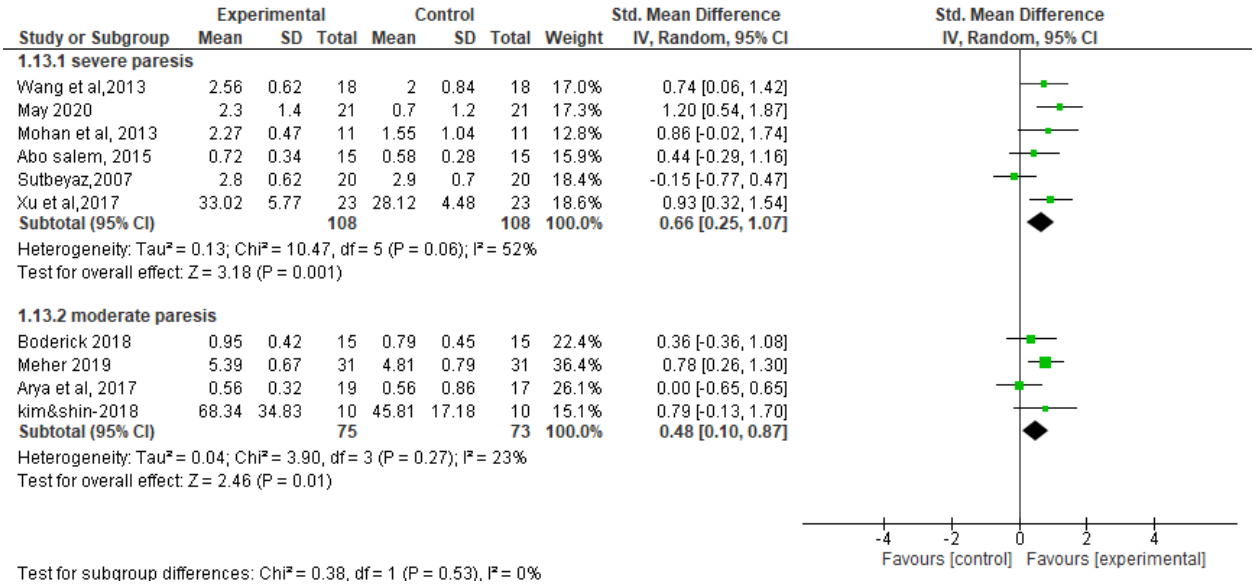


Figure 2-17 Forest plot shows the influence of the severity of paresis on the improvement of the functional capacity of the lower limb after mirror therapy.

From the forest plot, five studies (121,170,171,173,224) included participants with severe paresis after stroke, and these showed significant between-group difference in favouring the mirror therapy (SMD =0.66 [95% CI=0.25, 1.07], I^2 =52 % and P=0.001;Fig 2-17). Four studies included participants with moderate paresis, and these showed significant between-group difference favouring the mirror therapy (SMD =0.48 [95% CI= 0.10, 0.87], I^2 =23% and P = 0.01;Fig 2-17), (229,232–234). With no studies included participant with mild paresis.

c- Amount of intervention (dose)

Fourteen studies reported the time of therapy (121,170–173,222,223,227,228,231–235). However, that was varied between minutes, sessions, and repetitions of the training. First, we analysed the reported planned weeks among the included studies. The studies which excluded from this analysis are: Meher *et al*. (2019) (229), Wang *et al.(*2017) (224), and Ji *et al*.(2014) (225) that was due to insufficient reporting of the dose as number of weeks was not provided.

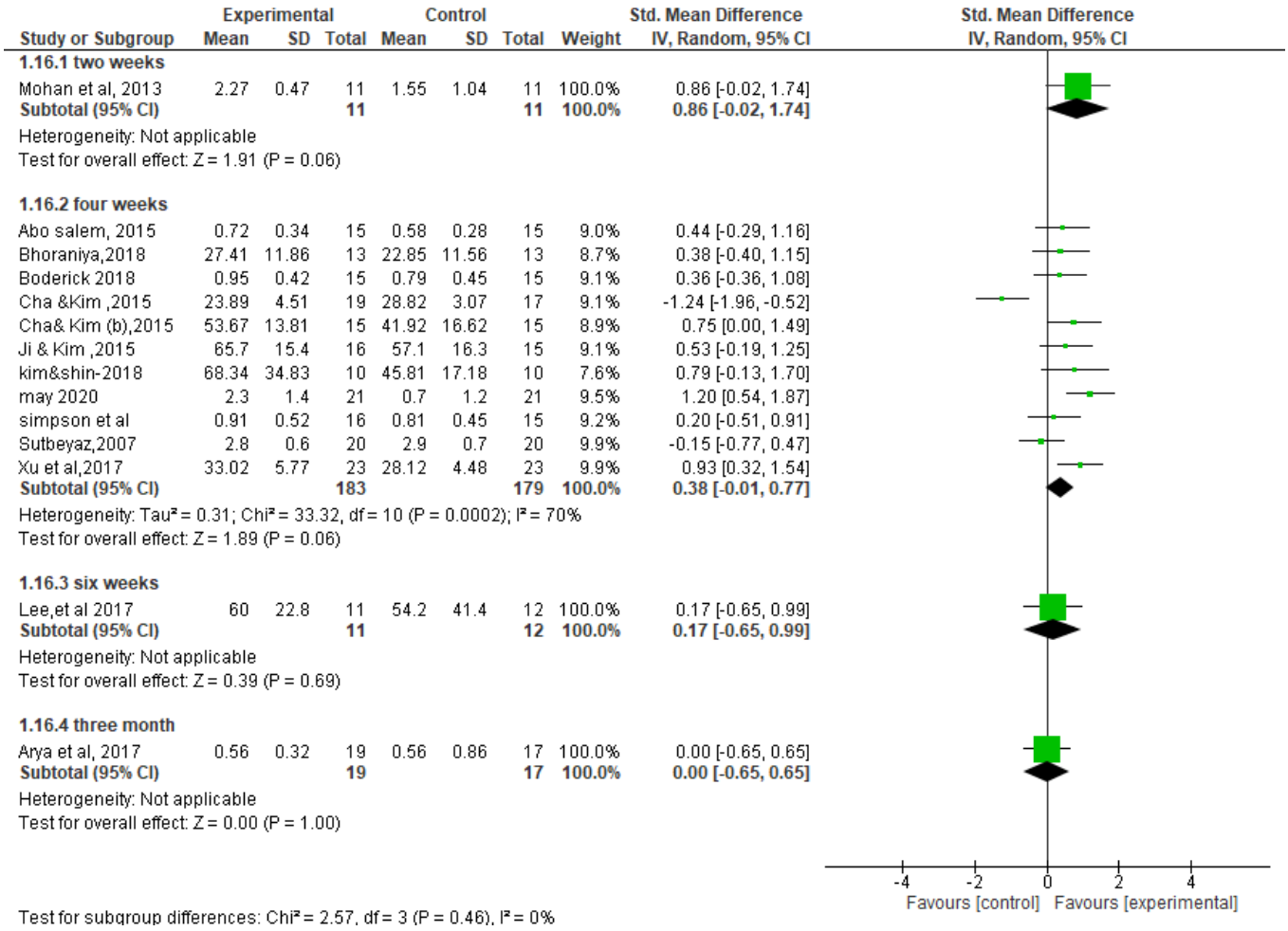


Figure 2-18 Forest plots shows the influence of the amount of intervention (dose in weeks) on the improvement of the functional capacity of the lower limb after mirror therapy.

From the forest plot, none of the available intervention time showed a significant difference toward the mirror therapy. One study only performed mirror therapy for two weeks (173), while eleven studies (121,170,171,222,223,227,228,231–233,235) performed four weeks of intervention with overall effect size showed no significant difference (SMD =0.38 [95% CI= - 0.01, 0.77], I^2 =70%, and P = 0.06). One study delivered six weeks of the planned intervention (172), and one study (234) delivered three months of intervention with an overall size effect for both categories, which showed no significant difference.

To investigate more about the effect of the dose on the functional capacity, the number of minutes of the planned therapy were added up per each study where this was reported. Then,

plotted it against the effect size of that study to explore whether there was a relationship between the dose provided and changes in the outcome measures. Four studies have been excluded from the graph for the following reasons: Simpson *et al*.(2019) (231) reported the number of sessions only, and Kim *et al*. (2018) (233) reported the number of repetitions only. Wang *et al*.(2017) (224) lacked the reporting of the dose in term of the weeks of therapy, whether it was one week or six weeks (224). While Ji *et al*.(2014) did not report the number of repetitions or intensity (225). Thirteen studies from the 17 studies included in the main analysis of the functional capacity reported the time of the planned minutes. The curve suggested that with an increase in dose, there was less influence on improvement on functional capacity. However, there was insufficient data to be certain.

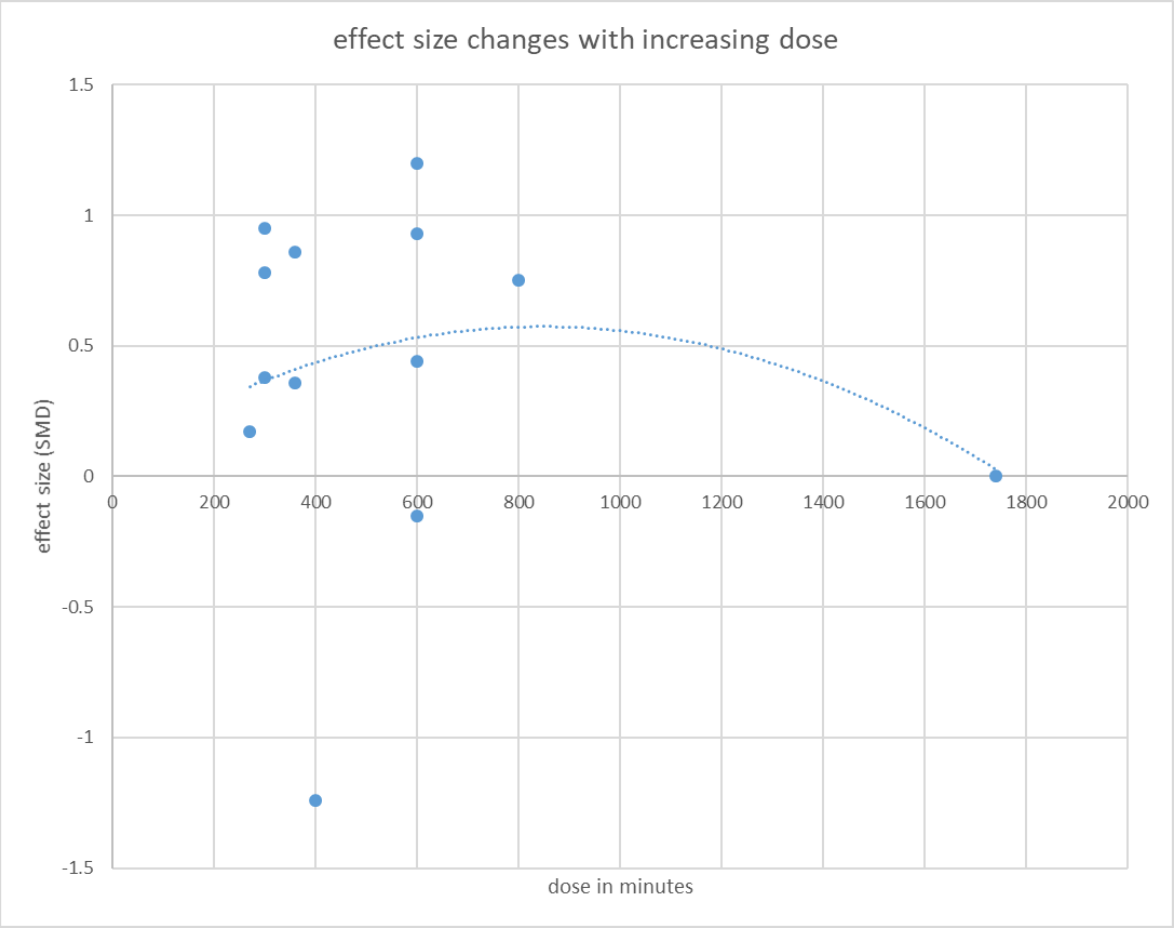


Figure 2-19 the influence of the dose of intervention (in minutes) on the improvement of the functional capacity of the lower limb after mirror therapy.

The graph above showed no relationship between the number of the planned minutes and the changes in the effect size. However, the number of the included studies in this analysis made the data insufficient to be certain about the results.

Reporting all the outcome measures for functional capacity among the included studies

To detect if the efficacy of mirror therapy was sensitive to changes by using different scales to further improve understanding of the effect of mirror therapy on functional capacity, all the outcome measures used to measure functional capacity were grouped among the studies.

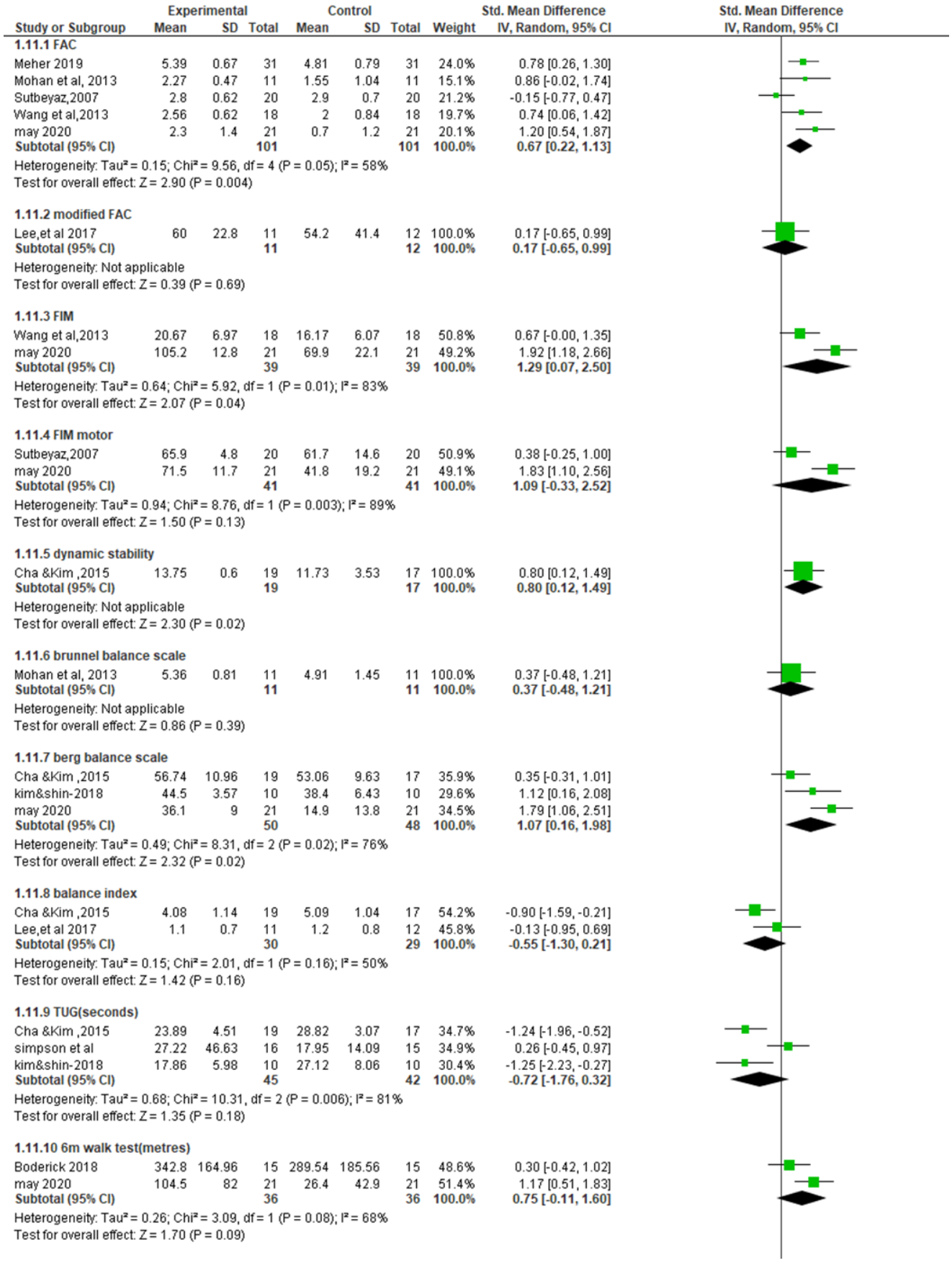


Figure 2-20 The Forest plot shows subgroup analysis on using different scales of functional capacity on the effect of LLMT.

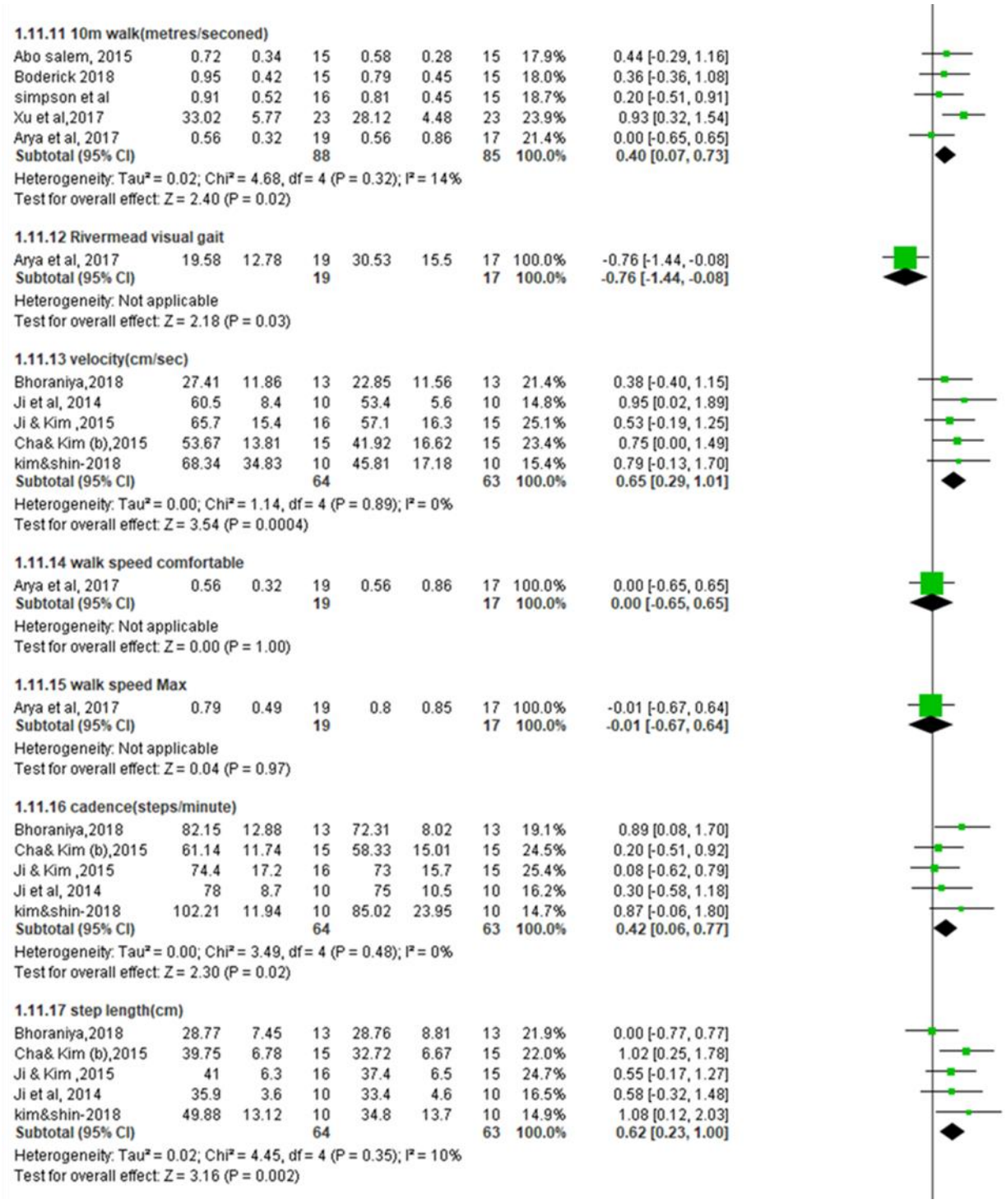


Figure 2-20 (continuous) The Forest plot shows subgroup analysis on using different scales of functional capacity on the effect of LLMT.

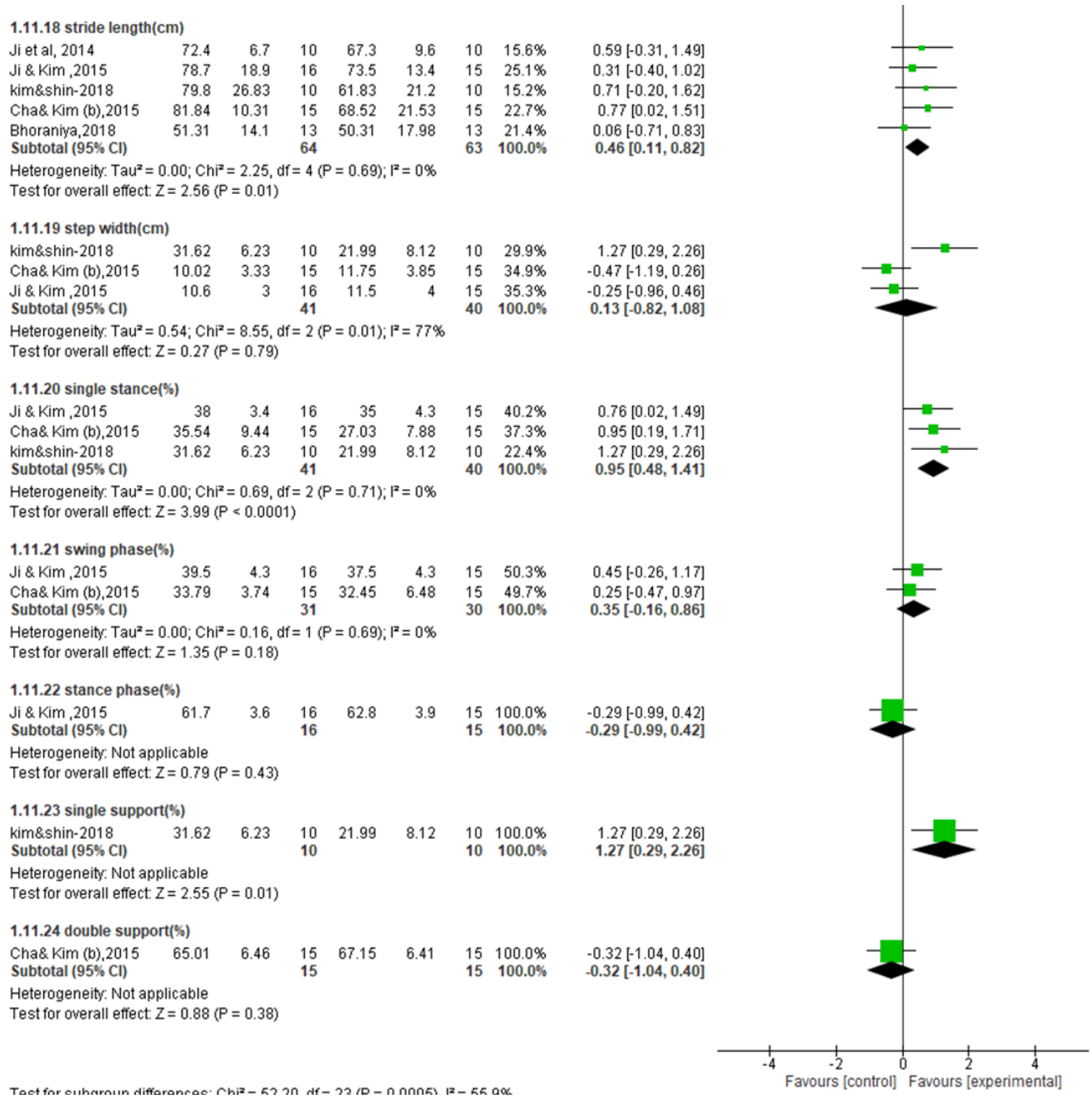


Figure 2-20 (continuous) The Forest plot shows subgroup analysis on using different scales of functional capacity on the effect of LLMT.

The above forest plot showed the different scales that were used by the studies to measure the improvement of functional capacity. Five studies (121,173,222,224,229) used the Functional Ambulation Categories (FAC) which favoured the mirror therapy, moderate size effect, (SMD =0.67 [95% CI=-0.22, 1.13], I^2 =58%, and P = 0.05). Modified FAC (172) was used by

one study with no significant effect. Functional Independent Measure (FIM) was used by two studies (222,224) which show a significant difference. FIM motor (121,222) was used by two studies per scale and showed no significant difference. Berg Balance Scale was used by three studies (222,227,233) and showed significant effect (SMD =1.07 [95% CI= 0.16, 1.98], I^2 =76%, and P = 0.02). Also, Balance Index was used by two studies (172,227) with no significant difference (SMD = - 0.55 [95% CI= - 1.30, 0.21], I^2 =50%, and P = 0.16). Burnnel Balance scale was used by one study (173), and it showed no significant difference. The dynamic stability was used by one study (227) as well but showed a significant difference favouring the mirror therapy.

Time up and go (seconds) was used by three studies (227,231,233) and showed no significant difference (SMD =0.07 [95% CI= - 1.31, 1.45], I^2 =89%, and P = 0.92). Ten-metre walk (metres/second) was used by 5 studies (170,171,231,232,234) and it favoured the mirror therapy (SMD =0.40 [95% CI= 0.07, 0.73], I^2 =14%, and P= 0.02). Velocity (cm/sec) was used in four studies(223,225,228,233,235) and it favoured the mirror therapy (SMD =0.65 [95% CI= 0.29, 1.01], I^2 =0%, and P = 0.0004). The 6-m walk were used by two studies(222,232), walk speed (comfortable) and walk speed (Max) were used by one study (234) showed no difference. While the Cadence favoured the mirror therapy (SMD =0.42 [95% CI= 0.06, 0.77], I^2 =0%, and P= 0.02).

Rivermead visual gait was used by one study and favoured the control group. Temporal-spatial gait parameters were used in the included studies; step length (cm) was used by five studies(223,225,228,233,235) which had moderate size effect with favouring the mirror therapy (SMD =0.65 [95% CI= 0.23, 1.00], I^2 = 10%, and P = 0.002). Also, stride length (cm) was used by five studies (223,225,228,233,235) which had small effect size with favouring the mirror therapy (SMD =0.46 [95% CI= 0.11, 0.82], I^2 = 0%, and P = 0.01). Single stance (%) was used by three studies (228,233,235) and it favoured mirror therapy with large size

effect (SMD =0.95 [95% CI= 0.48, 1.41], I^2 = 0%, and P= 0.0001). Single support (%) was used by one study only (233) and it favoured mirror therapy, while the step width (cm) was used by three studies (228,233,235) and showed no significant difference (SMD =0.13 [95% CI= - 0.82, 1.08], I^2 = 77%, and P = 0.79). Swing phase (%) was used by two studies (228,235)and showed no significant difference (SMD =0.35 [95% CI= - 0.16, 0.86], I^2 = 0%, and P = 0.18). Stance phase (235) and double support (228) were used by one study per each, and both scales showed more favour toward the control group.

Publication bias for motor recovery and functional capacity

The funnel plot was used to detect if there is a chance for publication bias among the current literature (Figure 2-21). The funnel plot for motor recovery (fig 2-21A) and functional capacity (fig 2-21B) was used. Studies showed a symmetrical pattern except for the studies, which were identified as outliers in the main analysis. Then the second graph (fig2-22) showed the studies after removing the outliers in motor recovery (fig2-22A) and functional capacity (fig2-22B) from the previous main analysis, which showed that studies had a more symmetrical pattern.

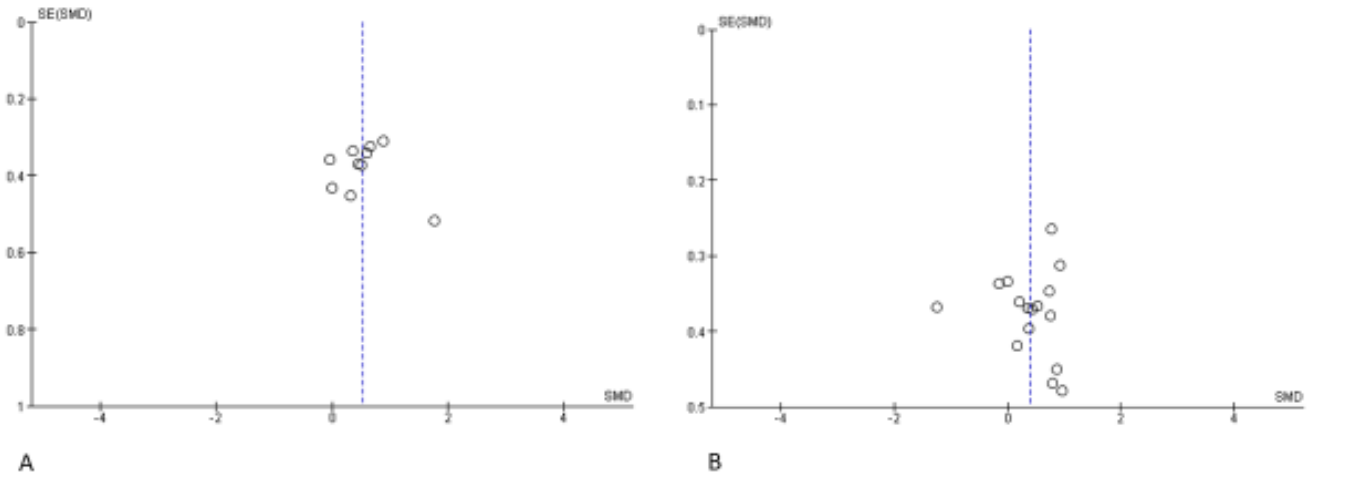


Figure 2-21 funnel plot shows the publication bias among the studies that investigated the motor recovery after stroke (A).funnel plot investigated the functional capacity after stroke *(B)*

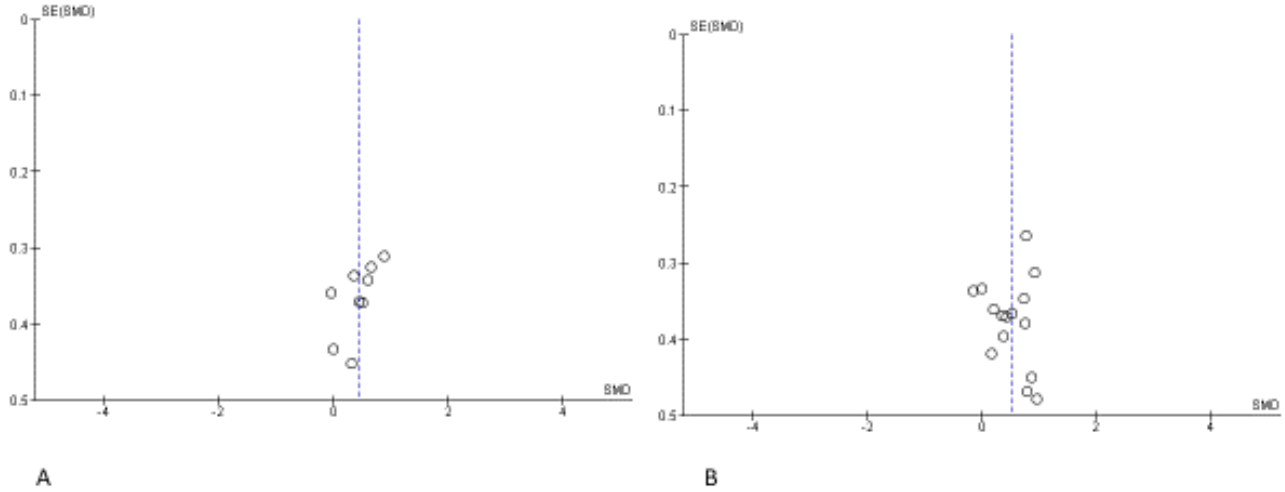


Figure 2-22 funnel plot shows the publication bias among the studies that investigated motor recovery after stroke (A). Funnel plot investigated the functional capacity after stroke (B) after removing the outlier from both analysis.

2.4 Discussion

This review included twenty studies in the narrative synthesis, and nineteen studies in the meta-analysis. The results showed that lower limb mirror therapy improved the motor recovery and functional capacity of the lower limb after stroke. In addition, this review focused on the influence of time after stroke, level of paresis, and the dose of the intervention on both the motor recovery and functional capacity. For the time after stroke, the results showed that participants less than six months after stroke showed more favour to mirror therapy in the improvement of the motor recovery. At the same time, participants from two-six months and more than six months post-stroke showed an improvement in the functional capacity, which favoured mirror therapy. For the severity of paresis after stroke, participants with severe paresis showed more improvement after using mirror therapy in both motor recovery and functional capacity. The dose of intervention is still unclear from the available evidence.

These results are in line with previous systematic review results (103,162,165–167), as they found mirror therapy might have a small effect on motor recovery and mobility (165) and large impact on gait (165). In this study, results showed that mirror therapy to have a moderate effect on motor recovery, and a small effect of improvement of functional capacity. However, to the researcher knowledge, none of these reviews investigated if time after stroke, level of paresis, and the dose of the intervention might influence the recovery using a detailed meta-analysis of these factors. Also, most of the reviews stated that the dose of mirror therapy is still unclear, and this is similar to our finding (103,165). Besides that, due to the lack of information, these reviews struggle to find how to apply the mirror therapy (166), which is similar to our findings.

In this review, eleven studies had an overall judgment of high risk of bias. Six studies have a high risk of bias in randomisation, which might affect the participants' characteristics among the study groups, and that will have a direct effect on the review results. Besides the occurrence of outliers, one in the motor recovery analysis which was Mohan *et al*.(2013) (173), and the other one in functional capacity analysis which was Cha& Kim (2015) (227) . These outliers were due to differences in baseline characteristics and method used, respectively. In addition, May *et al*. (2020) (222) had varieties between time after stroke in the baseline characteristic of the control group (30 days) and mirror therapy group (60 days), but the study did not appear as an outlier in the forest plot. Therefore, the interpretation of these findings should be cautious. In addition to the impact of the risk of bias assessments on the results, the publication bias could arise from pooling the results of published studies, leading to overestimation of the effectiveness of the intervention (220,237). This can be avoided by searching the published and unpublished data that is commonly called "grey literature" (220,237). In this review, a comprehensive search strategy among the published and unpublished databases was conducted to avoid such bias. Nevertheless, dropping some studies might happen by chance, which could lead to some unintended publication bias. It is recommended that this could be investigated using a funnel plot (238). The results showed that studies that had previously been identified as outliers were away from the scattered dots in the funnel plot, which could mean these studies might be heterogeneous due to participant characteristics, randomisation, statistical difference, or publication could be biased in some similar research areas. Therefore, interpretation of these findings should be cautious.

The main baseline characteristics of the participants varied among the included studies. The age of the participants ranged from 44 to 69, with a mean age of about 58.8 years. However, this is non-representative of the UK stroke population, which about 72 years for men and 78 years for women (stroke association). It is hard, therefore, to make generalisations about

stroke survivors using mirror therapy, especially that older stroke survivors face different challenges from younger ones. Further research using lower limb mirror therapy with older stroke survivors is indicated.

Only fifty percent of the included studies had reported the type of stroke, while the others did not mention any details. In addition, the included studies did not mention the exact location of the stroke, but they had mentioned the occurrence of the stroke in the right or left hemisphere only. However, knowing the stroke location and size as baseline characteristics (239) and how this might be connected to influence the outcome is very important in predicting the recovery (66,239–241). More information about the stroke location and size needs to be reported in future studies to better understand the recovery.

Not surprisingly, the lack of reporting was a major issue, according to the TIDier guideline items. Key elements were missing or not sufficiently reported, such as: the material, quality of the mirror, position of the participants, the set-up of the mirror therapy tool, and if there were any modifications for the therapy to meet the specific needs of stroke survivors. This information was varied among the limited number of the studies that reported these details. However, such technical information is essential for researchers and clinicians to replicate the tool and used it in their rehabilitation program, especially as there are no published protocols for lower limb mirror therapy (163). The lack of all this information made the replication and the way of delivering lower limb mirror therapy hardly possible. This is in line with the previously published review (167). Therefore, to allow easy application for future researcher and clinicians, it is recommended that future studies address the issues of how to use therapy, the type of materials required and the setup of the lower limb mirror therapy. Also, future studies must follow the Tidier guideline items and report all the details needed to replicate the

research, this was in line with the recent recommendation from the Stroke Recovery and Rehabilitation Roundtable about the need for a better reporting of stroke research (242).

It's been known from stroke rehabilitation research that time after stroke, level of paresis, and the dose of the intervention might influence recovery. For the influence of time after stroke, which is considered an essential factor in predicting the recovery (66). However, the time after stroke varied among these studies from one week to more than six months. Studies with one week to less than six months showed an improvement in motor recovery after using mirror therapy. However, only one study included participants within one week after a stroke (173). Although this study demonstrated a significant improvement when mirror therapy was used, this study was an outlier among the included studies, which might be due to differences in the baseline characteristic between groups. Therefore, this result cannot be generalised for early mirror therapy after stroke, and more investigation is needed. Also, an improvement in the functional capacity was noticed with participants from two- six months and more than six months after stroke. This could be related to the time stroke survivors needs to gain changes in function, such as walking and balance (210), or that mirror therapy might improve the participants who learned none use their paretic side by increasing the awareness of that limb (126). Nevertheless, the current evidence of stroke rehabilitation suggested that early rehabilitation might optimize the potential recovery, and the golden period for recovery is from the first days after onset to several weeks (29). This review has identified that current evidence about lower limb mirror therapy did not utilise this vital time window of spontaneous recovery. Nevertheless, as a result of the heterogeneity in the time after stroke in the current literature, and the high risk of bias, it was difficult to identify the best time to apply the therapy after stroke to improve the recovery. This presents an opportunity for future

studies to investigate the best time after stroke to enhance the effect of mirror therapy on motor recovery and functional capacity.

Secondly, the influence of baseline severity of paresis on motor recovery and functional capacity. Even though the studies varied with regard to the severity of the participants in their baseline, all the studies that included participants with severe paresis showed a significant improvement while using mirror therapy in both motor recovery and functional capacity. This is in line with published study concerning upper extremity mirror therapy (129). Also, we included two studies under the "severe paresis category", based on mathematical judgment. One was Mehr *et al*.(2019) (229), who stated that participants were between "stages 1 to 3", according to the Brunnstrom stage of recovery. The mean here will be 2.9 or below. However, if all participants scored 3 then the severe paresis was misclassified for this study. The same was the case with Kim *et al*.(2018) (233). Therefore, these results cannot be generalised because of the insufficient reporting and the small number of included studies. Future research should focus on the influence of the severity of paresis on motor recovery and functional capacity while using mirror therapy.

Thirdly, the influence of the amount of intervention (dose) on motor recovery/functional capacity. It is worth noting that most of the included studies reported the intervention's planned time, with no studies reporting the actual dose performed by the participants. Besides that, the dose of the therapy was poorly reported or missing in the included studies. Not surprisingly, studies varied in terms of the planned dose (weeks) of therapy from two weeks to three months. Overall, studies showed better outcomes in 4 weeks of intervention. That might be because most of the studies followed Sutbeyaz *et al*.(2007)(121) intervention for lower limb mirror therapy which was 30 minutes per day for 5 days a week for 4 weeks

(165). However, in the exploratory relationship that was conducted between the effect size and the number of minutes in either motor recovery or functional capacity, no pattern was discover. This led us to the big question of how much mirror therapy is needed to influence the effect of motor recovery after stroke. This was similar to other published reviews (103,165). It was recommended from the Second Stroke Recovery and Rehabilitation Roundtable meeting (59) that it is essential for future research to investigate the best dose of the therapy for stroke rehabilitation interventions. This is also the case with mirror therapy (103). Future studies need to obtain the best dose for lower limb mirror therapy to improve the desired outcome.

Also, an attempt to detect if the results are sensitive to change while using different outcome measures was conducted. Brunnstrom stages of recovery and the range of motion appear to be the proper scales to indicate motor recovery change. While the FAC, 10 m walking, and tempo-spatial parameters of gait might indicate the changes in improvement of functional capacity. However, due to the high heterogeneity across the scales used in studies, it was difficult to reach a definite conclusion. Further investigation is required to know the best outcome measures to be used to detect the changes in motor recovery and functional capacity after using mirror therapy.

Limitation of the review

It would be better to use individual participant data rather than group-level data in order to produce precise answers for the review questions. It was not possible to apply this golden method to the review for the following reasons: the time limitation of the PhD program and

the difficulty of having international authorship with all the authors of the included studies, and the ethical issue of sharing participants' data with us unless ethical approval was obtained. All of these limitations hamper the use of this method.

In addition, the total number of included studies and the number of participants were small, which might not provide enough statistical power to support the results. Alongside this, the high risk of bias and the methodological limitation among the included studies made caution necessary when interpreting these results.

Another limitation of this review was including studies written in English or Arabic only, which might create a publication bias. However, these studies were carried out across a variety of international centres or hospitals.

Strengths of this review

The main strength of this review was the investigation about the influence of time after stroke, the severity of paresis and the dose of therapy on the recovery. To our knowledge, this is the first review to examine these factors using comprehensive subgroup meta-analysis for lower limb mirror therapy.

Using specific time points after stroke in this review such as time from more than one week to less than two months, and avoiding the use of the "acute, subacute and chronic" terms help to decrease the uncertainty. This might provide more accuracy to understand the influence of time after stroke among the included studies, which might help in designing the initial step for further investigations.

Also, transferring the scores of motor impairment among the included studies to three categorisations might help to potentially understand the influence of severity of paresis on the recovery.

In addition, comprehensive searching in multiple databases without a date limitation provide strength to the search strategy that was develop. Also, having two independent researchers in all the process might limit the bias of this review.

Conclusion

Using mirror therapy improved motor recovery and the functional capacity of the lower limb after stroke. According to the subgroup analysis, participants less than six months post-stroke might show an improvement in motor recovery, while participants from two- six months and more than six months post-stroke might improve their functional capacity. Also, participants with severe paresis might show more improvement in motor recovery and functional capacity after using mirror therapy. The difficulty to find a dose-response relationship especially in the primary analysis that focused on motor recovery among the current evidence urgent the need to identify the dose of mirror therapy. However, because of the high risk of bias in the current literature, these findings need further investigation to draw definite conclusions and to make clinical recommendations Also, the lack of reporting in the technical details such as the tool and any modification used suggests the need for future interventions to be clearly described by following the TIDier guideline to allow better use of the lower limb mirror therapy. A future recommendation to confirm on who might benefit and when, and to investigate how much lower limb mirror therapy to improve motor recovery is still needed.

chapter 3. User perspectives on the design and set-up of lower limb mirror therapy equipment after stroke

3.1 Introduction

As it was highlighted in the introduction and the systematic review chapters, the current evidence presents challenges to adopting MT as an intervention for the lower limbs, the unclear methods, the lack of protocols and the insufficient technical details reported make replication difficult. To the researcher's knowledge, there is no evidence that the users of MT have been engaged in the development of the equipment in any of the published studies despite the user-centred design being considered crucial to the uptake and use of such technology (174,175,243). These limitations hamper the use of evidenced-based lower limb MT by stroke survivors and clinicians.

Objective

The purpose of the developmental work presented here is to co-design lower limb MT equipment and setup for ankle exercise from a sitting position that can be used in stroke survivors' own homes by working directly with stroke survivors and physiotherapists.

Research question

What is a user-friendly, feasible design for a mirror therapy device, for stroke survivors and Clinical physiotherapist, for the rehabilitation of the lower limb after a stroke?

3.2 Method

3.2.1Design

User centred system design via co-design approach was used through two sets of focus groups.

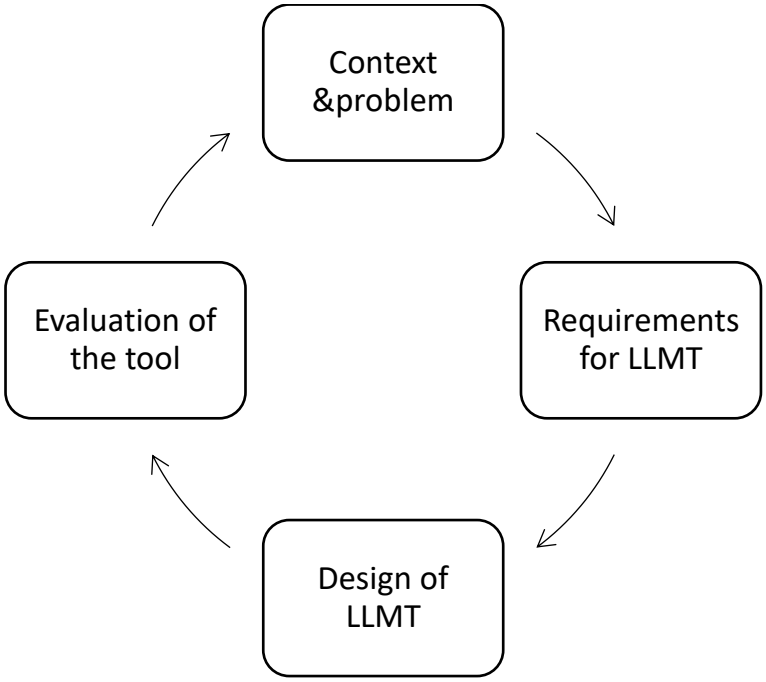


Figure 3-1 The iterative, cyclical process of the user-centred system design study. The cycle starts with identifying the main problem and context of using the design. After that, the user's requirements are identified by conducting a focus group. Then, the design is worked based on user requirements. After the design has been made, an assessment of the design is conducted with the end-user. If there any problems, the cycle starts again until reaching the final design.

The cyclical USCD process used to design the set-up of MT for use with the lower limb started by identifying the main problems users faced in the set-up of equipment. Once user requirements had been understood, the set-up of the equipment was designed according to user feedback. Later, the new set-up of equipment was tested by consulting again with the users. The cycle started again until we reached the final equipment set-up. This research and design process allowed us to change and adjust the equipment set-up at an early stage according to the users' feedback and then seek further feedback to improve the set-up's

practicality. In this project, only two cycles were carried out because of the PhD programme's time limitations.

In this study, a co-design approach was used through two sets of focus groups to understand the users' needs and to engage them closely in the iterative improvement of the lower limb MT equipment and setup (176,244). Central to the development of innovative technologies is the development of meaningful partnerships with key stakeholders (245), here defined as stroke survivors and clinical physiotherapists with experience in stroke. The most suitable method for engaging stakeholders was the focus group. Compared to one-to-one interview, focus groups enable participants to interact with and respond to the viewpoints of others (246), which allows for views to be generated and maintained through group discussion (247–249). For example, a comment from one participant on the intended mirror may trigger a series of responses from others. In addition, using prototypes of lower limb mirror therapy devices allowed for the users to consider the tool, an exploration of the idea, and enabled user-identified design benefits and challenges to be captured to produce an acceptable and user-friendly final version (250). GRIPP checklist (251) was also used as guidance for reporting the main items of the study.

3.2.2Ethics

The Faculty of Medicine and Health Research Ethics Committee reviewed this project and provided ethical approval for the study at the University of East Anglia (Reference: 2017/18 – 117). All participants provided written informed consent before taking part in the study. (Appendix- II for study approval, informed consents forms and participant information sheets for this study).

3.2.3Research setting

This research question was generated when the research team met in Movement and Exercise Laboratory (MoveExLab), and started to use the commercial mirror box that is available online for use with lower limb mirror therapy to check the possibility of using it with stroke survivors. The main issue that came up was the posture of the participant: in order to see the ankle reflection in the mirror, the user has to bend their back; this abnormal posture will be challenging for stroke survivors to maintain, even for a short period. In addition, the size of the mirror was unsuitable, as was the difficulty of holding the mirror in place to see a good reflection. The team identified the key requirements for lower limb mirror therapy while maintaining the visual illusion (see Table 3-1).

As was highlighted in the introduction, it is important for stroke survivors to practice functional activity that help them to achieve their walking goal, or at least practice key components of that task if they are unable to produce the whole sequence of the required movement.

One lower limb functional task that is important for stroke survivors is standing up from a chair (sit-to-stand). It is a common daily life activity and a precursor to walking. If a stroke survivor can stand from a seated position, then they need to practice the whole task. However, stroke survivors most likely to be prescribed MT are those with substantial paresis and, therefore, more likely to have balance challenges in performing the whole task. Therefore, practising ankle dorsiflexion in the closest position to that required for sit-to-stand performance, in this case, upright sitting, should improve sit-to-stand function in stroke survivors, and later walking. Therefore, this study's main focus was to design the lower limb mirror therapy to practice ankle exercise.

Table 3-1 Key requirements for mirror therapy directed at improving the ability to produce voluntary ankle dorsiflexion and plantar-flexion.

Requirement	**Rationale**
To enable a clear reflection of the less paretic foot and lower leg in the mirror.	The reflection needs to enable the visual illusion that the stroke survivor is watching their more paretic lower limb
To ensure that the more paretic foot and lower leg are unable to be seen by the stroke survivor	If the more paretic foot and lower leg can be seen by the stroke survivor, then this will interfere with the visual illusion
To ensure that dorsiflexion and plantar-flexion could be produced through their full anatomical range	Some stroke survivors may be able to produce voluntary ankle movement through the full anatomical range
Ensure sitting posture that: ▪ is upright and symmetrical ▪ allows 90 degrees angle at the hips, knees, and ankles ▪ It is comfortable for participants	Stroke survivors need to be comfortable and in a 'good' upright position whilst undertaking the exercise to avoid fatigue and pain whilst enabling them to see the reflection of the more paretic foot without pronounced tilting of their back or head.
Mirror therapy equipment material: ▪ Light enough for stroke survivors to set up/take down easily. ▪ Portable. ▪ It can be stored in peoples' homes when not in use. ▪ Ssufficiently robust so that the possibility of breakage is minimised.	The mirror therapy equipment needs to be (a) easy to use by stroke survivors in their own homes so that they can set it up and take it down with one hand if necessary, and (b) clinical therapists can transport it easily to and from different stroke survivors.

To meet the key requirements, a mock-up of the design for the proposed lower limb mirror therapy was made in the lab with the lab technician's help. Then the team met up again to view the mock-up and used it while testing the key requirements.

Figure 3-2 Mock-up for lower limb mirror therapy that was designed to meet the key requirements and to help building the first prototype.

The main aspects of the design were: ensuring that it could be used from sitting in an upright posture; giving users a clear reflection without bending the back; supporting the ankle to allow for unrestricted range of motion according to their available range; the ankle supporter needed to be adjustable in order to suit people of different heights; finally, the more paretic leg needed to be obscured so participants could not see it during the training session. After evaluating the mock-up, the researcher contacted the workshop in the School of Environmental Sciences at UEA to build the first, then the second prototypes for the study.

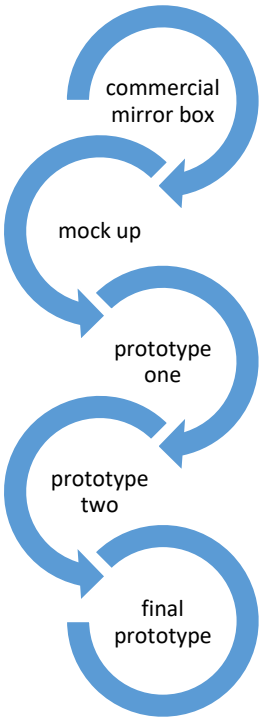


Figure 3-3 The phases of designing the lower limb mirror therapy in this project.

3.2.4Sampling framework and inclusion criteria

To select users for the process, a purposive sampling approach was used. This involves targeting participants with specific characteristics who have appropriate knowledge about the topic which allows achievement for the study aim (252,253). This allows for a range of participants to be included to ensure representativeness of the data, which might enhance the credibility and transferability of the finding (254). Therefore, stroke survivors and clinical physiotherapists were recruited according to the following inclusion criteria.

Stroke survivors were included if they were:

a) Community-dwelling participants who had received a clinical diagnosis of stroke (to be recruited after being discharged from stroke rehabilitation).

b) Aged at least 18 years and had the capacity to give consent.

Stroke survivors were excluded if they were:

c) Unable to follow and understand a one-stage command, for example, "please lift your hand."

The physical therapists were included if they were:

d) A qualified physical therapist (band five and above).

The physical therapists were excluded if they were:

e) Not currently involved in stroke rehabilitation or had no previous experience in stroke rehabilitation.

3.2.5sample size

It is essential to consider the group's size: in a small group size there might be insufficient interaction and, as a result, less likely to generate new knowledge, while in a large group size might affect participants' willingness to share their opinion and might make data management challenges. A focus group usually has between six to ten participants in each group (255).

Regarding the number of the groups, the researcher needs to consider the segmentation and saturation of data (253,256). The majority of the themes should be identified from three to six groups according to the recommendation from Guest *et al*.(2017) (257). The target was, therefore, to recruit enough participants for at least three groups per phase, unless new insights were not fully developed, in which case, more recruitment would be considered.

3.2.6 Recruitment procedure

3.2.6.1 *Stroke survivor's recruitment procedure*

Stroke survivors were recruited from stroke support groups in Norfolk, Suffolk, and Cambridgeshire areas. First, an e-mail was sent to the gatekeepers of these groups to inform them about the study and ask if they were interested in hosting a visit to the group meetings to explain the study and find potential participants. Three of those gatekeepers were interested in the study and gave access to the group. The researcher visited the support groups at their regular meeting time to describe the study, answer any questions and find potentially interested participants. For those interested, a second visit was organised via the gatekeepers and arrangements made to run the focus group during their weekly meeting time. The process is illustrated in Figure 3-4.

Figure 3-4 The process of conducting the focus group with stroke survivors

3.2.6.2 *Physical therapist recruitment procedure*

Two gatekeepers were contacted by e-mail to explain the study and to find potential participants. The participant information sheet was attached to the e-mail. One of the gatekeepers showed an interest in the study. Then, the physiotherapists recruited from the stroke unit at a local hospital. After making an appointment with the head of the rehabilitation unit, the researcher visited the stroke unit team, described the study and answered any questions. Those who were interested were asked to sign the informed consent before starting the focus group.

3.2.7 Data collection procedure

Data collection in the study was an iterative process but due to time limitations of the PhD program, involved only two phases of collecting user feedback about the development of lower limb mirror therapy.

The focus groups were held at different times and places. During the focus group, participants were seated in a circle, and the researcher was the moderator (SB). Ground rules for the focus group, agreed before the group started (253). Such as: no right or wrong answers, please respect other views, avoid talking about any personal health information during the meeting and do not discuss details outside the group.

The participants were reminded that their participation was voluntary and that they could withdraw at any time without giving any reason. All the focus groups were audio-recorded and lasted between 45 to 60 minutes. Lower limb MT was discussed in both phases, based on the key considerations listed above (table 3-1); the topic guide was as follows:

- Visual illusion:
  - A clear reflection in the mirror.
  - Obscure the movement of the more paretic ankle.
  - Ensure the distance between the mirror and the subject provides a good reflection.
  - The vertical angle of the mirror to ensure a good reflection.
  - Further feedback to improve visual illusion.

  - Ankle movement:
  - Enable the full range of motion (ROM) of the ankle joint through the available range.
  - Use of different boxes to support the ankle to allow full ROM.
  - Adaption to the seat to allow full ROM.
  - Further feedback to improve the ROM.

  - Posture:
  - Ensure upright sitting posture, and this has to allow full ROM and good reflection.
  - Use of a chair with back support.
  - Ensure comfortable 90 degrees of all lower limb joint angles.
  - Further feedback to improve posture.

  - Mirror characteristic or design
  - Size
  - Height
  - Width
  - Weight
  - Storage
  - Portability
  - Fragility and sharpness of the edges-safety of the design.
  - Further feedback to improve the design

Phase 1

After identifying the interested participants among the groups, a second visit was made to run phase one with the participants. A reminder e-mail was sent to the gatekeeper about the visit date and time. During this phase, the researcher explained about mirror therapy and revisited the purpose of the study. Participants were then invited to use both the commercial mirror box and the prototype one lower limb mirror therapy. After that, the keys consideration of lower limb mirror therapy was discussed.

At the end of the focus group, the researcher thanked the participants and reminded them that a second visit would be held to run phase two as soon as the second prototype was ready.

Phase 2

After constructing prototype two of the lower limb mirror therapy, e-mails were sent to the gatekeepers to arrange a second visit to the groups.

The participants were asked to use prototype two, followed by a discussion of the key considerations of lower limb mirror therapy. The focus groups were held until data saturation was reached, and no new information was generated by the groups (253).

3.2.8 Data analysis

After taking the feedback from stroke survivors and the physiotherapists, a verbatim transcription was made for each focus group discussion; each participant was given a unique ID code to ensure anonymity and any written data were stored in a locked area in the university; electronic data were stored on the university secure password-protected computer in line with protocols and data protection.

Thematic analysis was conducted, which involves discovering and interpreting pattern and meaning within the data (258). In qualitative analysis, the thematic analysis approach usually contains deductive and inductive analysis. The inductive approach is more suitable in grounded theory, where the researcher needs to search for themes with no prior assumption. By contrast, the deductive thematic analysis uses pre-defined codes and themes, which help the researcher to answer the research question (259). In this case, the study aim was to explore ideas about design aspects that had been identified previously as well as allow for new ideas to be generated by users that had not been specified before. The analysis proceeded as follows:

1. Familiarisation of the data.

The researcher conducted the focus groups then used a verbatim transcription afterwards the discussions. Using this method enabled the researcher to have enough familiarisation with the data.

2. Generating initial codes.

Initial codes were created using the NVivo software (NVivo 12 Pro) and manually. These codes were prespecified to meet the required requirements of the design. Any additional new codes were recorded as additional thoughts.

3. Searching for themes.

Then, after having all data coded, similar themes among the groups were searched. After that, themes were generated. Then, NVivo software was used to generate codes in each group, the codes were connected among the groups using node characteristics in the software to help allocate the proper feedback under each code to help creating themes and sub-themes.

4. Reviewing the themes.

The themes related to the design of the mirror and the set-up were then reviewed. Then, additional themes that had not been pre-defined were identified and a separate section created for these. A second reviewer read the transcripts to check the themes and codes and to enhance the trustworthiness of the analysis (254,260). The intention was to discuss any disagreement and, if necessary, to refer to a third party, but no major disagreement occurred.

5. Defining and naming the themes.

The data were then organised under each pre-defined theme while additional themes that had not been specified were placed in a separate section. Data from the nodes in Nvivo was gathered in a word table to generate the final themes. To make sure that no data was missing, the researcher used charts and notes to finalise the ideas from the groups

6. Producing the report.

These findings were then discussed with the supervisory team and fed iteratively into modifications to the design in producing the final prototype device.

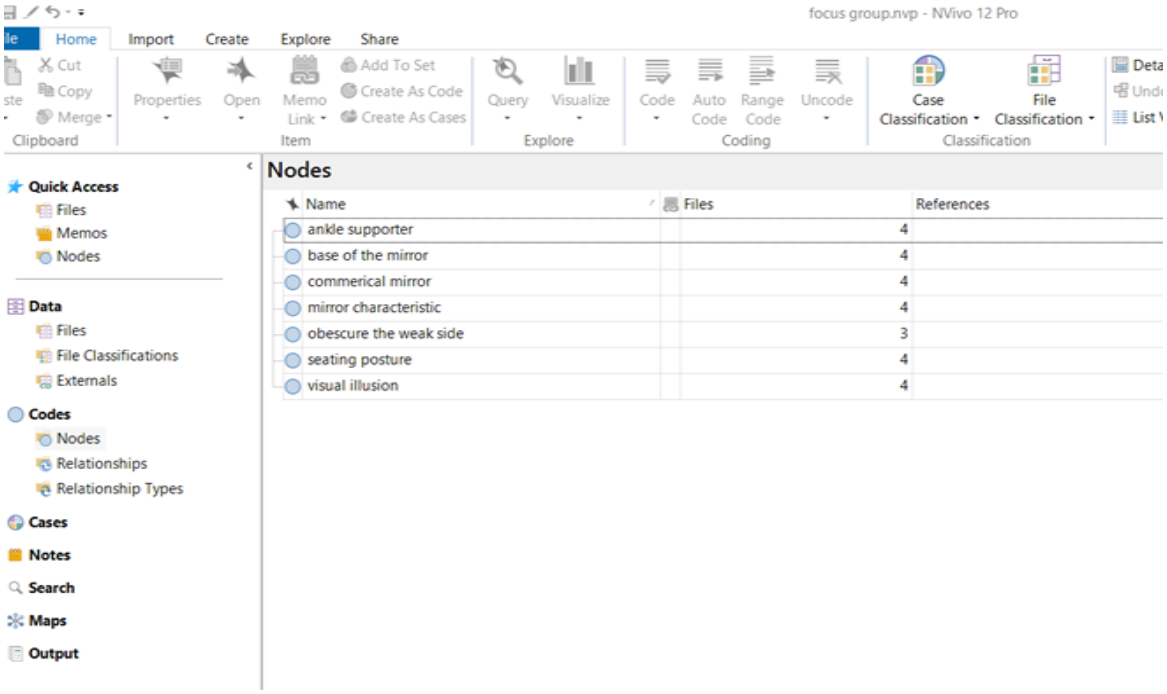


Figure 3-5 Common themes among the groups using the nodes in NVivo.

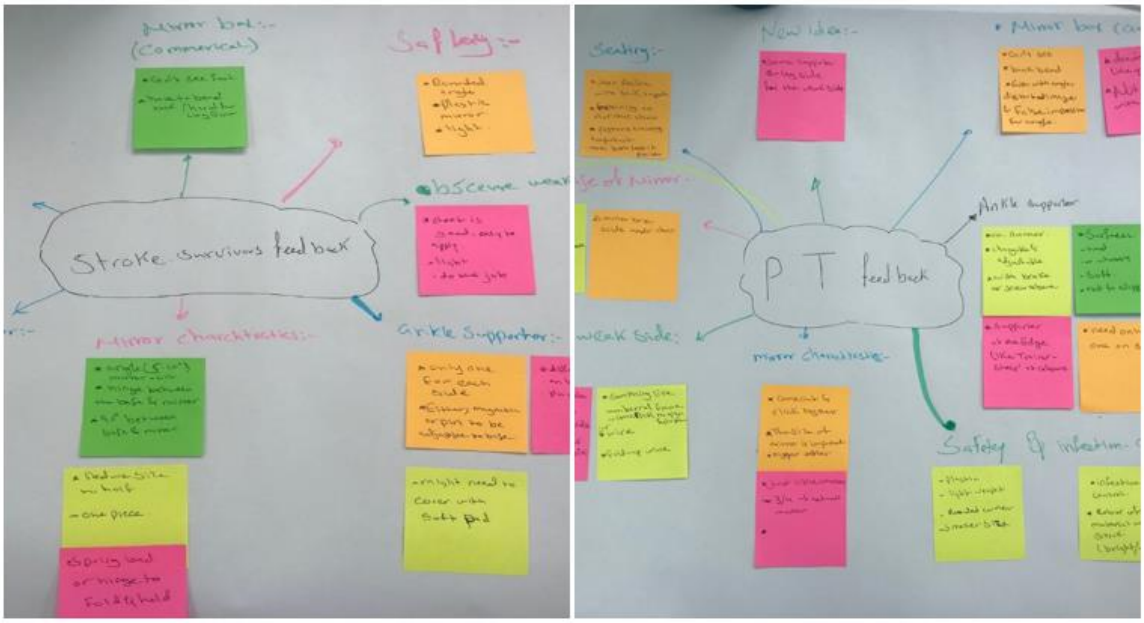


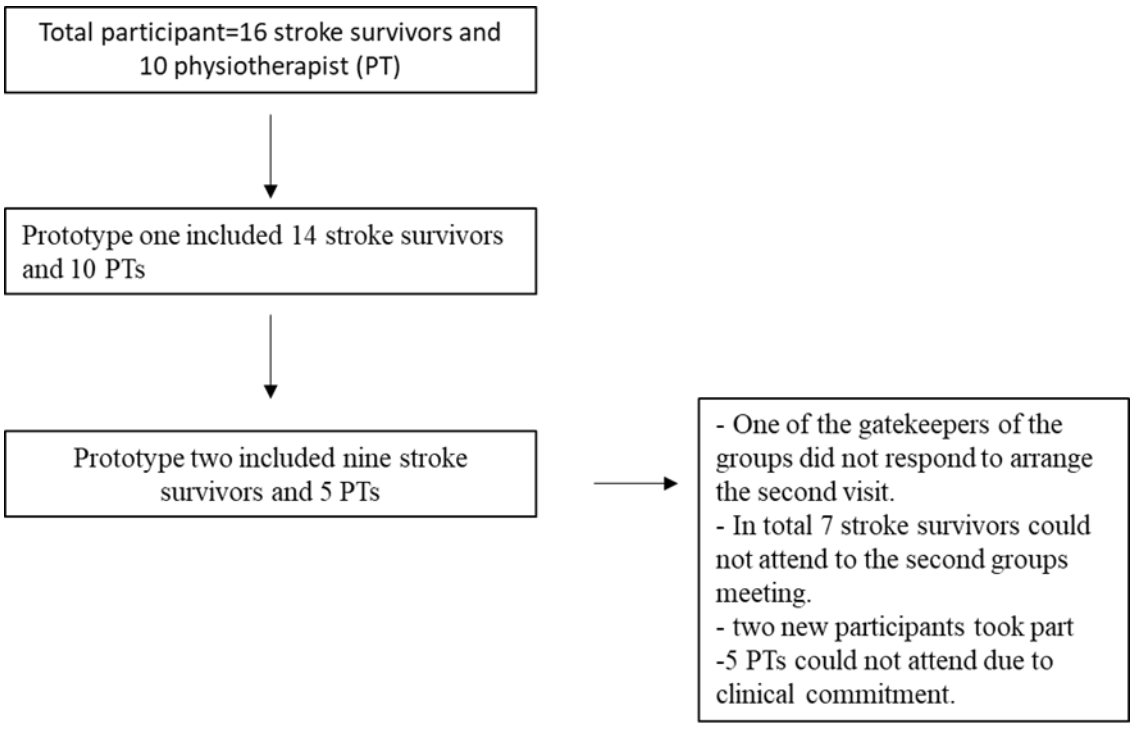
Figure 3-6 The stroke survivor's and PT feedback using a chart and different sticky notes to highlight the main ideas

3.3 Results

3.3.1 Participant characteristics

Twenty-six participants (10 physiotherapists; 16 stroke survivors) aged between 30-70 participated in this study involving eight focus groups (five groups in phase I, three groups in phase II). All physiotherapists were recruited from the stroke rehabilitation service at a local hospital. All stroke survivors were recruited from local support groups, and the stroke had occurred more than six months before the start of the research. There were twelve males and four females; all lived independently in the community. All participants provided written informed consent before being recruited to the study.

Table 3-2 the flow of the participants in the two phases of the study.



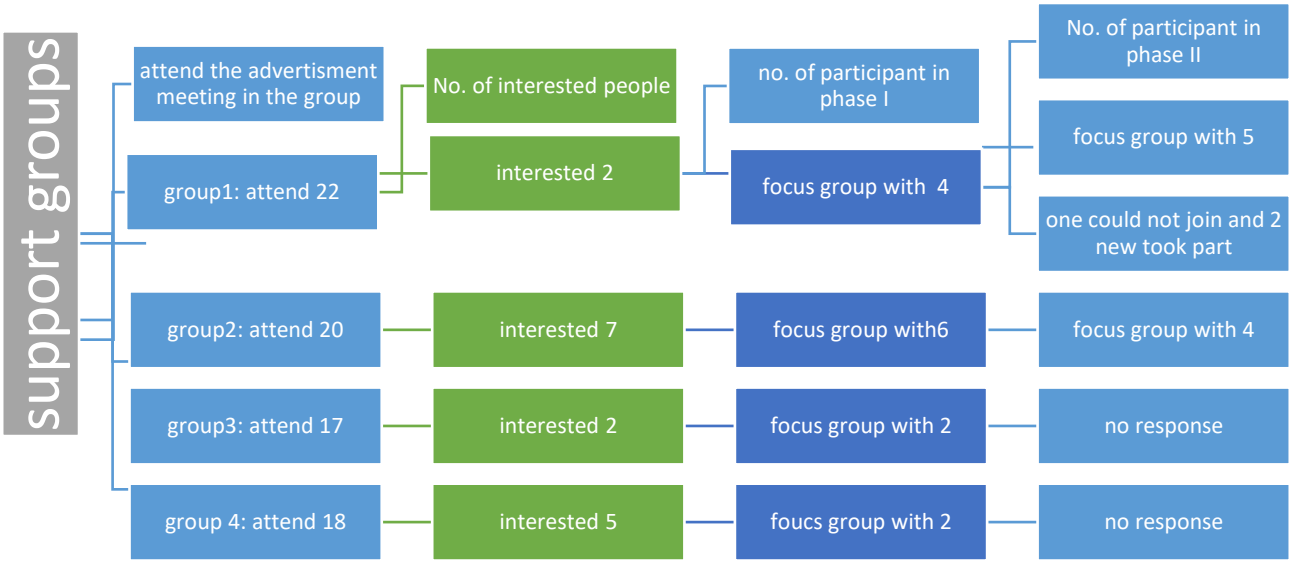


Figure 3-7 The number of support groups, and stroke survivors who attended the first meeting and who joined phase I, then phase II.

3.3.2 Best equipment set up

To define the best equipment set up for the lower limb mirror therapy, this project was divided into two main phases. These phases were incorporated with the users to identify the best equipment set-up and main key considerations in the design.

3.3.2.1 *prototype one*

This phase focused on the usability of the commercial mirror box and prototype one. Key considerations for both designs are listed below.

Figure 3-8. A) prototype-one (on the left side), b) commercial mirror box (on the right side) that were used in the focus groups during phase I.

Prototype one characteristics:

- Size of the mirror 90×60 cm.
- The mountain board is 100×70 cm.
- Sharp corners.
- The mirror was separated from the base.
- The angle of the mirror and the ankle supporter were adjusted using screws.

After analysing the feedback from the stroke survivors and physiotherapists, common ideas arose among the groups regarding the commercial mirror box and prototype. Specifically, there was a high similarity between the groups regarding the key consideration of the lower limb mirror therapy.

Both stroke survivors and physiotherapists were dissatisfied with the commercial mirror box design. The design's main issue was that they couldn't see a good reflection of the foot in the mirror and that they had to bend their back to see the ankle, or angulate the mirror to be able to see, which gave a distorted image of the ankle. Both users (stroke survivors and physiotherapists) did not recommend using it with the lower limb after a stroke. The

participants were more satisfied with the design of prototype one lower MT. They could see the lower limb easily by keeping a good body posture. The main aspects of the design were discussed among the groups, and the following ideas were put forward:

- Mirror angled between 5 to 15 degrees is essential to maintain a good seating posture while seeing the real ankle reflection.
- For the usability of the design with stroke survivors, the mirror parts need to be connected.
- The ankle supporter needs to be movable with pins and holes to adjust according to people's leg lengths.
- Obscuring the weak side is essential; the sheet is a practical and straightforward idea.
- The size of the mirror and the base need to be cut to the half size of the original one.
- For the safety of the design, the corners need to be rounded using plastic material to avoid injury. Also, materials need to be easily cleaned with alcohol wipes to prevent infection.
- Stroke survivors asked for a lighter material that would help them to set up the tool and store it easily in their homes.
- It was considered important to maintain an upright seating posture by using a regular chair with back support.

Table 3-3. Codes and themes from phase I about the commercial mirror box and the prototype one lower limb mirror therapy from both groups

Codes	***feedback stroke survivors***	***Physiotherapist***

Commercial mirror box	• Can't see their foot, have to bend their back which is hard for them
	• distorted image
	• not good design
		• Can't see the foot.
		  • Have to bend the back to see
		  • Even with the angle, distorted image, and false impression of the foot.
		  • Not recommended for use for lower limbs

Prototype one LLMT	***feedback stroke survivors***	***Physiotherapist***
The angle of the new mirror *(reflection)*	• 5-10-degree angle to see the foot without bending the back	• 10-15 degree of inclination of the mirror to able to see the foot without bending the torso. • The bigger mirror is better to see the foot.
Mirror parts	• Hinge or spring load to connect the mirror with the base, preferably one piece.	• Connect and click together, to use with a patient who has one hand strength.
Ankle support	• Need one on each side only, pin, or different slots to adjust according to person height or use magnetic supporter so easy to use. • Need to be covered with soft padding.	• Better on a runner with brake. • Or screw above to adjust the position according to patient height. • Needs to have one supporter on the side, movable and adjustable. • Different surfaces; hard, soft, wobble. • A not slippery surface like the current one. • Curve in the middle to support the ankle, like the one in trainer's shoes with soft padding.
Obscure the weak side	• The sheet is a good idea and easy to use.	• The sheet is a good idea. • Maybe a big mirror to hide the weak side. • Frame & cover it with fabric, so fully obscured. • Use something like an umbrella frame to click to open and close. • Use wireframe to fold up
Mirror characteristics *(size)*	• The mirror needs to reduce to half the size of the current prototype. • Use a big box for the mirror • Hinge or spring load to connect parts	• Keep ¾ the size. • The bigger mirror is better to see the foot
The base of the mirror	• Smaller, narrow base than the current one, that can be slid under the chair	• Different surfaces: use texture to prevent foot sliding.

	• Hinge or spring load to connect the mirror to the base • Preferably a one-piece base	• Use rubber underneath to prevent sliding the tool if someone has a laminate floor.
Storage and portability	• Handle on the mirror so easy to carry • Lighter weight • Able to store it in the house easily	• One-piece, easy to store
Safety of the design	• Rounded corner • Plastic mirror • Lighter weight	• Plastic mirror • Rounded corner • Lightweight • Smaller size
Sitting posture	• Preference for upright posture with back support. • Use regular dining chairs.	• Teach the patient how to sit and use mirror therapy. • Use a regular chair with back support
Another idea	• Use para-scope above so you can adjust and see the foot easily • Use a big box for the mirror. • Use another mirror in front of the foot to see the reflection and the foot easily • "I like the idea of including us in the design of the equipment, that's very nice." • "We will be motivated to use the equipment because of the simplicity of the design" • Needed are clear instructions, e.g., where to place the foot • It is important that the cost of the mirror therapy equipment is reasonable so that it can be used by most people	• Use some support for the weak side to prevent the leg from externally rotating.

The following themes not directly concerning the design came up while discussing the use of mirror therapy:

1- The lack of use of lower limb mirror therapy in clinical practice. Most users were concentrated on the upper limb rather than the lower limb.

2- The stroke survivors highlighted the importance of the practicality of the design. If the design was simple and easy to use, the stroke survivors would be motivated to use it without asking for help or waiting for their carer to adjust it for them.

3- Clear instructions for the use of lower mirror therapy are needed. For example, when one of the stroke survivors used it during the focus group, the foot position was away from the mirror and therefore didn't work for her, which was frustrating. When the explicit instruction is provided to place the foot close to the mirror, it changes the whole idea to make it work.

4- It is essential to ensure that mirror therapy is affordable and accessible for everyone to buy and use, or make it available in the hospitals, so that the NHS covers the cost if it is too expensive.

5- It is essential to make the setting of the lower limb mirror therapy relevant for both home and hospital use.

Figure 3-9 the usability of lower limb mirror therapy

These are the main themes that emerged from the first phase of the focus groups with stroke survivors and physiotherapists. All the requirements of the end-users were sent to the workshop engineer so that changes could be made to the prototype in line with user requirements. Due to the time limitation of the PhD, most changes were made based on feedback from phase one. Because of time limitations, the main changes were made to the size of the mirror and the base only.

3.3.2.2 *Prototype two*

In this phase, prototype two was taken to the end-users to collect their feedback about the design, especially the mirror's size, and to check the usability of the design for use in rehabilitation.

The prototype two main characteristics:

- adjustable angle of the mirror to the base between 5 and 15 degrees to allow clear reflection of the less paretic foot;
- people undertaking MT to be seated in a regular dining chair for back support to allow an upright posture and minimize fatigue;
- adjustable position of the foot support using a system of pins and holes to allow easy adjustment according to the leg lengths of individuals;
- round corners to the mirror and its mounting board to minimise injury potential;
- mirror dimensions reduced to 60×40 cm.
- base and mirror mounting board made with a plastic material, to enable easy cleaning.

Figure 3-10 Prototype 2 of lower limb mirror therapy: changes were made to the size of the mirror and the base; the ankle supporter were adjustable with pin and holes, and corners of the frame were rounded for user safety.

The main feedback in phase two was similar among the groups: both stroke survivors and physiotherapists were satisfied with the design of the mirror, but their main feedback about it was as follows:

1- the smaller size of the current version works better as it helps reduce the weight of the equipment.

2- The angle of the mirror to the base needs to be varied in the range of 5 to 15 degrees from the midline using frame rather than screws.

3- Lighter weight material to carry the mirror tool with one hand would be preferable.

After this feedback, a meeting was arranged with the workshop engineer to discuss the available options to change the design according to the end-user feedback within a reasonable time period.

Table 3-4 Codes and themes for prototype two from both groups

Codes	Stroke survivors' feedback	Physiotherapist feedback
Overall design	• Approval of the overall design • "I like it" • "I can see all my foot. personally, it's perfect for me like this, that's all you need for not leaning over" • "that's brilliant" • "its clever the concept of this" • "I can see my foot" • "It's good and seems is much lighter, I can see my foot" • "it's much better than the last one."	• Approval of the overall design • "that's a lot better"
Size	• Reduction of the size is still needed • "it's too big; smaller will be better" • "if you could reduce the size of the mirror." • "you definitely can reduce this size, no doubt about it"	• Reduction of the size is still needed • "yeah that's quite heavy now"
One piece	• The need for connected one piece • "yeah, I need it to fold up and put it away somewhere, I'm happy with the size; the sheet is good" • "yeah, just try one piece" • "hinge to each other to make it connect, with this (meaning the base with the mirror), and handler on the base "	• approval for one piece • "That will do" • Can use it with one hand
Angle	• Importance of the angle • Different angles of the mirror would be preferable to allow sight of the ankle and avoid having to bend the back • "five-degree angle for the mirror will be good, so it can see your ankle without bending over if the mirror is leaning over 5 degrees; that's what we need is the solid angle." • "yeah, if it's too much, then you will get a distorted image of the ankle that would enable you to see it" • "you might want to go with 10 degrees," • "the angle is important, I think" • "The only thing I would say, when you are fixing the angle, it will be good even in the finished part. It would be good if you could vary the angles if you need to, adjust the angle because someone with a huge leg might be different with small feet, I don't know"	• Importance of the angle • The mirror needs to be angled to allow a clear reflection, but with a certain limit to avoid a distorted image. • "how much is the mirror tilted, then that might distort the image" • "the angle is an important issue, the more the angle, the more distortion you got"
Usability	"yeah, I need it to fold up and put it away somewhere, I'm happy with the size; the sheet is good"	• "yeah, as soon as I got it in place, I don't need to keep taken it apart. If they can use it every day, they might have some space in their house"

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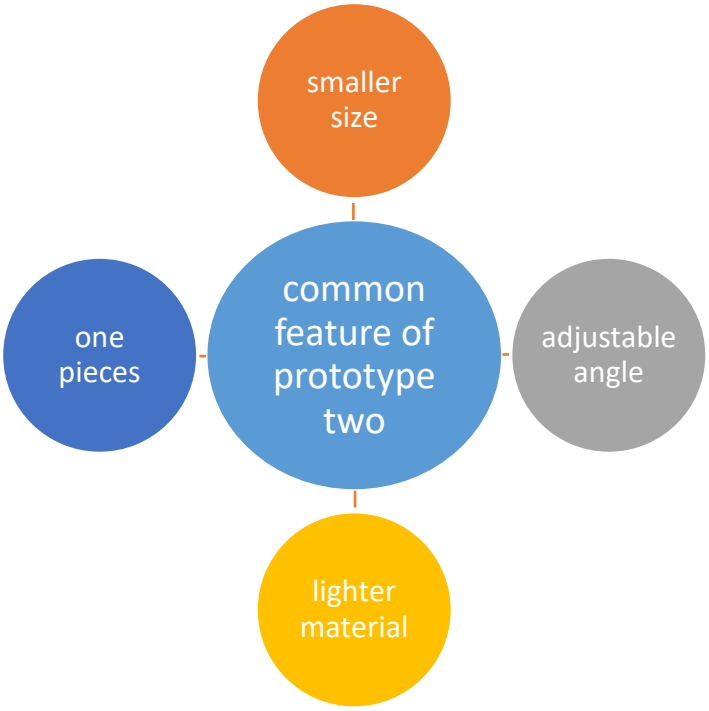


Figure 3-11. The common features of the second prototype lower limb mirror therapy.

3.3.2.3 *The final mirror therapy equipment and set-up*

The final design of the lower limb mirror therapy was made according to the end-user feedback. All user's requirements were met as closely as possible. The final prototype of the lower limb mirror therapy met the main considerations of the design.

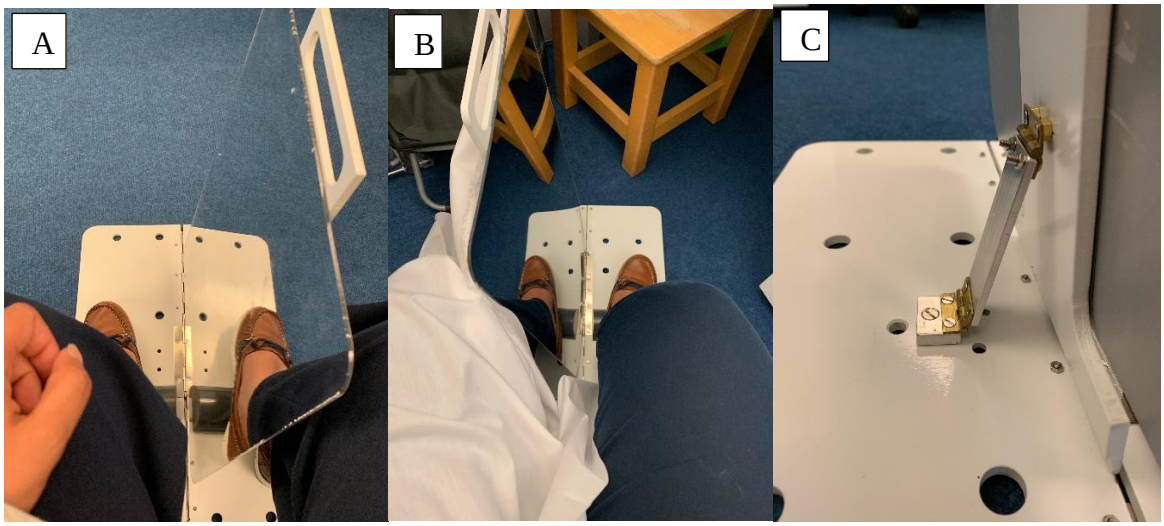


Figure 3-12 The final prototype for lower limb mirror therapy; a) overview of the mirror with rounded corner with handler at the top, b) the foot is resting on the ankle supporter with the sheet covering the weak side. c) The adjustable frame at the back of the mirror allows a change in the mirror's angle with three slots at the base that allows 5, 10 or 15 degrees.

The main characteristics of the final prototype mirror are:

- Users can sit in an upright posture on a regular dining chair with back support whilst seeing a good reflection of their less paretic foot;
- The more paretic lower limb is covered by a sheet that is attached to the back of the mirror mounting board;
- The mirror is composed of a good quality plastic mirror (acrylic) with rounded corners to reflect the right image and for the design's safety.

- The dimensions of the mirror are 51cm ×37 cm;
- The dimension of the mirror mounting board is 58 cm× 7.5 cm; The mirror mounting board is connected to the baseboard with a hinge and 14 cm wide handle so that the equipment can be folded flat and carried;
- The mirror-to-base angle is adjustable in positions of 5, 10 and 15 degrees from the vertical line, with an adjustable frame attached to the back of the mirror mounting board;
- the foot support is adjustable with a pin and holes system providing different positions for people of different heights; also, it helps produce the full available range of motion for ankle movement;
- The dimensions of the base are 43 ×35 cm, and 43×17cm when folded; with a rubber underneath to prevent sliding.
- The mirror weighs two kilograms.
- The material of the mirror makes easily cleaned to prevent infection.
- The mirror is connected to the base with a hinge to make the storage process easier for the stroke survivors;
- Explicit instruction for the stroke survivors has to be delivered to avoid any misunderstanding.

Figure 3-13 Prototype One, Prototype Two, and final mirror therapy equipment and setup

A. Prototype One: mirror was supported by screws at the base to adjust the angle. Also, the ankle supporter was attached to the base with screws; the mounting board was bigger than the mirror size with a sheet attached at the back to cover the weak side. B. Prototype Two: changes in the size of the mirror and the base; the ankle supporter was adjustable with pins and holes system, and corners of the mirror were rounded. C. Final mirror therapy equipment and setup: an overview of the mirror with a rounded corner with a handle at the top; the foot is rested on the ankle supporter with the sheet covering the weak side. An adjustable frame at the back of the mirror with three slots at the base allows the angle of the mirror to be set at 5, 10, or 15 degrees.

3.4 Discussion

The aim of this study was to produce equipment and set-up that can be used in stroke survivors' homes to deliver MT ankle exercise. To our knowledge, this is the first such co-design with stroke survivors and physiotherapists of an MT device for lower limb rehabilitation after stroke. There were a few studies that assisted us with the initial design of the mirror and the set-up (165), but these used a mirror twice the size of our final product to ensure that the more paretic limb was obscured (121,170,173). Stroke survivors in this study preferred using a sheet to cover the more paretic lower limb as this reduced the weight of the equipment and enhanced the usability of the tool.

Most of the stroke survivors preferred to use the mirror in the midline between lower legs, which is in line with an earlier investigation using a mirror perpendicular to the midline (103). However, they preferred to perform the ankle exercise MT in an upright sitting posture using a standard dining-type chair and preferred to adjust the equipment rather than bending their back or tilting their head to see the reflection. Other investigations do not appear to have considered participants' posture and how sustainable this is over the exercise period. For example, participants were in half lying or sitting position involving trunk flexion (173) and trunk inclined towards the less paretic side to allow the view of the reflection of the lower leg in the mirror (224). Also, few studies mention the mirror angle (225,234), such as the mirror could be on the acute angle between 75 and 85 degrees (234). By contrast, our participants highlighted the importance of the angle to prevent having to shift the body to see the reflection, and they recommended that the angle needed to be at a restricted level to avoid distortion of the images.

Strength

This study's main strength was the use of an iterative process to incorporate the views of stroke survivors and physiotherapists in improving the design of lower limb mirror therapy prototypes. Also, having two completed set of the iterative process provide in-depth insights about the required set-up and the design.

Limitation

It is recommended to bring other partners such as engineers in a multidisciplinary team meeting to bring together participants views, but PhD timeline and resources did not allow for that.

Also, including the participants from stroke support groups in their chronic time after the stroke limited the feedback as they become more independent. However, getting feedback from stroke survivors at different times and stages of recovery might highlight other challenges in using lower limb MT. As participant early after stroke or who had severe paresis might have some challenges in set-up the tool individually.

Conclusion

Nonetheless, this study provides clinicians and researchers with some ideas about setting up of MT to produce ankle exercise; these results need to be used in subsequent studies to check usability.

chapter 4. Maximum tolerable dose of lower limb mirror therapy after stroke

4.1 Introduction

The introduction and the systematic review chapters, especially in the primary analysis of the systematic review chapter of this thesis that investigate the influence of dose on motor recovery, highlighted the variation and the insufficient dose reporting in the current literature about mirror therapy. The few studies that report the doses are variable in terms of quality. Furthermore, little justification is provided for the chosen doses (190), this is due to a lack of appropriate experimental designs and dose-response relationship in improving motor recovery as identified from the systematic review of this thesis (Chapter 2). This stressed the need for dose-finding studies to determine the MTD as an early phase I dose. Then, the identified MTD can be used in a subsequent dose-ranging study to find the recommended Phase II dose (RPTD) for evaluation in later clinical efficacy trials (261,262). This will help to save time and reduce the number of participants (261).

Dose-finding trials can be divided into two groups: rule-based design or model-based design (263). The rule-based design is simple and more accurate in targeting doses. The model-based design is complex and needs preceding knowledge to conclude the dose-response curve, requiring expensive complicated statistical software (264). These designs protocols are well defined in pharmacological research for medication. This is not the case with stroke rehabilitation, as this consider an area under investigation (59). However, to the researcher knowledge, there are two studies conducted dose-finding studies in stroke rehabilitation (59,89). One used the rule-based design (265), while the other used the model-based design (266).

Both studies used the common 3+3 design, which considered the most common design in Phase I pharmacological studies (195,267). It allowed the sample size to be decreased as this

is challenging in stroke rehabilitation (268,269), and provided a precise design about dose (267).

In the model-based design, they used the dose escalations method only and applied a high number of doses from the first cohort, which led to stop the study after the second cohort. While in the rule-based design, they used the Modified Fibonacci Sequence (mFBS), which considered one of the most common methods to increase the dose. The mFBS allows large increases initially, when adverse consequences tend to be less (270) then a smaller incremental increase later, when the adverse consequences tend to be greater. The mFBS reduced the likelihood of subtherapeutic doses being used and provided acceptable doses spread to help assess the dose-response relationship (270). In addition, they used the pre-set rules, which help to escalate and de-escalate the dose simply, check the dose, and stop the trial (265). However, none of these designs was used before in mirror therapy.

In conclusion, to the Researcher's knowledge, a review of the literature revealed no studies have investigated the MTD for mirror therapy to improve motor recovery. Therefore, dose-finding research is needed to investigate the maximum tolerable dose (MTD) per day of ankle dorsiflexion/plantarflexion exercise delivered via mirror therapy.

The purpose of the study

To identify the MTD per day of mirror therapy for the lower limb, specifically, ankle exercise. The results will inform a subsequent dose-ranging study, which in turn will inform the design of an efficacy study of mirror therapy. In addition, the results will provide some initial guidance about dose setting in clinical situations, based on research evidence.

Research Question

What is the maximum tolerable dose (MTD) a day of mirror therapy for ankle dorsiflexion for use in a subsequent dose-ranging study?

4.2 Method

4.2.1 Design

To find the MTD a dose-finding via a 3+3 rule-based, dose escalation/de-escalation and the mFBS, was used (265). This is considered one of the earliest research designs to be used for dose-finding in rehabilitation. It was also, recommended by the second Stroke Recovery and Rehabilitation Roundtable (59).

4.2.1.1 *Starting dose and subsequent doses*

The study started with the first cohort (n=3), then each of the subsequent cohorts were also of three participants. The starting dose was 15 minutes per day, as this is the lowest number of minutes used in the current literature about mirror therapy (9). The participants were asked to do ankle exercises (see introduction chapter for justification) for two weeks in their home (details below). In this study, the frequency of training was daily ankle exercise for 14 days. The total training length was two weeks, as the previous literature suggests that improvement in motor function occurs in response to two weeks of training (271). The duration of the training session e.g., 15 minutes, was defined by the total time (in minutes) per day participants spent on ankle exercise mirror therapy for that cohort. The participants were provided with a daily record form to report the number of the achieved minutes per day. Then, the second and subsequent cohorts exercised at a dose set in accordance with the nine pre-set rules and the modified Fibonacci sequence (mFBS) (table 4-1).

In this study, the mFBS was used as follows: the initial dose D1 was 15 minutes per day. If the results from the first cohort were positive, and depending on the pre-set rules, the dose increase for the second cohort was to be 100% of the first dose, i.e., D2=2×D1. Thereafter, as

long as a next cohort was required, and following the pre-set rules, the incremental increase would be 67%, 50%, 40% and 33% of the preceding dose. However, If the dose needed to be decreased, it would be 50% of the previous increment. If this occurred after the starting dose, the following dose would be decreased to 50% of the starting dose.

Table 4-1. Modified Fibonacci sequence (mFBS) for dose escalation.

Cohort	mFBS	Dose (D) increments	Dose (in minutes)
1	D_1	D_1	15
2	1.00	$2D_1$	30
3	0.67	$1.67D_2$	50
4	0.50	$1.5D_3$	75
5	0.40	$1.4D_4$	105
6	0.33	$1.33D_5$	140
7	0.33	$1.33D_6$	186
8+	0.33	$1.33D_{7+}$	247

4.2.1.2 *Pre-set rules (including stopping rules)*

The study followed the pre-set rules as identified by Colucci *et al. (2017)* (265), because these rules had previously been applied in stroke rehabilitation intervention and had been deemed applicable. The reason for following pre-set rules was to guide the dose for escalation/de-escalation and to stop the trial. This was based on dose tolerability or benefit.

A tolerable dose was defined as when two or more of the participants in a cohort adhered to the set daily dose for that cohort. If the participants were unable to adhere to the set dose for a

reason not related to the study design (such as an appointment) they were still considered as adherent (265).

The beneficial dose was defined as when two or more participants in a cohort demonstrate an increase in the outcome measures over the two-week training period (265). In addition, for this study, the dose was considered beneficial when there was an increase of one level or more in the Motricity Index (see outcome measures section) score for two participants or more in the same cohort. If the Motricity Index score did not increase, then one of the secondary measures (see outcome measures section) had to change. The changes were considered if there was an increase or decrease of 10% or more of the values from the baseline. The secondary measures also detected biological changes that might not be seen within the Motricity Index. If there was no change in the primary and the secondary measures of the dose benefit, then the stopping rules (rules 8 and 9 below) were considered.

The nine rules for determining exactly how the study proceeded are illustrated in Fig 4-1 and detailed below following the same rules as identified by Colucci *et al*. (2017)(265):

1. " The target dose was not achieved by all three participants then the consequent action was to decrease the dose by 50% of the previous increment for the subsequent cohort.

2. The target dose was tolerable and beneficial for a cohort. The consequent action was to increase the dose for the subsequent cohort.

3. If the target dose was not tolerable for the cohort, then rule 6 was applied.

4. If the target dose was tolerable but not beneficial:

    a. If there was no change in the dose benefit measure pre and post the training points for at least two of the three participants, then rule 7 was followed.

b. If there was a decrease in the dose benefit measure between the pre- and post-training measure for at least two of the three participants, the dose of the subsequent cohort was decreased by 50% of the previous changes.

5. If the dose was decreased for a cohort and then deemed tolerable and beneficial, the action for the subsequent cohort was to increase the dose by 67% of the previous change.

Rules 6 and 7 were applied to reduce the possibility of the dose being intolerable or beneficial because of the individual rather than the target dose itself (the checking rules) (265):

6. If the dose was not tolerable for two of the three participants, the next cohort received the same target dose. If this dose was not tolerable for the two participants in the second cohort, the next cohort was decreased by 50% of the last increment.

7. If a particular dose was tolerable but not beneficial for at least for two participants of the three, then mFBS informed increase of the dose for of the subsequent cohort. If that second cohort also did not show at least one level of improvement in the outcome measure, then stopping rules were considered.

   The stopping rules were (rules 8 and 9) as follows (265):

8. If after at least one beneficial dose, the subsequent two target doses were tolerable,

   but no further gains in motor function outcome were made in at least two participants in each of two consecutive cohorts, the study was stopped.

9. If the dose difference between the two cohorts (time in minutes) was equal to or less than 10%, the study was stopped."

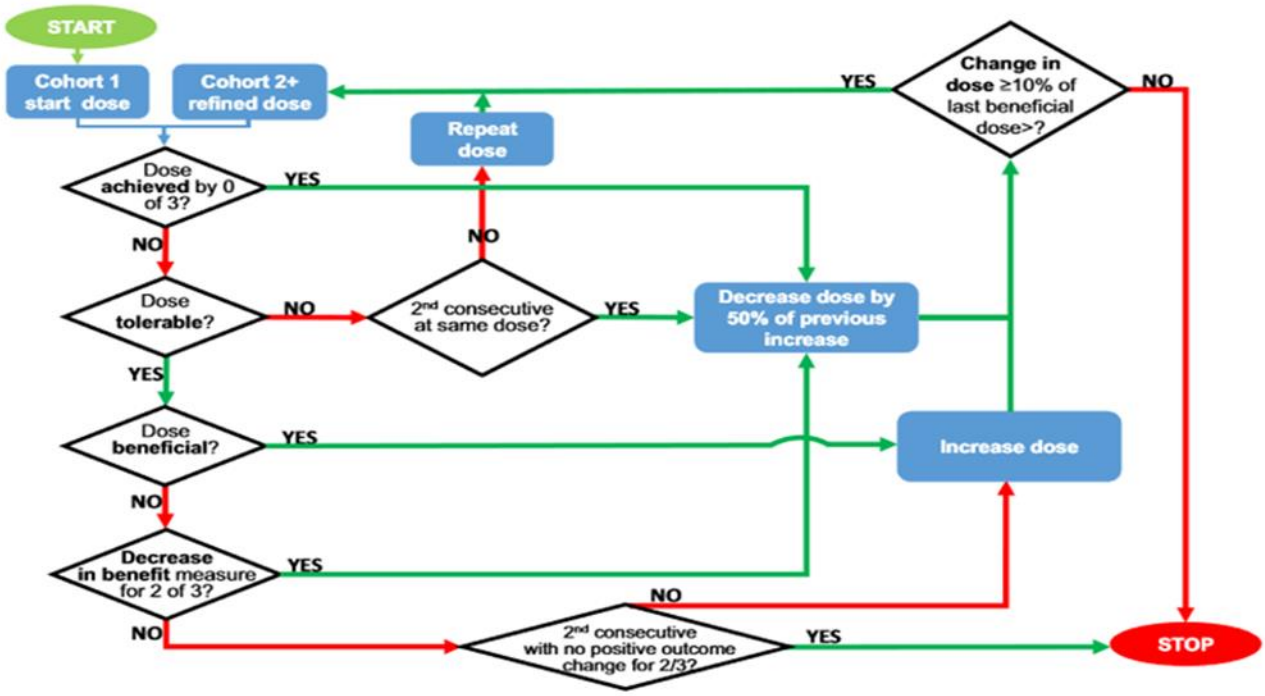


Figure 4-1 Flowchart to illustrate the dose-finding design (265)

The dose to which the stopping rules applied will be considered the MTD.

4.2.2 Ethics

The London- Stanmore Research Ethics Committee, UK (Health Research Authority) provided ethical approval for the study (19/LO/0422). All participants provided informed consent. (further information is in Appendix III). In addition, this study was registered in ClinicalTrials.gov (Identifier: NCT04339803).

4.2.3 Target population and inclusion criteria

All participants met the following criteria.

Inclusion criteria:

- Participants had had a stroke six weeks or more before recruitment to this study and had been discharged from NHS statutory stroke rehabilitation.
- Participants were at least 18 years of age.
- Ability to produce some voluntary contraction of the paretic lower limb ankle only (score between 9 to19). Justification for inclusion of people with moderate to severe paresis was that people with moderate to severe paresis may benefit more from the visual illusion induced by MT than those with mild paresis (table 4-2) (8).
- Ability to understand and follow simple verbal instructions (one-stage commands), i.e. sufficient communication, orientation and memory to participate in mirror therapy.
- Participants had had no lower limb injury in the last six months and were able to walk independently indoors before the index stroke.

Exclusion criteria:

- If potential participants had foot or ankle contracture that prevented 50% of the passive range of motion.
- If the participants had any condition that could be exaggerated by performing the therapy.

Table 4-2 Justification of inclusion criterion for Lower limb Motricity Index score

Quality of muscle contraction	Motricity index	Include in the study	Why
No movement	0	✗	Very severe paresis could improve from mirror therapy, but they might need more than two weeks to show changes.
Palpable contraction in a muscle, but no movement	9	✓	People with severe to moderate paresis could benefit from the visual illusion, and may show improvement in motor function (107).
Visible movement, but not full range against gravity	14	✓	
Full range of movement against gravity, but not against resistance	19	✓	
The full movement against gravity, but weaker than the other side	25	✗	Can already produce full movement against gravity, so exercise such as resistance training is thought to be more appropriate than the mirror therapy for this group.
Normal power	33	✗	Need a higher level of training like task-specific functional activity training (8).

4.2.4 Sample size

According to the pharmaceutical dose-finding studies, the estimated sample size could be between 12 and 40 (272). However, this is not usually pre-defined as this determined by the results of the cohorts to the set dose (264,273) and the pre-set rules.

Screening and recruitment procedure

Following the 3+3 design, participants were entered to the study in group of three, as a multi-stage recruitment procedure was followed. Some of the participants were told to wait until the current cohort had finished and the data had been analysed following the pre-set rules. If the study did not reach the stopping rules, then participants were contacted by the Researcher to set a date for a lab visit. Using this method helped to avoid over-recruiting and avoid the risk of contacting people who were not going to take part in this study.

Participants were recruited from six main settings as follows:

1. Potential participants identified by the clinical team during attendance at the 6-months post-stroke clinic.
2. Potential participants identified by the clinical Early Supported Discharge Team.
3. Support Groups in Norfolk, Suffolk, and Cambridgeshire (non-NHS).
4. Participants identified through the RHITE database (NIHR Brain Injury MedTech Cooperative).
5. Participants who gave their consent to be contacted from a previous study.
6. If the Researcher received an email from an interested potential participant who had heard about the study from friends.

Then the standard procedure was followed as set out below:

- In both 1& 2, the clinical team identified potential participants using an initial screening form. A meeting for the potential participant with the Researcher was then planned for full screening.
- For support groups, the Researcher first contacted a support group gatekeeper. If the gatekeeper agreed, then the Researcher visited the support group to explain the research to those attending and asked for potential interest in the study.
- For the RHITE data base, the Researcher emailed the PIS to the gatekeeper of the database to reach interested participants in Norfolk, Suffolk and Cambridgeshire areas.
- For participants who gave their consent to be contacted from a previous study, they were contacted by the Researcher to see if they were interested in participating in this study.
- If the Researcher received an email from the interested potential participant, then the Researcher contacted the potential participant to check if they were still interested.
- For any potential participants identified from the settings described above, the procedure was as follows:
- Potential participants were given a consent-to-contact form. This also asked for a potential participant's preferred method of contact (e.g., post, phone, email). Once a potential participant had agreed to consider participating in the study then the Researcher made contact to check that the study criteria were met. Then a full explanation of the study was provided, which included the provision of the written participant information sheet (PIS). Participants were given at least seven days to consider providing informed consent (IC) and encouraged to discuss the matter with family, friends, clinicians and the research team. At the end of this

consideration time, those people who provided informed consent were recruited as participants in this study. When a participant enrolled, a letter was sent to their GP, enquiring as to whether they had any medical concerns about their patient's participation in the study. If no concerns were raised, then the participant was formally enrolled, and start date of the study was agreed between the Researcher and the participant.

- The PIS, IC, GP letter are provided in Appendix III.

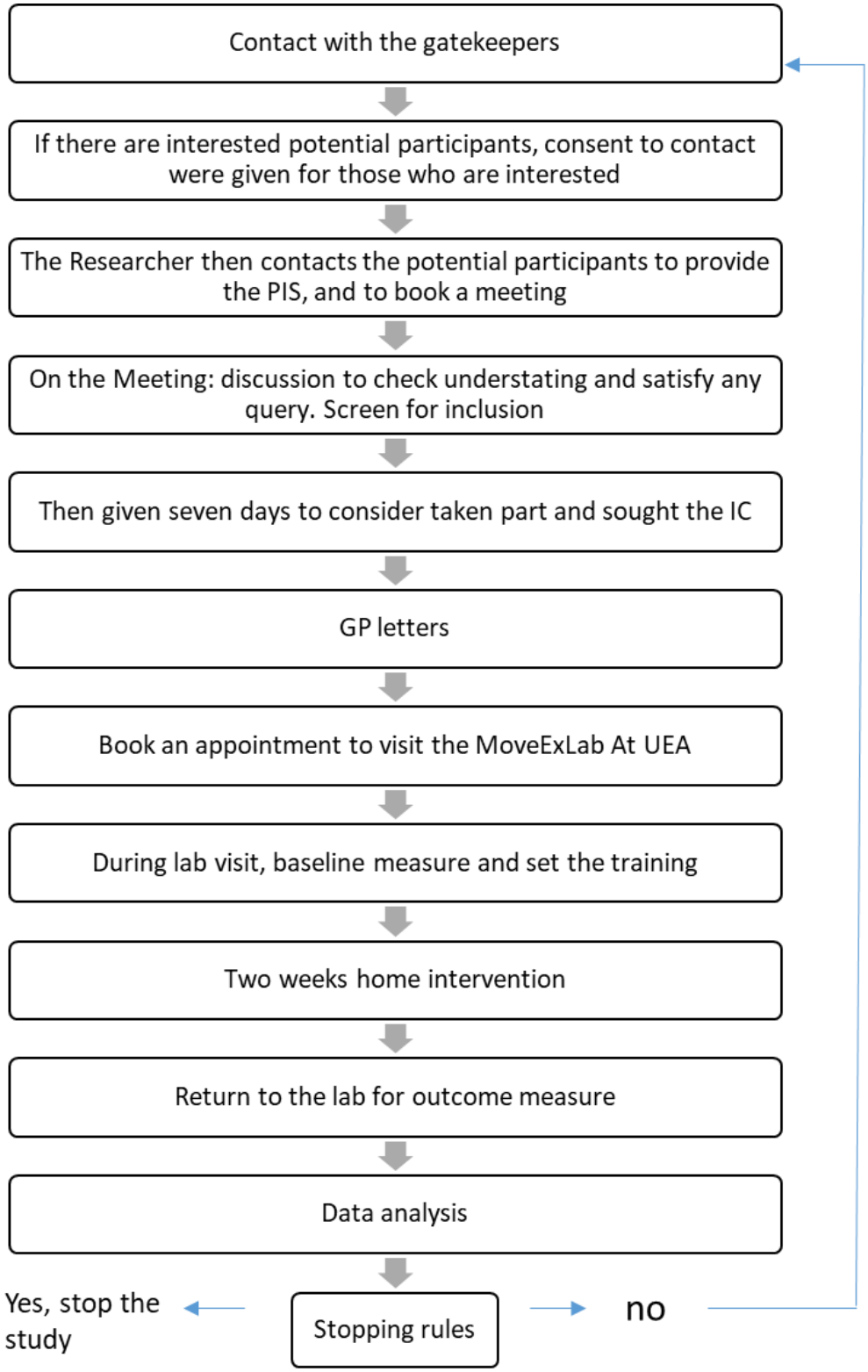


Figure 4-2 flow chart of the summary of the recruitment procedure and participation in the study.

4.2.5 Data collection and baseline measure

The following section was described in the timeline frame from the participant's enrolment in the study to the outcome measure visit.

Firstly, participants were invited to attend the Movement and Exercise Laboratory (MoveExLab) at the University of East Anglia twice: the first occasion was for baseline measurements and to set the training, and the second for the outcome measures. They were asked to wear a t-shirt and shorts for the MoveExLab as they needed to undertake some movement analysis measures (see outcome measures section below).

On their first visit to the MoveExLab (day 1) participants undertook the baseline measurements in accordance with the following procedure:

4.2.5.1 *Primary measure*

Primary outcome focused on the impairment level as the factor most sensitive to change by the intervention, and as predictive of neurological and functional recovery after stroke (274). Here, the Motricity index (MI) for lower limb was used as the primary benefit measure. This was measured as to check eligibility for the study (inclusion criteria), at baseline and at outcome. The MI is used widely in clinical practice and in research to measure the ability to voluntarily contract a paretic muscle. The MI has been shown to have validity and reliability when used with stroke survivors (24,275). The scale ranges from 0 = no voluntary muscle contraction to 100 = normal voluntary muscle contraction. The three-movement categories are hip flexion, knee extension, and ankle dorsiflexion (275). The main focus for this study was on ankle dorsiflexion scores, which range from 0 to 33 (see Table 4-2 in the inclusion criteria). The Motricity index was performed from a sitting position with a 90-degree angle for hip, knee and ankle joints.

If there were no changes in the MI, then changes in the secondary outcome measure were assessed.

4.2.5.2 Secondary measures

Secondary outcome measures were undertaken using different equipment. All data collection occurred in the MovExLab at the University of East Anglia, and for data accuracy data was collected by the same Researcher (myself) in all sessions. These measurements were as set out in the following section.

The secondary outcome measures were collected to investigate changes occurring between pre-and post-measures. These measures were used because the neurophysiology underlying the ability to contract a paretic muscle could be a more sensitive indicator of the benefit from mirror therapy than the MI. The EMG-derived measure, H-reflex and TMS-derived measure were used as described in the following section.

4.2.5.2.I. Neuromechanical data

The motion analysis system (Vicon), surface EMG and force plate were used to collect kinematic and kinetic data. The TA symmetry of time from the onset of movement to peak activation of TA muscle in both the paretic and non-paretic side were derived from those data during a standardized sit-to-stand activity (further details in data collection section).

To capture the movement an eight-infrared VICON motion analysis cameras was used alongside the Vicon lower limb plug in gait model (3D motion analysis system VICON, Oxford Metrics Ltd, Oxford, England). This has a reported accuracy <0.6 mm(276,277), intrarater reliability of >0.8 (ICC) (277,278) and a standard error of measurement <5° (278). Also, for muscle activation, four wireless EMG surface electrodes were used (non-invasive), via the Delsys system (Trigno Wireless EMG System, 23 Strathmore Road, Natick, Massachusetts 01760, USA). Three Bertec force plates were used to record ground reaction

forces throughout the movement, and to identify the initiation of the movement (279). The following protocol was used:

Before participants came to the lab, they were asked to wear shorts and a t-shirt for this measure, if they had them; if not, these were provided in the lab. They were also asked to wear the same shoes in both sessions.

During their lab visit, preparation of the equipment took place before participants arrived using the following set-up:
Eight infrared Vicon cameras were masked and fully calibrated using the active wand and the refinement frame 1500, after which the volume origin was set. When the participant arrived at the MovExLab, they were screened for any known allergies. If a participant had any known allergies to anything used in the lab, e.g. adhesive products, then alternative, hypo-allergenic products were used. The participant's height, weight, leg length, knee width, and ankle width were measured to create the subject data in the Vicon Nexus software that was needed for model reconstruction. Participants removed any orthosis for ankle or knee, if they had one, during measuring.
A set of 16 lower body markers, 1cm spherical reflective markers were used to capture the 3D movement in space using a lower limb plug-in gait model (see Figure 4-3) which were then attached to participants. Two markers of 5 cm were used at the anterior superior iliac spine while the remaining markers were 1 cm (see Appendix III for the reason for the change). The markers were attached to: the right and left anterior superior iliac spines; the right and left posterior superior iliac spine; right and left thighs; right and left lateral epicondyle of the knee joints; right and left mid-shanks; right and left ankle lateral malleoli;

right and left calcanei; and right and left second meta-tarsal heads. Kinematic data were captured at 100 Hz.

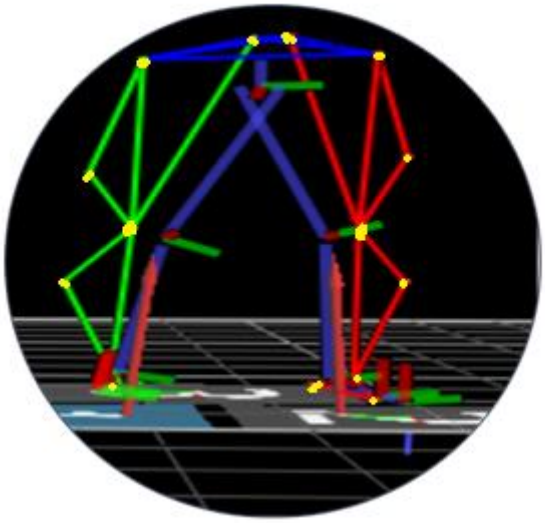


Figure 4-3 the lower limb plug-in gait model after processing with yellow dots show markers placement.

Then, the four wireless surface EMG electrodes were placed over the TA and soleus muscles on both sides, in accordance with the SENIAM guideline (seniam.org) (280). Skin areas for these EMG were cleaned with alcohol swabs or an alternative, to reduce impedance of the signal. EMG signals were collected at 2,000 Hz. The EMG signal and noise levels were then visually checked by asking the participant to perform ankle dorsi/plantar flexion using Delsys acquisition (EMG works-acquisition software). The EMG was then added to the Vicon by using “add digital tringo”. Next, the participants were asked to stand “using the anatomical position” to capture the static model. For dynamic movement, sit-to-stand, the participant’s feet were placed on two separate force plates and the plinth legs on the third force plate. After placing the plinth in the right position in the lab, the force plate was put to zero. The force plate data were collected at 2,000 Hz.

Standardised task to perform during the neuro-mechanical data collection

Participants were asked to sit in the plinth and maintain 90 degree of hip/knee/ ankle position, by adjusting the height for each participant, and measuring the joints using a goniometer. The plinth height from the floor, and distance from the knee to plinth were also recorded to ensure consistency between the baseline and outcome measure for each participant. The participants then performed a standardised sit-to-stand activity.

Participants were asked to stand up from a plinth, the height of which was adjusted to 100% of their knee height, with no assistance provided. Participants were instructed not to use their arms; any attempts that included the use of arms were considered as failed attempts and were not included in the analysis. Then before data collection began, participants were instructed to rest for about 15 seconds before they heard the buzzer (trigger). This was needed to know the resting EMG for that participant and to ascertain the initiation of the movement after the trigger. Then, participants were instructed to stand up when they were given the signal (a trigger which produces a buzzer sound) and maintain the standing position, then, sit back when they heard the buzzer again. Participants who were unable to do the sit-to-stand activity independently, were asked to try to perform the sit-to-stand movement.

4.2.5.2.II. H-reflex data

Spinal excitability was measured using the Hoffmann reflex (H-reflex). The H-reflex may be considered as the electrical analogue of the tendon jerk reflex (281).

The neurophysiology characteristic of the H-reflex is as follows: applying an electrical stimulation of a mixed peripheral nerve above motor threshold produces two responses in the muscle: M-wave and H-reflex.

The electrical stimulation to elicit the H-reflex measures the efficacy of synaptic transmission as the stimulus travels in afferent (Ia sensory) fibres through the MN pool of the corresponding muscle (TA & soleus) to the efferent fibres (motor). To elicit H-reflex, it is usual to start with low intensity stimulation and increase it slowly. This results in the depolarization of the primary afferent fibres arising from the muscle spindle

During the maximum stimulus intensity, the H-reflex is absent, due to collision of the antidromic (toward the spinal cord) motor volley with the orthodromic (toward the muscle) afferent volley and the M-wave is maximum (282). Neither M-wave nor H-reflex recruit the same alpha motor neuron, which is recruited from the smallest to the largest. The small motor neuron innervating slow motor units are recruited first in the H-reflex, then activating the larger axons elicits the M-wave (283).

Neural excitability at the spinal level was measured using the H-reflex. H-reflexes are evoked either in the soleus or tibialis anterior muscle by supramaximal stimulation (1 ms rectangular pulses) of the posterior tibial nerve (PTN) or common peroneal nerve (CPN), respectively. For both reflexes, a surface EMG (blue chloride pre-gelled electrodes) over the required muscle (using Digitimer Neurolog System) were used. For good recording practice, equal length electrodes were used. The electrode cables were same length and material that gently twisted together so as not form gaps, a reference electrode was used. A constant current stimulator (Digitimer DS7A, Digitimer Ltd, Welwyn Garden City, UK) was then used to produce the peripheral stimulation over the required nerves. Mr. Kick software was used to help visualise the recorded M & H waves and stored data offline for analysis (Mr. Kick is data acquisition software used in the acquisition of the physiological data in the research fields of sensory and neurophysiology, motor control, reflexes. It was developed at the centre for sensory-motor interactions at Aalborg University).

Procedure for H-reflex:

A- H-reflex and M-waves were evoked by the percutaneous stimulation of the posterior Tibial nerve and recorded from EMG places over the soleus muscle (on the more paretic side). Participants were sitting on a chair with back, head and leg supported, a cathode stimulation electrode was place over the posterior Tibial nerve behind the knee in the area near the popliteal fossa, and the anode was placed superior to the patella. The skin was prepared by using alcohol swabs with medium pressure to produce light red colour over the skin. This was to decrease the impedance. The surface EMG electrodes (Ambu-blue sensor) were placed over the soleus muscle. Following the SENIAM guidelines (280) "the electrode was placed in the 2/3 of the line between the medial condyles of the femur to the medial malleolus". Reference electrodes were placed over the lower part of the Tibial bone. Before starting the stimulation, the EMG signal was checked by asking the participant to move the ankle down (or push the Researcher's hand down with their feet), if they could. If not, a passive ankle movement was carried out to check the quality of the signal by using MR. Kick software (data acquisition). After that, the participant was told that they would feel a "bee sting" or "static carpet shock" that might increase or decrease according to the stimulus intensity. The amplitude of the H-reflex and the amplitude of the M-wave were measured as peak-to-peak values. After checking for the presence of H-wave, the stimulus strength was slowly adjusted to find the H-max and M-max. The stimulus intensity was increased or decreased based on reaching the M-max and H-max wave. M-max is obtained by applying a few stimuli to the peripheral nerve with a successively larger stimulation current until a supramaximal current produces the largest M-wave. This ensures the M-max can be found quickly without administering too many uncomfortable, stimuli (282,284). However, two seconds were between each stimulus, rest time was increased if the participants asked for it.

B- H-reflex and M-waves were evoked by percutaneous stimulation of the common peroneal nerve and recorded from EMG places over the TA muscle (on the more paretic side). Participants were in a sitting position, with head back and lower legs supported in a relaxed position. Stimulation pin electrodes were placed over the common peroneal nerve area located superior to the popliteal fold (between the neck of the fibula and the Tibial tuberosity) and the anodes were placed superior to the patella. Surface EMG recording electrodes were placed over the Tibialis anterior muscle, following the SENIAM guideline (280) in which "the electrodes were placed at 1/3 on the line between the tip of the fibula and the tip of the medial malleolus" (in the middle of the muscle belly). Reference electrodes were placed over the lower part of the Tibial bone. Before starting the stimulation, the EMG signals were checked by asking the participant to move the ankle up, if they could. If not, a passive ankle movement was carried out to check the quality of the signal, using MR. Kick software (data acquisition). After that, participants were told that they would feel a "bee sting" or "static carpet shock" that might increase or decrease according to the stimulus intensity.

In both procedures, H-reflex recruitment curves were constructed by plotting the H-reflex versus stimulation intensity, to determine the intensity at which a stable M-wave amplitude corresponds to an H-reflex amplitude on the ascending part of the curve. As part of this procedure, the maximal M-response (M-max) was obtained, and this measure was used to normalize all motor evoked potentials (obtained in participants with no contraindications to TMS) and H-reflexes to allow direct comparison of results within and between participants. In these measurements, the intensity of stimulation increased from a subliminal level until there was no further increase in the peak-to-peak amplitude of the M-response with increasing stimulation intensity (282).

For normalization between baseline and outcome session, the maximal peak-to-peak M-wave amplitudes for the baseline session that were used to normalize the EMG data were calculated.

The H- reflex amplitudes and the M-wave showed wide variation with changes in stimulus and were affected by the central nervous system (282). They were also influenced by the participant's tension level, age, duration of stimulation, and the location of the electrodes between sessions. Therefore, the H-reflex was known to have wide of variation between participants and within the same subject (282,285).

Therefore, to standardize the measure between the baseline and outcome within the same participant, participants were in the same position, and the ratio of the mean M waves/M-max was calculated as a baseline. Then, on the outcome day, if this did not have the same value as M-Max which was recorded, the ratio was multiplied from baseline by the new M-max. Ten stimuli were then elicited at that range of the M-max value. This was used for standardization within participant sessions to avoid any changes in electrode positions. In addition, because it was not possible to elicit an H-wave from the TA muscle in most of the participants, the TA was used to normalize TMS data for those who were eligible. While the H-wave from the soleus was used for the dose-decision,

4.2.5.2.III. TMS data

Corticospinal excitability using the transcranial magnetic stimulation (TMS) was measured. TMS is a noninvasive tool to measure the connectivity between the motor cortex and the distal muscle in the leg (Tibialis Anterior muscle). It is considered a useful tool for the assessment of the corticospinal excitability (286–289). TMS uses magnetic pulses to stimulate the contralateral primary motor cortex, which can travel through the scalp and cause a motor evoked potential (MEP) in the target muscle. The MEP is the standard measure of

motor response to TMS. This is done by applying the TMS coil above the M1 to stimulate the required muscle, which the TA in this case, by generating a transient current in the cortex (287).

Each participant completed a safety screen before a decision about their suitability was made (Appendix III) - screen based on Keel *et al*.(2001) (290)). This study used the technique that was developed to provide rapid online data accusation of the TMS stimulus-response curve (291) to assess the strength of the connection between the brain and the Tibialis Anterior (TA) muscle. This is an extension of the standard transcranial magnetic stimulation (TMS) technique that has been used world-wide. Briefly, an electromagnetic double cone-shaped wire coil is placed on the participant's head over the area of the brain that controls the TA muscle. Then, a short stimulus/pulse were delivered with a MAGSTIM stimulator (using the Magstim Company). Then the Motor evoked potential (MEP) is detected in the muscle using surface electromyography (electrical recording of muscle activity) via disposable electrodes placed on the skin on the TA muscle over the more paretic side and the reference electrodes were placed at the lower part of tibia. Participants were seated on a comfortable chair with their arm supported by a pillow to relax the corticospinal pathway, The Double Cone Coil was used, with positioning about 45 degrees to the midline while the handle pointing backward to allow the magnetic field to penetrate. This coil is suitable for stimulating the motor cortex areas controlling the muscles of the lower limbs (288).

Neuronavigation

In addition, for Magtismes, an image-guided frameless stereotaxy neuronavigation system was used (BrainSight 2, Rogue Research Inc, Montreal, Canada) to track and record the coil position though conducting the TMS assessments. Using this helped to obtain a good estimate

of the motor threshold, and reliably measure MEPs by using the same hotspot (target) for the participants in the outcome measure for standardization. Brainsight also helped to track the coil position to the participant's head during the session (292).

The BrainSight makes it possible to track coil position and orientation in real-time following a calibration procedure using camera to record the position of the reflective markers. An elastic band with three infrared reflective marks was placed over the participant's head. The position of the marker is related to the participant's head by registering eight facial landmarks (e.g. nose bridge, nose tip, top and middle and bottom of the ears for both side). A similar set of reflective markers is attached to the TMS coil, with its position being calibrated with respect to the centre of the TMS coil. Accurate landmark registration and coil calibration is crucial to allow for within and between session replication of stimulation sites, this when the headband moves or needs to be taken off, and to facilitate between and within session re-registration. After calibrating the participants, the hot-spot was identified using signal software and Brainsight, if any MEP was elicited from the TA muscle, then, a stimulus response curve was constructed. If there was no MEP, the participant was stimulated at 3 high intensity (100% of stimulus output) and then the test was stopped, using the same setting and the predefined hot-spot for the outcome measure. In addition, to reduce TMS variability; the participant was placed in the same position, no caffeine having been taken within the last hour, the same hot spot was used as identified from the baseline session and normalization of the data (286).

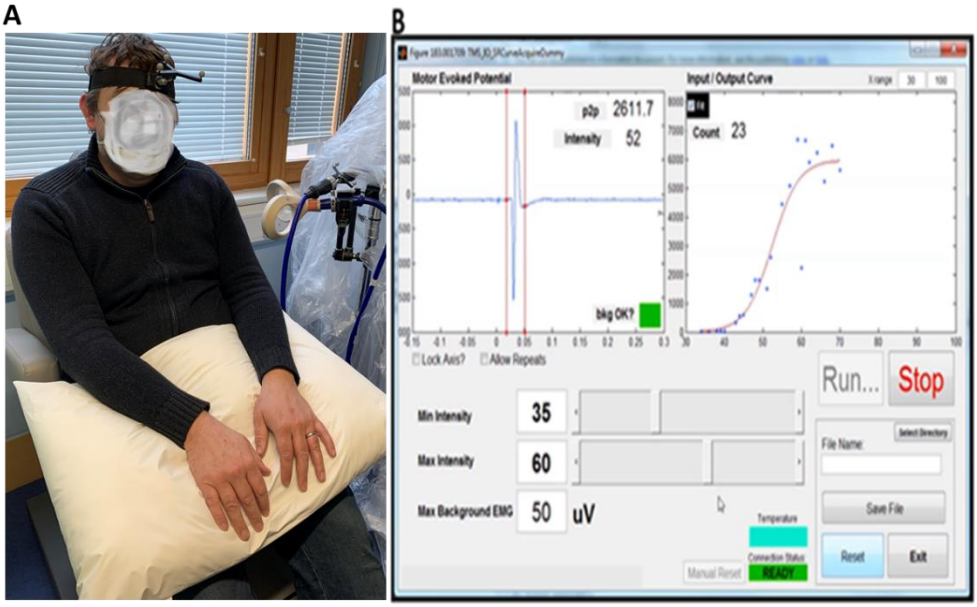


Figure 4-4 TMS produces a Motor Evoked Potential (MEP) that produces a Motor Evoked Potential (MEP) that provides a measure of the strength of the connection between the brain and the Tibialis Anterior muscle. A) The position of the participants during the procedure. B) Stimuli are delivered at various intensities.

All EMG records for H-reflexes and TMS were amplified (2khz), band pass filtered (20–1,000 Hz), and digitally sampled at 5 kHz (Digitimer Neurolog System), and to be stored for offline analysis (Mr. Kick for H-reflexes/Signal for TMS).

4.2.6 Undertaking the intervention

When participants had completed the baseline measurements, they were set their training dose of mirror therapy for a period of two weeks. The first session was supervised by the Researcher in the lab to ensure that the participants were (a) doing the mirror therapy correctly, and (b) that they could set up the equipment correctly. All participants were provided with the lower limb mirror therapy equipment (figure 4-5) that had been designed in the previous study (see Chapter 3), and the tool was placed inside a shopping trolley to allow easy transportation and storing. In addition, a daily record form (Appendix III) and stop-

watch were provided to the participants so that they could record the number of performed minutes per day during the training period. The Researcher asked the participants to write a daily log about the duration of the exercise performed.

During the training, participants were asked to cover the weak side completely, place their bare feet on the ankle support in the same position for both sides, in a way that allowed a clear reflection of the less affected foot in the mirror, to perform the ankle exercise on the less affected side and try to move their more affected side if possible. The exercise was performed in a sitting position, and participants were encouraged to maintain an upright sitting posture. In addition, participants were asked to concentrate on the mirror reflection and avoid any external distraction such as watching the television (293). The same set up was used with all the participants in the study to avoid any differences.

Figure 4-5 The lower limb mirror therapy tool that was used in the study.

During home training, the participants were encouraged to perform the therapy, and they were allowed to split the target dose into training sessions during the day in order to achieve the target minutes per day for that cohort, especially for the cohorts that had a high number of minutes, to prevent any fatigue. Also, they were encouraged to note down the number of sessions and the number of performed minutes per each session. In addition, they were asked to record any reasons that had prevented them from providing the target minutes per day, such as fatigue or another commitment, such as a hospital appointment using the daily record form. In addition, participants were contacted by phone at least twice times during the training period to check on possible challenges and the dose adherence. If required, further phone calls were agreed with participants and planned according to their preferred times and days.

4.2.7 Outcome measures

After two weeks of doing the therapy at home, the participants came to the lab to undertake the outcome measurements. Visits to the lab were planned before the baseline measure, and participants were set these dates according to their preference to enable them to return at the end of the 14-day intervention periods. During their outcome visit, the participants brought back their MT tool with the daily record sheet. Then Motricity index, TA symmetry, H-reflex and TMS were undertaken again as described in the earlier section.

4.2.8 Data processing

After collecting the data from the baseline and outcome session for each participant in each cohort, the data were processed as follows:

4.2.8.1 *The primary outcome measures*

Changes in Motricity index from the baseline value were entered into an Excel spreadsheet to enable comparison of pre- and post-values for the participants in each cohort.

4.2.8.2 *Secondary outcome measures*

4.2.8.2.I. For TA symmetry:

- For trajectory data collected, a pipeline was used to semi-automate the data processing. First, the gap was filled using a series of gap filling functions: spine fill to fill small gaps (max gap of 2 frames), rigid body fill to fill gaps in the pelvis (max gap 5 frames), and a pattern fill max gap of 5 frames.
- Then the force plate data were filtered using a Butterworth filter (fourth order (zero lag –low pass at cut off frequency 300 HZ) and the Vicon marker trajectories were filtered using a Woltring filter. Then the Vicon plug in gait model was applied and the data was exported as CSV files.
- For EMG and force plate data, the script was ran using the exported CSV files by using Spyder (Python3.7). (The script was made with the help of Elizabeth Chandler who is the clinical movement analyst within the research team at UEA). This script was used to process the EMG data as follows:

1- Calculate the mean of all samples and remove this value from all values – DC Offset removed.

2- Apply a band pass Butterworth filter 4^{th} order high level 20Hz, low level 450Hz.

3- The data was fully rectified by calculating the absolute value.

4- A low pass was applied, 10Hz, Butterworth filter 4^{th} order to create an EMG envelope.

5- Resting means were calculated from force plate, ankle velocity and EMG data using 10 seconds of data before the go signal.

6- Onset of movement was calculated from the force plate data. Onset was said to have occurred when the force on any force plate changed from the value at rest so that it was more or less than the resting mean ± 2 standard deviations of the resting mean.

7- After the go signal (adding the buzzer as stimulus), the onset of movement to peak EMG activity was measured for both TA muscles. All EMG signals were considered on when they were above the resting mean + 3 standard deviations of the mean resting data. The changes in ankle velocity were considered on if their value was resting mean ± 3 standard deviations of the mean resting data.

8- Visual plots of the graphs were then exported from the script to check the accuracy of the scripts and data (Figure 5-6).

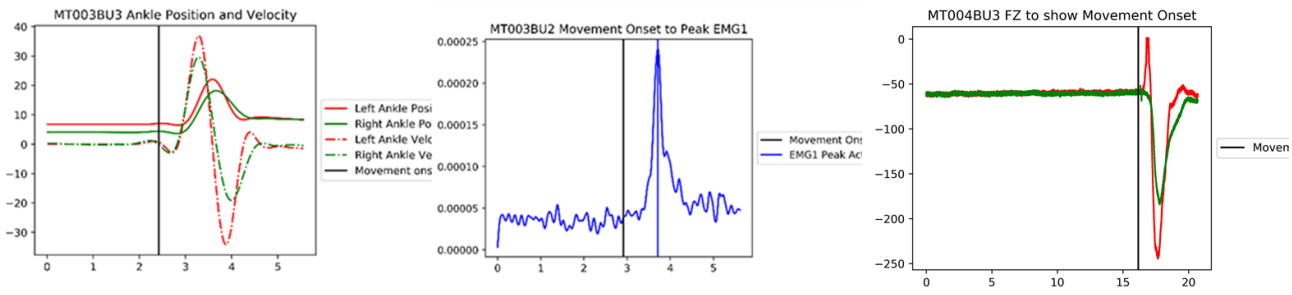


Figure 4-6 visual plots presentation of the ankle position and the onset of the movement to peak EMG after the trigger.

After running scripts, an Excel sheet was used to compare the results between the baseline measure and the outcome measure. An average of the trials was taken from the successfully recorded trial, and followed by the equation below to calculate symmetry (277):

$$\frac{2\times(P)}{(P+NP)} - 1$$

Where P = paretic value, and NP =non paretic side value. Where the changes were 10% ≥ from the baseline, this was considered a clinically significant change. (Improved by ≥ 10% toward the symmetry, or deteriorated by ≥ 10% away from symmetry or no changes). Zero mean normal symmetry, and ± 100 asymmetry between both sides.

4.2.8.2.II. H-reflexes

Mr. Kick (data acquisition 2000-2012, Knud Larsen,MScEE,SMI, Aalborg University) was used to collect the data and stored it for offline analysis. Then data was exported to the Excel sheet by exporting the RMS, peak-to-peak value for H-reflex and M-wave by placing the cursors over the required waves (Figure 4-7). After exporting the data to Excel, RMS values were checked to see if there were any abnormal values that might be considered to be muscle contraction to determine if there was any muscle activity before or during the measure. If there was any abnormal value, that frame was deleted. Subsequently, all data was converted volt to microvolt (Mv) by multiple the raw data (1000000). The M vs H for the participant was plotted before and after the therapy to see if there were any changes. The changes measure the peak-to-peak values of the H-reflex, and whether it increased by ≥ 10% or deteriorated by ≥ 10% or no changes occurred from the baseline values.

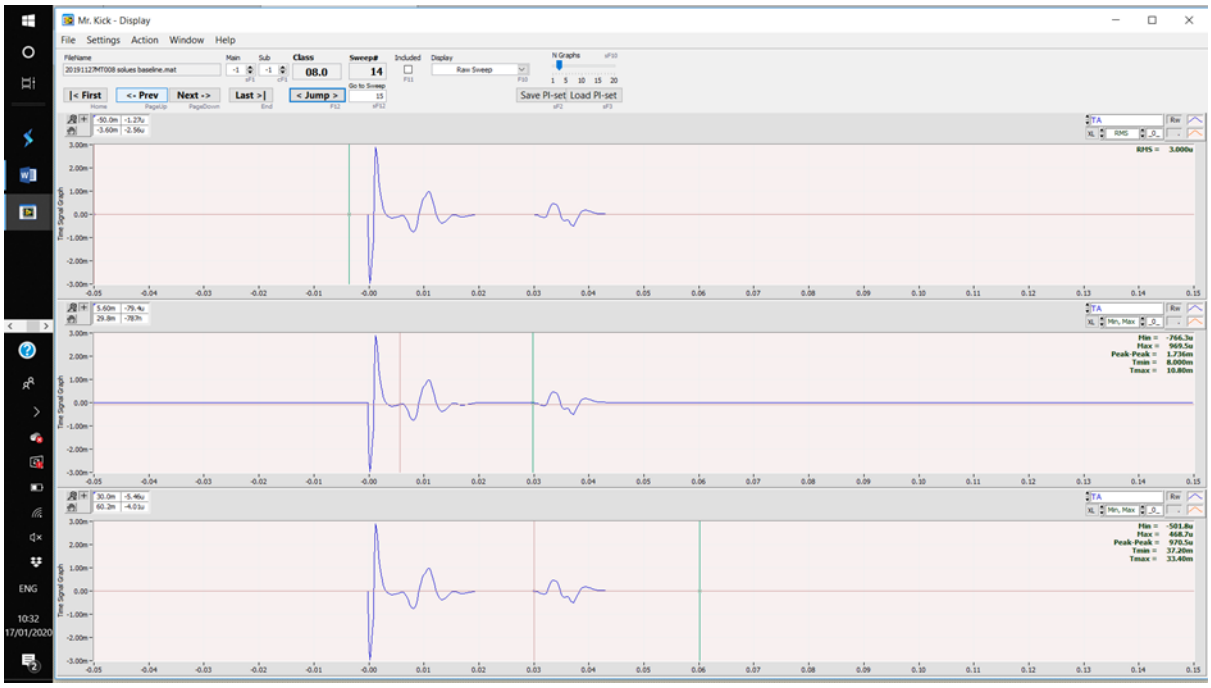


Figure 4-7 the figure shows the cursors positions to visualise the RMS, M-wave and H-reflex.

4.2.8.2.III. TMS

After collecting data, they were stored for offline analysis using signal software. The last three frames at 100 stimulus output were used for the baseline and then for outcome for those where an MEP could be found. The MEP was quantified by the peak-to-peak values extracted from a window 0.50 to 0.100 ms after stimulation. Then, the median values were used and divided by the M-max for either pre or post data, after which a t-test was carried out to compare the results.

Then after processing all the data for the participants in the cohort, an Excel sheet was used to judge the dose decision as described in the following section.

4.2.9 Data analysis for dose decision

After all the data was collected, processed and exported to an Excel sheet, a meeting was held between the Researcher and the primary supervisor (and the secondary supervisor if available) to inform the dose decision for the next cohort. This was based on dose tolerability and benefit following the pre-set rule (defined in the method section/pre-set rules) and the mFBS as follows:

4.2.9.1 *Dose tolerability assessment*

In detail, the dose was defined as tolerable if two of more participants in a cohort adhere to the set daily dose for that cohort, over the two weeks of the training period. An Excel sheet was used to report adherence to the fourteen days of training, to be used in dose decision. However, to accommodate the participants' daily life there was some flexibility. If a participant reported that they had a commitment, such as a hospital appointment, that prevented them completing the set dose on a specific day, then they were considered to be adherent. However, if a participant reported that they were too tired (such as pain, aches, fatigue, or if minutes too high) to complete the set dose then they were considered non-

adherent i.e. the dose was not tolerable. Then after checking dose tolerability for the three participants in a cohort, and if it was applicable according to the pre-set rules, the dose beneficial measures were checked as set out below:

4.2.9.2 *Beneficial dose assessment*

4.2.9.2.I. Primary measure

MI scores were used to determine if the dose was beneficial. If there were changes (one level or more from the baseline) in two or more participants per cohort, then the dose was considered beneficial and it was not necessary to check the secondary outcome data.

4.2.9.2.II. Secondary measure

If there were no changes in the primary beneficial measure for two participants or more in a cohort, changes were sought in the secondary outcome measures. These measures were judged by using three terms: “no change”, “improved by 10% or more” or “deteriorated by 10% or more”.

The TA symmetry activation values from sit-to-stand activity were checked. If no changes/improvement or deterioration had occurred, the pre-set nine rules were followed to inform the dose decision for the next cohort.

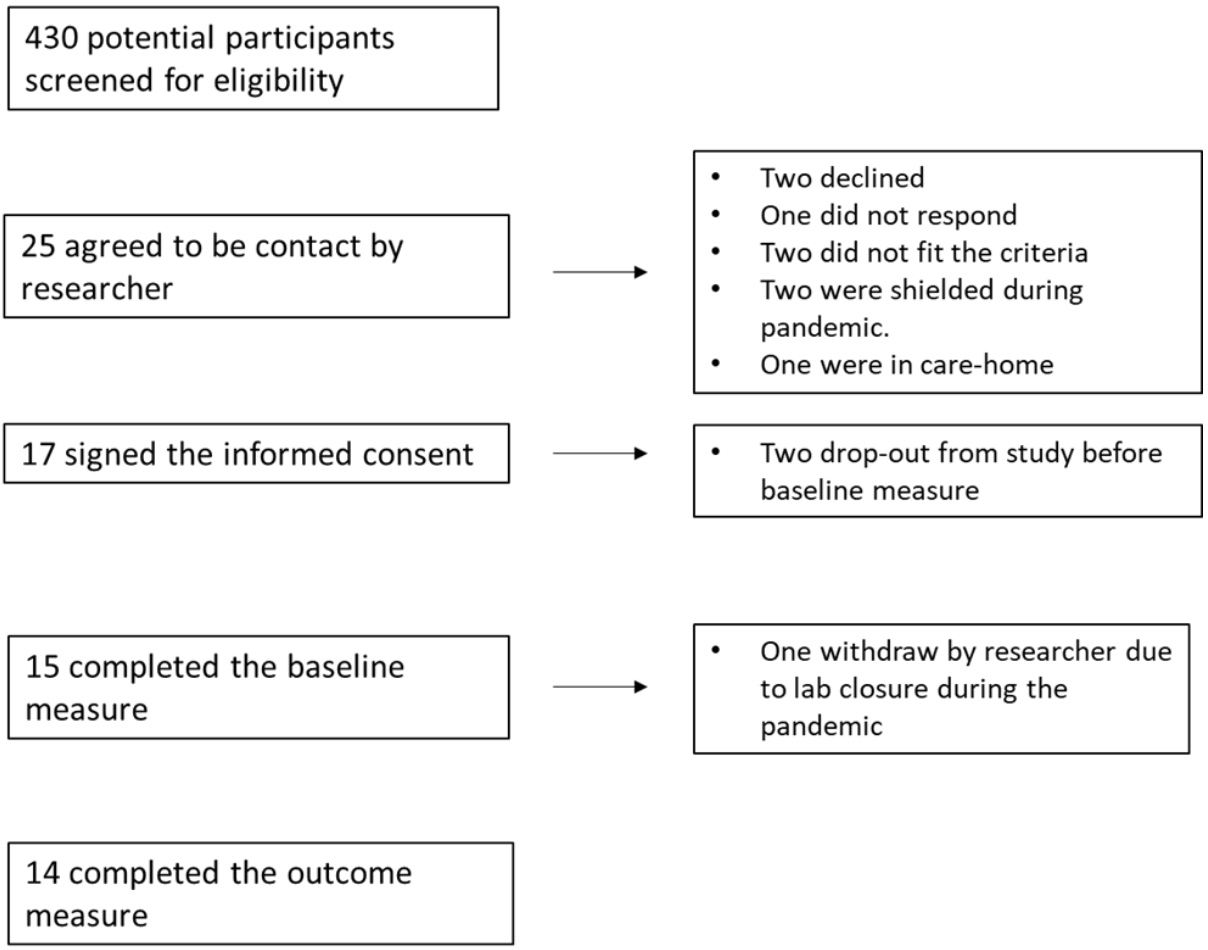
However, data from Soleus muscle was not analyzed during the dose decision due to the variabilities between participant in their ability to perform sit-to-stand movement. Also, TMS and H-reflex data could not be used for dose decision because it was not available for all participants in a cohort.

4.3 Results

4.3.1 Flow of the participants through the study

Most of the participants in this study were recruited from support groups and early support discharge team, as described below (table 4-3):

Table 4-3 the flow of the participants in the study



4.3.2 Data collection period

Potential participant screening for this study started in July 2019 and continued until December 2020 (18 months). The Covid-19 pandemic affected the progression of the PhD program in general and, in particular, this study. The pandemic started eight months after the

starting date of the recruitment for this study, so recruitment stopped for eight months due to the national lockdown. One participant had to be withdrawn before the outcome session due to lab closure early in the pandemic. Recruitment re-commenced in late October 2020, but it was challenging to find the last two participants in cohort five. One was recruited and completed outcome measures but then the second lockdown occurred in December 2020 until May 2021. Therefore, recruitment of the last participant in cohort five was not possible.

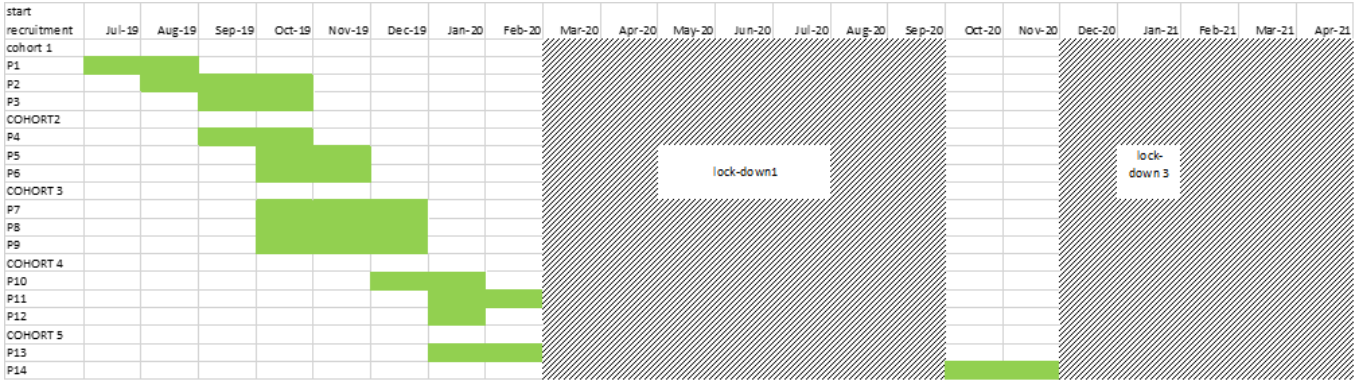


Figure 4-8 timeline of the screening and recruitment procedure of the study

4.3.3 Participants' characteristics at baseline

Fourteen participants took part in the study, nine males and five females, their ages ranging from 41 to 78 years with average 61.23 years (SD 9.412). Thirteen of those had had a stroke just once. Seven of those had left side weakness, and six had right-side weakness. Their mean time after stroke was 36.6 months (SD 43.10). Table 4-4 provides the summary characteristics overall and per each cohort.

Table 4-4 Participants' characteristics at baseline

	All cohorts	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort5
Age in years, mean (SD, range)	61.14(9.4, 41-78)	52.33(9.86, 59-41)	59.3(2.3, 62-58)	64(11.2, 51-71)	67.6(11.67, 55-78)	63(21.7, 60-66)
Months post stroke, mean(SD, range)	36.6 (43.10, 3-168)	39.6 (29.26, 6-59)	71.3 (84.7, 10-168)	28.66 (25.10, 5-55)	27 (21, 6-48)	6.5 (4.94, 3-10)
Female N (%)	5 (35.71%)	0 (0%)	2 (67%)	3 (100%)	0 (0%)	0 (0%)
Right side affected N(%)	7 (50%)	2 (67%)	2 (67%)	1 (33%)	1 (33%)	1 (50%)
Motricity index Mean (SD, range)	11.5 (3.79, 9-19)	12.33 (2.88, 9-14)	9 (0,9)	15.66 (5.77, 9-19)	10.66 (2.88, 9-14)	9 (0,9)

4.3.4 Completion of the measures

All participants completed the outcome measures except for the TMS and H-reflex. For h-reflex participants in cohort two did not have H-reflex data due to data acquisition error. For TMS, it was only possible to use TMS with five of the 14 participants (Table 4-5). Participants who undertook TMS were spread among the cohorts as follow: two participants in cohort one, one participant in cohort three, two participants in cohort four. The remaining participants had the following limitation: six of those did not meet the inclusion criteria for TMS; on two occasion, there was a technical issue with the device, while one of them could not collect the TMS & H-reflex data as a safety measure during the Covid-19. Therefore, due to the insufficient data from the H-reflex &TMS it was not possible to include it in dose-decision.

Table 4-5 Number of participants' in each cohort who completed each measure.

Cohorts	Motricity index	TA symmetry	H-reflexes	TMS
One	3	3	3	2
Two	3	3	0	0
Three	3	3	3	1
Four	3	3	3	2
Five	2	2	1	0

**(0-3) referred to number of participants' who completed the measures in each cohort.*

4.3.5 Identification of the Maximal Tolerable Dose per day

In total, five cohorts were included in this study. The trial was stopped because the dose difference between two cohorts was less than 10%.

A summary for each cohort is given here in Table 4-6 shows the changes in the primary and secondary beneficial measures. This information alongside the pre-set rules and mFBS was used to identify the MTD. The summary for each cohort is as follows:

Table 4-6 Dose tolerability, and the primary and secondary beneficial measures informing the dose decision for the subsequent cohort.

					Motricity Index			TA symmetry value			
Cohort	Participants	Target dose (minutes)	Minutes performed (mean)	Dose tolerable	MI at baseline	MI at outcome	change one level or more	TA symmetry at baseline	TA symmetry at outcome	improvement of 10 % or more	Dose beneficial
	1		15		14	14	No				
	2		15		9	14	Yes		NA		Yes
1	3	15	15	Yes	14	25	Yes				
	4		30		9	9	No	0	0.04	No	
	5		30		9	9	No	-0.135	-0.09	Yes	No
2	6	30	30	Yes	9	14	Yes	0	-0.107	No	
	7		46		19	19	No				
	8		43		9	9	No		NA		NA
3	9	50	36	No	19	25	Yes				
	10		38*		9	9	No	0.0435	0.1622	No/deteri	
	11		26		9	14	Yes	-0.04627	-0.12704	No/deterioration more than 10 %	NO
4	12	40	40	Yes	14	14	No	0.17366	0.185247	No	
	13		35		9	9	No	0.2869585	0.1331273	Yes	
5	14	35	35	Yes	9	9	No	-0.0702232	-0.0494734	Yes	Yes

NA not applicable

**participant did not adhere because of hospital appointment therefore considered adherent.*

All participants in cohort one adhered to the target dose of 15 minutes per day and two participants showed benefit in the primary outcome measure (Table 4-6). Therefore, the dose was increased for cohort two. The increases followed the modified Fibonacci sequence. Dose two was 2D1: 2×15= 30 minutes of training per day for cohort two (Table 4-1-mFBS).

Cohort two participants all adhered to the target dose of 30 minutes per day but did not show any improvement in the primary benefit measure (Table 4-6). Therefore, the change in the secondary outcome measures was checked. Neither of the secondary outcome measures showed changes in two or more participants (Table 4-6). Therefore, rules four (a) and seven applied: if a particular dose was tolerable but not beneficial for at least two participants, the mFBS informed the increase of the dose for the subsequent cohort. Therefore, the dose for cohort three, D3 was 1.67 D2: 1.67×30=50 minutes (Table 4-1 mFBS).

In cohort three, none of the participants adhered to the target dose per day of 50 minutes. Therefore, it was not applicable to check for beneficial dose measures (Table 4-6). According to rule one of the pre-set rules, the consequent action was to decrease the dose by 50% of the previous increment for the subsequent cohort. In this case the increase in the increments between this group and the previous one was 20 minutes (cohort two had received 30 minutes while, this group received 50 minutes) so 50% of 20 minutes is 10 minutes. So, the next cohort received 40 minutes of therapy.

In cohort four, two participants adhered to the target dose of 40 minutes (one of those did not adhere to the target dose on one day of training due to a hospital appointment, and was therefore still considered adherent), but there was no increase in the primary benefit measure

(Table 4-6). Then, the secondary outcome measures were checked, which showed a decrease of more than 10 % from the baseline values for two participants (Table 4-6). According to rule 4-b of the nine pre-sets rules, if there was a decrease in the dose-benefit measure between the pre- and post-training points for at least two of three participants, the dose for the subsequent cohort was decreased by 50% of the previous increments. The change were 10 minutes. As 50% of that is 5 minutes, the next cohort received 35 minutes of mirror therapy training.

In cohort five, two participants adhered to the target dose of 35 minutes. For the dose beneficial measure, there was no improvement in the primary benefit measure. For the secondary benefit measure, there was an improvement of 10% or more in the TA symmetry activation for the two participants in this cohort. Following the pre-set nine rules, rule 5, if the dose was decreased for a cohort and then deemed tolerable and beneficial, the action for the subsequent cohort was to increase the dose by 67% of the previous increments. However, according to the stopping rules (rule 9) if the dose difference between the two cohorts (time in minutes) was equal to or less than 10%, the study was stopped. The study stopping rule was triggered. In this cohort, two participants were recruited out of three due to Covid-19 as it was very difficult to find a participant during that time. However, because the dose decision for cohorts relies on similarity of the data for two participants or more in that cohort to make the decision, as was the case here, the two participants adhered to the target dose and showed an improvement in the secondary beneficial measure. Due to the time limitation of the PhD, the decision was taken to submit the thesis with 14 participants as the result of the 15^{th} participant would not have changed the dose decision of that cohort.

Table 4-6 details the dose tolerability and benefit for each cohort. The identified MTD for the training intervention used, was determined as 35 minutes/day.

Impact of the Covid-19 pandemic

In addition, special lab training was conducted to adapt to the “new normal” with the pandemic, to maximize the Researcher’s and participants' safety. Also, the Covid-19 test had to be done before each participant's lab visit. During the lab visit, all safety procedures were followed to minimize the risk, such as covering the face, maintaining the two-meters distance as much as possible, and checking for Covid-19 symptoms before and after lab visits (see PIS for Covid-19-Appendix III). Due to safety reasons, and to maintain the participant's social distance, the H-reflex and TMS measures were excluded as it was not possible to keep the safe social distance during these measures.

4.4 Discussion

In this study, the maximum tolerable dose of ankle exercise mirror therapy identified was 35 minutes per day. This was derived from the inclusion of 14 participants divided among five cohorts. Following the 3+3 design there should have been 15 participants among five cohorts not 14; this s limitation was due to Covid-19. However, having the 15th participant would not have changed the results of that cohort as the two participants in that cohort showed a similar response to the given dose, and the data from a third participant would not have changed the decision about the dose for the subsequent cohort. Based on the used design and following the nine pre-set rules, there needed to be a similarity in the results across two or more of the participants, as was the case here.

In the current literature about lower limb mirror therapy the planned doses for interventions vary from 15 minutes (172,223,235) to 40 minutes (224) with the most common dose being 30 minutes (121,170,171,222), while the number of weeks ranges from two (173) to four (224,228). However, none of these studies used doses based on dose-finding studies, as far as can be ascertained from reviewing the literature. To the Researcher's knowledge, the identified MTD for mirror therapy exercise in this study can therefore be considered the first dose-finding study for mirror therapy, based on the systematic review chapter and from the currently published systematic reviews that recommend investigation of the mirror therapy dose (103,165).

Dose based studies in stroke rehabilitation is a new area and needs more research in future (59). The currently available evidence about the use of this method is limited. The Researcher

is only aware of two studies that used dose-finding methodology in stroke rehabilitation. One of them was the role model that was used in this study (265), but the main difference was that this study was for the lower limbs and the dose was self-reported, counting the dose as minutes not repetition, and the role model was a methodological study (265). The other study investigated the dose-finding in rehabilitation used a different design of 3+3 dose escalation, only with no pre-set rules, and was used for 12 weeks (266) while the period was two weeks in the study with pre-set rules and mFBS to increase or decrease the dose. Other designs have been used such as intervention cross over (294) or randomized, controlled observer blinded feasibility trial (295) dose response Phase II (193). Again, it would seem that this study is the first dose-finding study for mirror therapy.

The two-weeks period was sustainable as an intervention time for this research as it was a Phase I dose-finding study involving dose variation across the cohorts. In other sources of evidence, change in motor function has been reported for two weeks of therapy and deemed applicable for use in dose-finding studies (265). Nevertheless, it is possible that two weeks is not enough to produce maximum benefit from MT. This might explain why no changes in the Motricity Index were found in most of the participants but there were changes in the sensitive measure that was used as the secondary beneficial measure.

Using the pre-set defined rules and mFBS, helped to safely increase or decrease the doses. Using dose tolerability and benefit to inform the dose-decision for the next cohort among two participants or more per cohort appeared to be a correct balance. This also helped us to provide an acceptable level of precision in finding the MTD per day, which could inform subsequent dose ranging studies to help find the recommended Phase II dose (RPTD).

This study has highlighted the effect of using different levels of measures and how this has a direct impact on determining dose efficacy. Using the MI as the primary measure to assess the TA voluntary contraction, alongside the secondary measure of symmetry of TA time of onset to peak muscle activation, helped to determine the efficacy of the set doses for each cohort. However, the MI did not change in most of the cohorts. Nevertheless, TA symmetry was more sensitive to the changes before and after the treatment. This could indicate that MI needs more than two weeks' treatment before the required changes can be observed, while other sensitive measures can detect changes earlier (274). Future studies could investigate further the relationship between these measures, as this could provide a better guide to determining the time required before the benefits from the intervention become apparent (274). This would then indicate the correct direction for the therapy to take (296). As the case with cohorts here, the secondary measure either showed improvement or deterioration before and after the intervention, and this was as a precursor to increasing or decreasing the dose.

Limitations

Participants' characteristics varied in this study. This heterogeneity could have an impact on participants' performance and ascertainment of the MTD. The characteristics that may have an impact are age and time since stroke (37,57,63,64,297,298).

In this study participants' mean age was 61.23 years ranging from 41 to 70. This is lower than the average for UK stroke patients where the mean age is about 72 years for men and 78 years for women (stroke association) (15). However, the variation in age could limit the

results as younger people could respond differently to older people (37). Future studies could investigate the differences in age groups.

One of the limitations is the broad eligibility criteria, especially with regards to time after stroke. In this study, the time after stroke varied among participants, with the mean time being 36.6 months post stroke. Nevertheless, the current evidence of stroke rehabilitation suggests that early rehabilitation might optimize the potential recovery (57), and the golden period for the brain to begin repairing is from the first days after onset to several weeks (29,66), but also still unclear wither mirror therapy might improve " learned non-use" of the affect limb by increasing the attention (126). This was, therefore, a limitation in this study. Future studies might recruit participants at specific time points after a stroke.

Another potential limitation is the use of the dose-record form only as a self-reported measure This could lead to imprecise reporting of the achieved dose. To the Researcher's knowledge none of the studies using lower limb mirror therapy reported or measured the exact performed dose of the therapy (103,165). In addition, studies that test the dose in other forms of rehabilitation interventions either use self-reported forms (295), accelerometers (294), both electronic timer and self-reported form (265) or they rely on the physiotherapist to count the dose (193). In this study, because of resource limitations, none of the previous methods could be used to count the dose other than the self-reported form. Future studies might use a counter to monitor the repetitions rather than the minutes to provide a more accurate outcome, as repetition is considered a more accurate representation of dose in rehabilitation than minutes (55,89,299).

It was only feasible to undertake the TMS for less than half of the participants, due to TMS contraindication with many of the participants, which made the use of the TMS data for dose-decision impossible. This was because the data for cohort decision needed to be available for all three participants in that cohort to determine benefit. TMS was a challenging tool to apply in stroke rehabilitation to determine the changes in neuroplasticity in a dose-finding study. Similarly, H-reflex data was not included in the analysis to determine the dose beneficial as this was not available to all participants due to data acquisition error in one of the cohorts.

The Covid-19 pandemic adversely impacted on the study as cohort five had only two participants out of three. Some eligible potential participants were shielding because they were considered extremely vulnerable because of co-morbidly or they were in care homes. To try and complete cohort 5 took a year due to the closure of the laboratory and the UK national lockdowns and where able to recruit only one participant. In addition, the Health and Safety procedures required to mitigate the risk of transmission of Covid-19 prevented the collection of H-reflex and TMS data.

Strengths

As far as can be ascertained from the literature, this is the first study to find a maximum tolerable dose for mirror therapy in general and specifically for lower limbs ankle exercise.

In addition, participants had similar levels of severity after the stroke. This was to ensure that participants had the same severity at the baseline so the identified dose could be generalized

across that population. Previous literature suggests that participants with severe paresis after stroke can improve more from mirror therapy (129).

Also, a variety of sensitive measures were used to detect changes because the neurophysiology underlying the ability to contract a paretic muscle could be a more sensitive indicator of the benefit from mirror therapy than the MI. This allowed the dose to be increased or decreased based on these changes.

The data here were more representative to the UK population. 64% of participants in this study were male, in line with published stroke data indicating that males have more strokes than females in the UK, with 25% higher stroke incidence in males than females (Stroke Association Statistics ,2018) (15).

Future recommendation

This was a Phase I study to find the MTD per day of LLMT. It is recommended that future studies use the MTD identified in this study and apply it to Phase II RPTD studies. The Phase II results can then be used in a Phase III efficacy trial (194). In addition, future studies could investigate the impact of potential factors and patient demographics, such as time after stroke and the age of the participants on the influence of the mirror therapy dose.

chapter 5. Thesis discussion and implications for future research

This chapter discusses the contributions that the thesis has made to the knowledge regarding lower limb therapy and proposes a number of recommendations in terms of future research and practice. The discussion is framed according to the research questions as set out in chapter one and how the findings from the three studies relate to current published work. The chapter begins by discussing how the research questions were addressed, providing a summary of the main results for each research question, how these findings relate to current literature about lower limb mirror therapy and what new insights were generated. This is followed by an integrated discussion of all the findings in relation to the current literature. Lastly, contributions to knowledge and recommendations for future research investigation that emerged from this thesis are identified, and strengths and limitations discussed.

Summary of the results according to the research questions

The first research question had four parts:

Primary research questions:

"Does provision of lower limb exercise via mirror therapy enhance motor recovery after stroke? Does time after stroke influence response to mirror therapy? Does the level of paresis influence response to mirror therapy? Does the amount of mirror therapy (dose) influence response to mirror therapy?"

The first research question was addressed in Study One with a systematic review and meta-analysis of the existing research relating to the efficacy of lower limb mirror therapy. The results demonstrated that lower limb mirror therapy improves motor recovery (aim 1-a) after stroke. The unique contribution is the synthesis of the available evidence about the influence of time after stroke, the severity of paresis, and the dose of the therapy on motor recovery. With regards to the time period, results show that less than six months after a stroke, participants in the mirror therapy group recovered (aim 1-b). Participants with severe paresis also showed an improvement in motor recovery after using mirror therapy (aim 1-c). However, the review was unable to establish a more precise relationship between the ideal dose of therapy and change in motor recovery because of insufficient details provided in the studies and/or the variety of approaches to reporting the dose in the studies reviewed (aim 1-d).

Secondary to the main aim of the meta-analysis, the study ascertained that lower limb mirror therapy improves functional capacity after a stroke. In terms of the influence of time after a stroke, the severity of paresis, and therapeutic dose on functional capacity, results showed

that: participants whose stroke occurred from two- six months and more than six months showed more changes in functional capacity in the mirror therapy group; the functional capacity of participants with severe paresis improved; it was not possible to ascertain dose because of reporting ambiguities in current literature. The systematic review also identified a gap in terms of technical details regarding the set-up of the lower limb mirror therapy and the dose of therapy. These gaps are addressed by Studies Two and Three in this thesis.

The second research question was:

"What is user-friendly, feasible equipment and set-up of the mirror therapy for lower limb rehabilitation after stroke?"

The second research question is addressed in Study Two, which consists of lower limb mirror therapy equipment and set-up, iteratively co-designed with physiotherapists and stroke survivors via focus groups. The result of the study was a user-friendly piece of equipment enabling stroke survivors to perform ankle exercises using mirror therapy from a sitting posture (Aim 2). The main contribution of this study was the development of user-friendly prototype mirror therapy equipment that addresses the limitations of currently available mirror boxes in three ways: it enables the stroke survivor to perform the exercise from a sitting position by adjusting the angle of the mirror to allow a clear reflection of the less paretic ankle; it includes a sheet to cover the more paretic side; it is easy to store in the home. After co-designing the set-up and the equipment for lower limb mirror therapy, it was essential to identify the MTD for lower limb mirror therapy early phase I dose, as this was not well defined in the current literature about lower limb mirror therapy.

The third research question was:

"What is the maximum tolerable dose (MTD) a day of mirror therapy for ankle dorsiflexion for use in a subsequent dose-ranging study?"

The third research question was addressed through a 3+3 rule-based, dose-escalation/de-escalation design. The third study's main contribution is to have identified a daily MTD dose (Aim 3); 35 minutes per day was found to be the maximum tolerable dose to improve motor recovery of ankle exercise via mirror therapy.

All findings in the context of the literature:

According to the MRC framework (197), this thesis set out to address the development stage of research due to the lack of the information regarding "knowledge units", as discussed in the stroke recovery trial framework (59). The limitation of the information regarding who might benefit from the therapy, when to apply it, and how much, made it very difficult to make the GO decision to conduct a RCT. According to Dobkin (2009), the need for progressive staging of pilot studies is essential to improve phase III trials (194) as is the case here with lower limb mirror therapy. Therefore, this thesis used a sequential multiphase multiple methods design to answer the research questions, to allow for progressive staging in the evidence regarding lower limb mirror therapy.

In summary, this thesis has filled empirical gaps in the current "knowledge units" about lower limb mirror therapy, as it provides potential insight about who might benefit from the therapy and when. Also, it has identified the set-up of the lower limb mirror therapy and developed prototype equipment to be used for lower limb mirror therapy especially designed

to perform ankle exercise. It also identifies the MTD per day to undertake ankle exercise via mirror therapy.

Who and when

From the available rehabilitation techniques designed to enhance lower limb recovery after stroke, mirror therapy is considered one of the effective interventions for improving motor recovery, one that can save time, effort and money as it can be done individually at home without the supervision of a physiotherapist.

According to the MRC framework (197,198), it is essential to conduct a systematic review, especially in the development phase of a complex intervention, so as to evaluate the evidence and answer some key questions related to the intervention. Through analysing existing evidence about the efficacy of lower limb mirror therapy, the systematic review study was able to confirm the benefits of lower limb mirror therapy in term of improving motor recovery and functional capacity among stroke survivors. This finding is in line with the currently published reviews about lower limb mirror therapy (103,165,168). This thesis's unique contribution was to provide insight on who might benefit from the therapy and when, by conducting a subgroup analysis to investigate the influence of time after stroke, level of paresis and the dose of therapy on recovery.

With regards to the time period (**when**), most studies do not refer to a “golden” window for recovery, and the time variations after the stroke of the interventions described in the studies make it difficult for clinicians to know who might respond to the therapy and when to apply it. Added to this, certain contradictions between the studies were found. For example, some studies identified less than six months post-stroke as being critical for improvements in motor

recovery. Other studies showed that improvements in functional capacity are more likely from two- six months and over six months after the stroke. Thieme *et al*. (2018) (103) stated that mirror therapy is effective in "acute", "subacute", and "chronic" stages, which is similar to a certain extent to the findings reported in this thesis; however, their results could be seen as “general” as their review combined studies that involved upper and lower limb deficits after stroke. With regards to improving gait speed and motor recovery, Louie *et al*. (2018) found that lower limb mirror therapy was more effective in subacute strokes (165) while for participants with a chronic condition, no significant changes were found. Their findings differ from the results of the subgroup analysis conducted in this review. However, this study used specific time points without referring to “acute, subacute or chronic” stages, which provides more accurate interpretation for the current literature. The results from this review potentially identify the best time to apply the therapy in terms of the changes in motor recovery or functional capacity.

In terms of the extent of paresis severity (**who**), the studies analysed in the review indicated that participants with severe paresis showed better improvement in motor recovery and functional capacity of the lower limb when compared with participants who had moderate paresis. However, to the researcher’s knowledge, no systematic review has investigated the influence of paresis severity on recovery of the lower limb. Only Dohle *et al*. (2009) (129) suggested that participants with severe arm paresis might show better recovery after mirror therapy; however, this result was for the upper limb, with no clinical trials or systematic reviews investigated that use lower limb mirror therapy. The systematic review conducted in this thesis addressed this gap by identifying who might benefit more from the mirror therapy, although the results cannot be generalised due to the methodological limitation and small

sample size. Therefore, further investigation needs to be undertaken in subsequent efficacy trials to identify the “time window” in performing the therapy and who might be the “responder” to the therapy. In summary, to potentially fill the knowledge units as to who might benefit and when, it is crucial to identify equipment setup and dose of therapy.

Set-up of the equipment

The thesis has shown that while there is a body of literature reporting on mirror therapy interventions with the upper limb, lower limb mirror therapy is still in its infancy. This gap in the current literature regarding protocols to be used in lower limb mirror therapy (163,165) after a stroke is one that this thesis set out to fill. It was essential to involve the user perspective to iteratively co-design the tool and to better understand their needs. Thus, the aim of Study Two was to co-design mirror therapy specifically with lower limb exercise in mind. The few existing lower limb trials translate the mirror's position in mid-sagittal plane view between the arm to the leg and do not consider the difficulties stroke survivors might have in maintaining a good posture. In addition, exercising the lower limb using mirror therapy is more of a challenge compared to upper limb therapy, because whereas in the latter, the mirror can sit on the table, in the former, the mirror has to be positioned between the lower and upper limb if it is to provide good visibility. Although mirror therapy interventions are used for the lower limb, physiotherapist participants in Study Two pointed out the limitations of the commercial mirror box that is currently available and in contributing to the co-design of the equipment, highlighted the difficulties with setting up the mirror therapy. Based on input from the physiotherapists and the stroke survivors, the main aspects of the designed prototype that were developed by this study were: the size and angle of the mirror,

designed to produce a clear reflection of the ankle, while maintaining a good posture and the sheet to cover the weak side. Including user feedback in the iterative prototype development process increased the usability of the final prototype, as it could be used in participants' home environment as well as in clinical settings. However, to ensure that the prototype was sufficiently robust, a feasibility and efficacy trial still needed to be designed for use in clinical practice.

How much

After establishing who might benefit, when, and identifying the set-up of the equipment, to further current knowledge, the next step was to identify the dose of motor recovery as was highlighted in the systematic review study in this thesis. This is based on the stroke recovery trial development framework, as it highlights the importance of investigating HOW MUCH, while maintaining the other knowledge units constant (59). From the systematic review conducted in this thesis, the meta-analysis showed the difficulty in detecting any relationship between dose and motor recovery, due to study variations and insufficient reporting of doses in the limited literature. Also, none of the doses in the included studies were based on dose-finding studies. This study has highlighted the need to investigate the dose for mirror therapy, in line with recommendations from the current published reviews (103,162,165). Therefore, it was essential to conduct a study that investigated the maximum tolerated dose of lower limb mirror therapy. Study Three in this thesis identifies the MTD per day as phase I research to investigate the dose. MTD for ankle exercises was 35 minutes per day. This dose was not used before in the current trials in which a variety of doses were used between 40 to 15 minutes, with a common time intervention of 30 minutes per day (165).

Moreover, this is the first study to apply the pre-defined methodology used by Cloucci *et al.* (2017) (265) for dose in stroke rehabilitation to a real physical therapy intervention, and find it applicable. Usually, dose-finding methodology is well defined in pharmacological studies and the next step after identifying the MTD is well designed. However, this is not the case with stroke rehabilitation, where both dose-finding and next stage are still in their infancy. Lang *et al.(*2016) (193) conducted a phase II dose-response in stroke rehabilitation but the doses used in their study were not based on MTD per day. Therefore, there is a methodological limitation for dose studies designs in stroke rehabilitation, and careful planning of the protocol for the next step is required.

Various outcome tools were used to measure the changes while using LLMT. These outcomes were divided into primary and secondary outcome measures, although not all of these measures were used in making decisions about the dose. The primary aim of ankle exercise via mirror therapy is to improve motor recovery by enhancing the ability of the paretic muscle to voluntarily contract. The primary outcome measure used to capture this change was the Motricity Index (MI). This tool was chosen to measure changes among all participants pre and post intervention due to being quick, easy and simple to use (275). It is also widely used in clinical settings to assess the severity of motor impairment (275). However, MI may not be sufficiently sensitive to measure the physiological changes that happen prior to the change in ability to contract the paretic muscle. Therefore, three secondary outcome measures were used to capture these changes, namely, TA symmetry, neural excitability at the spinal level, and corticospinal excitability.

TA symmetry was used to measure the symmetry of time from the onset of movement to peak activation of TA muscle on both sides during the standardized sit-to-stand activity using Vicon, EMG and force plate. As stroke causes a delay in the time TA muscle activation takes

(279,300), it was important to measure changes in symmetry before and after the therapy: moving towards symmetry means moving towards normality as sit-to-stand is a symmetrical activity. No contraindications or limitations have been reported while using this tool but its use in clinical practice is limited due to it being an expensive piece of equipment; therefore, it might only be available in research laboratories. Future studies could investigate how the measure might be used in clinical settings, alongside further research into the connection between symmetry and recovery after stroke using mirror therapy is needed.

Neural excitability at the spinal level using H-reflex was used to measure the reflex evoked via Soleus and TA muscles. In the field of sport, the H-reflex has been used to measure excitability at the spinal level for over 20 years (301). In this study, however, the H-reflex data was not sufficient for the dose-finding study due to a data acquisition error that happened during data collection. Dose decisions based on the H-reflex can only be used if all the data is available for each participant in each cohort as well as the cohort as a whole. Given that these types of error can happen while collecting data and large sample sizes are needed to confirm any results, the tool's usefulness is limited in does studies, particularly in a 3+3 design. Future studies could investigate the applicability of using the H-reflex in dose studies, but this was not the main focus of this study.

The third outcome measure was to assess the corticospinal excitability between the motor cortex and the TA muscle using the TMS. As with the H-reflex, the data collected was incomplete. The measure could not be used with all participants due to contraindications to TMS. However, to allow generalisability of the data among all stroke survivors, these participants were not excluded from the study and TMS derived measure was used as an optional measure. Therefore, the TMS data was not used when making decisions about dose. In the FAST Indicate trial (302) the use of TMS was similarly limited due to

contraindications as well as other reported limitations. Therefore, due to stoke heterogeneity and variation among trial participants, the use of TMS might be limited when used in dose-finding studies, especially in a 3+3 design, due to the limited sample size. Future studies could investigate the potential use of TMS in dose studies as this was not the focus of the study.

In conclusion, dose-finding studies using rule-based methods and 3+3 design was applicable for identifying the MTD of LLMT. However, the use of a variety of outcome measures as predictive markers of recovery needs further investigations.

Briefly, knowing the MTD per day could set the next phase of the dose research to investigate the dose-ranging as phase II, which might use random groups with low, moderate and higher doses based on the identified MTD. Then, results from phase II could be implemented to phase III to assess efficacy, which might use prospective, randomised controlled trials, with a planned number of participants (194).

According to the MRC framework for developing complex interventions, the process needs to follow a systematic and rigorous number of steps for the intervention to be successfully implemented into the health system (198). In this thesis, a multiphase comprehensive approach was used to answer the research questions. Key steps taken in this study consisted of carrying out a systematic review and meta-analysis, co-designing a device with stakeholders and identifying the MTD dose through progressive staging. The focus on who, when, how much and the equipment set-up is also important as the answers to these questions can ensure effective implementation in clinical practice. Each of these elements is important in terms of the successful future implementation of LLMT into the health system. Results

from this thesis helped to identify the best setup and design of the equipment to be used with LLMT, when to use it, with whom and the MTD as phase I dose of the therapy.

As stated in the MRC framework, thinking about the implementation phase of the intervention early on in the development process is important as it reduces the time it then takes to translate the research into clinical practice (198,199). Involving the main users of LLMT in the early co-design iterative development phase helped to understand users' needs and to identify solutions that meet their needs. According to MRC (198), including users' voices in the early iterative development of the prototype design enhances the future usability of the device for the stroke survivor and the physiotherapist, leading to the successful implementation of the device in the clinical setting. Taking forward the final prototype into the next phase of feasibility also ensures that problems can be addressed before proceeding with the more expensive future investigation phases in the MRC framework. After testing its efficacy, including a multidisciplinary team, i.e., physiotherapists, stroke survivors, engineers, in the next phase will enhance the implementation of the LLMT in clinical settings and in patients' homes. The economic evaluation of the tool also needs to be considered in the next stage (198) as it is important that the device is affordable for stroke survivors, whether purchased directly from the market or via the health system such as the NHS.

Also, defining the MTD per day of ankle exercise via MT means that the appropriate dose can be implemented in the next stage. Further investigation will be required to move the dose phases progressively toward the RCT (194), which in turn will help with dose of LLMT in clinical practice. Taking the identified MTD to be used in the dose ranging study will ensure

that future decisions about dose of LLMT in clinical practice are based on scientific research, thereby increasing the likelihood of the intervention being successfully implemented. These further investigations to fill the gaps in the main knowledge units will help to integrate mirror therapy into health system as complex intervention to be used with stroke survivors, especially those with severe paresis. This will help save time and resources as using MT alongside other rehabilitation interventions might help recovery after stroke.

According to O'Cathain *et al.* (2019), there are no established principles in terms of the completion of the developmental phase and the decision to move on to the next phase. Instead, there is an implicit iterative principle, in that although the investigation may be taken to the next phase, the developmental phase can be revisited prior to the implementation of the intervention into the existing health system (199), if problems in feasibility are identified or issues arise in the evaluation phase. Nonetheless, the work carried out in this thesis in terms of taking the design and the dose to the next phase, is important in term of the effective implementation of LLMT in the health system based on scientific research evidence; physiotherapists can then use it based on published guidelines.

Thesis limitations

As the main knowledge units are lacking for lower limb mirror therapy, this thesis only provides a starting point for further research. Due to the methodological limitations of the included studies in the systematic review about mirror therapy, the synthesis of existing research findings is inconclusive. Thus, the gap identified in the literature in terms of data about lower limb recovery, has only been partially filled: further investigations are needed.

Another limitation is that although the lower limb mirror therapy prototype was designed based on physiotherapist and stroke survivors' feedback, the stroke survivors had already recovered some independence as they were recruited from local support groups where participants are more than six-month post-stroke. Thus, the study was unable to explore the use of the prototype by stroke survivors in the acute stage. Including a wider range of stroke survivors might highlight different needs in using lower limb mirror therapy. In addition, the broad inclusion criteria for the time after stroke might influence the identified MTD as the mean time after stroke among participants in the dose study was 36.6 months. Also, due to resource limitations, the dose was counted in the number of minutes performed rather than repetition. Reporting of the exact repetitions is also needed to provide an accurate "active" dose.

Thesis strengths

The research strategy and the use of multiple research methods to address different aspects of lower limb mirror therapy intervention after a stroke and the sequential phases of the studies, made it easier to develop holistic research questions, and by reviewing existing research, identify knowledge and practice gaps which could then be filled.

A comprehensive search strategy through searching multiple databases followed by a systematic review of extant evidence highlighted the gaps in current knowledge of lower limb mirror therapy. The analysis resulted in a synthesis of current understanding about the influence of time after stroke and the severity of paresis on both motor recovery and functional capacity, which helped to potentially identify who might benefit and when. The

review identified that equipment set-up for lower limb mirror therapy was problematic and underdeveloped.

The devised prototype with the inclusion of the service user voice in the iterative development of the prototype, eased subsequent implementation in clinical practice and provided a platform for future iterative design and implementation of lower limb mirror therapy. Through taking the first step towards identifying MTD per day for ankle exercise, the study has provided a good foundation for future studies to establish lower limb mirror therapy dose. Given the gaps and uncertainties in the literature and the issues in practice, this thesis makes a significant contribution to lower limb mirror therapy by partially filling the gap in "knowledge units".

Future directions for research

A progressive staging is recommended to move current knowledge to the next phase in the research, before conducting a randomised control trial. The next phase needs to systematically move from stage I to stage II through to stage IV. This will provide a strong empirical foundation upon which to implement the findings into clinical practice. Therefore, no clinical recommendations can be made at this stage of the research as it is an early development phase. However, clinicians who are already using lower limb mirror therapy, can draw potentially on the main findings highlighted in this thesis when designing a lower limb mirror therapy intervention, especially in terms of planning when and who might benefit from the therapy and whether the equipment is set-up in the clinic or in people's homes. After, completing the developmental phase, feasibility, effectiveness and implementations of the finding can be translated into clinical guidelines (197).

Overall, the effect of mirror therapy on lower limb is promising. However, there is a lot that is still unknown; the "active ingredient" of mirror therapy needs further investigation to understand the mechanism beyond recovery, identifying the "responder" from the therapy by developing a better "biomarker of stroke recovery", as recommended in the consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (303), to help distinguish patient subgroups, is still needed. This might lead to better use of outcome measures of the "true recovery" rather than compensatory behaviours (274). Also, the best time window within which stroke survivors will benefit from using mirror therapy is still unclear. Unfortunately, developing robust interventions is a complex process and often fails to translate into clinical practice, as it is a common dilemma of "the translation pipeline" from the preclinical to clinical studies (78). Therefore, for future research Bernhardt *et al*.(2019) suggest the involvement of an interdisciplinary collaboration between preclinical and clinical scientists to develop an intervention that targets the knowledge unit's component to provide better evidence that supports the GO or NO-GO decision (59). Consequently, it is clear that further investigation of the lower limb mirror therapy is required.

The thesis concludes that lower limb mirror therapy is an intervention worthy of future investigation. As mentioned earlier, many knowledge gaps remain. Hence, the following research directions are recommended:

- Collaboration with a multidisciplinary team including engineering and rehabilitation practitioners (PT and OT) to enable the development of a prototype lower limb mirror therapy device. Also, there is a need for an electronic counter to count the repetition of the performed exercise rather than counting minutes within the prototype.

- Further feasibility work with the current prototype device will be required to gain additional insights from the users in the form of a qualitative investigation about the current device's usability in home and clinical settings. Also, participants at different time periods after a stroke need to be included to identify if there are other potential challenges that might emerge from using the tool.
- Subsequently, the identified MTD dose of ankle exercise could be used in a dose-ranging study.
- Participants with specific time after stroke would need to be included in order to understand the dose-response relationship between time after stroke and the performed dose.
- Clinical efficacy will then be required with regards to lower limb mirror therapy to investigate the influence of time after stroke and severity of paresis on recovery.

Concluding remarks

This thesis has presented novel component aspects of lower limb mirror therapy for people with severe paresis after stroke to practice an essential component activity, in their own home without the need for supervision, which can help them later to perform walking. This would be a time and resource efficient approach to enhancing motor recovery after stroke.

Firstly, the systematic review and meta-analysis showed that mirror therapy has an influence on motor recovery after stroke. The subgroup analysis potentially identified that participants with severe paresis might benefit more from mirror therapy and that participants who are less than six months post stroke show an improvement in motor recovery. Participants from two to six months and more than six months post stroke might show an improvement in

functional capacity. However, due to the methodological limitations of the included studies, these interpretations must be treated with caution, and further investigation involving more robust initial investigations are needed to provide a more solid empirical foundation for larger clinical trials. The systematic review also highlighted that the current literature on lower limb mirror therapy is limited; in particular, it identified a lack of information regarding the dose of therapy.

Secondly, the iteratively co-designed set-up and the tool, involving the end user of the mirror therapy (physiotherapist and stroke survivors), provides a good foundation for clinicians and researchers with setting up MT for the specific purpose of ankle exercise; these results need to be used in subsequent studies to check usability, while the identified maximum tolerable dose per day to perform ankle exercise provides a foundation for further dose investigations. Thus, the work reported in this thesis has filled some of the gaps in the "knowledge units" about lower limb mirror therapy. Further investigation is still required to provide better understanding and development of the therapy.

As a final note, while conducting this thesis, the global pandemic due to Covid-19 broke out. The need for more home interventions to take place became urgent as receiving the required rehabilitation in clinical settings became problematic at best. This highlights the need for mirror therapy for stroke survivors that can be easily used at home with minimal supervision..

References

1. World Health Organization. Cerebrovascular disorders : a clinical and research classification. 1978.
2. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: A global response is needed. Vol. 94, Bulletin of the World Health Organization. 2016. p. 634A-635A.
3. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: The copenhagen stroke study. Arch Phys Med Rehabil. 1995;76(1):27–32.
4. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol [Internet]. 2009 Aug;8(8):741–54. Available from: www.thelancet.com/neurology
5. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet [Internet]. 2011;377(9778):1693–702. Available from: http://dx.doi.org/10.1016/S0140-6736(11)60325-5
6. Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, et al. Physical rehabilitation approaches for the recovery of function and mobility after stroke: Major update. Stroke. 2014;45(10):e202.
7. Ramachandran VSS, Rogers-Ramachandran D, Cobb S. Touching the phantom limb. Nature [Internet]. 1995 Oct;377(6549):489–90. Available from: http://www.nature.com/articles/377489a0
8. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. Cochrane Database Syst Rev [Internet]. 2012 Mar

14;44(1):e1-2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23390640

9. Altschuler EL, Wisdom SB, Stone L, Foster C, Galasko D, Llewellyn DME, et al. Rehabilitation of hemiparesis after stroke with a mirror. Lancet [Internet]. 1999 Jun;353(9169):2035–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673699009204

10. Cheung R. A systematic approach to the definition of Stroke. Austin J cerebrovasc Dis Stroke [Internet]. 2014;1(5):1–5. Available from: http://dx.doi.org/10.1111/j.1475-4754.1974.tb01091.x

11. Intercollegiate Stroke Working Party. National clinical guideline for stroke. 5th edition,Royal College of Physicians. London; 2016.

12. Hankey GJ. The global and regional burden of stroke. Lancet Glob Heal [Internet]. 2013 [cited 2020 Nov 13];1:e239–40. Available from: www.thelancet.com/lancetgh

13. National Institute for Health and Care Excellence. NICE impact stroke [Internet]. London; 2019. Available from: www.nice.org.uk

14. SSNAP, School of Population Health and Environmental Sciences KCL, Party on behalf of the ISW. SSNAP Annual Public Report. London; 2019.

15. Stroke association. State of the Nation Stroke statistics [Internet]. 2017. Available from: Stroke.org.uk

16. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. Stroke. 2001;32(6):1279–84.

17. Young J, Forster A. Rehabilitation after stroke. Br Med J. 2007;334(7584):86–90.

18. Ekman M. Economic evidence in stroke: a review. Eur J Heal Econ [Internet]. 2004 Oct;5(S1):s74–83. Available from: http://link.springer.com/10.1007/s10198-005-0292-

19. Xu XM, Vestesson E, Paley L, Desikan A, Wonderling D, Hoffman A, et al. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. Eur Stroke J. 2018;3(1):82–91.

20. Dombovy ML, Sandok BA, Basford JR. Rehabilitation for stroke: A review. Stroke. 1986;17(3):363–9.

21. Department of Health National Audit Office. Progress in improving stroke care [Internet]. National Audit Office. London; 2010. Available from: http://www.nao.org.uk/wp-content/uploads/2010/02/0910291.pdf

22. Wolfe CDA. The impact of stroke. Br Med Bull [Internet]. 2000 Jan 1;56(2):275–86. Available from: https://academic.oup.com/bmb/article-abstract/56/2/275/303250

23. Wade DT, Langton Hewer R. Functional abilities after stroke: measurement, natural history and prognosis. Vol. 50, Neurosurgery, and Psychiatry. 1987.

24. Collin C, Wade D. Assessing motor impairment after stroke: A pilot reliability study. J Neurol Neurosurg Psychiatry. 1990;53(7):576–9.

25. Sainburg RL, Duff S V. Does motor lateralization have implications for stroke rehabilitation? J Rehabil Res Dev [Internet]. 2006;43(3):311. Available from: http://www.rehab.research.va.gov/jour/06/43/3/pdf/sainburg.pdf

26. Emos MC, Agarwal S. Neuroanatomy, Upper Motor Neuron Lesion [Internet]. StatPearls. StatPearls Publishing; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30725990

27. Patel AT, Duncan PW, Lai SM, Studenski S. The relation between impairments and functional outcomes poststroke. Arch Phys Med Rehabil. 2000;81(10):1357–63.

28. Stinear CM, Byblow WD. Predicting and accelerating motor recovery after stroke. Curr Opin Neurol [Internet]. 2014;27(6):1. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00019052-900000000-99472

29. Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. Ann Neurol. 2008;63(3):272–87.

30. Skilbeck CE, Wade DT, Langton Hewer R, Wood VA. Recovery after Stroke. J Neurol Neurosurg Psychiatry. 1983;56(5–8).

31. Carey L, Walsh A, Adikari A, Goodin P, Alahakoon D, De Silva D, et al. Finding the Intersection of Neuroplasticity, Stroke Recovery, and Learning: Scope and Contributions to Stroke Rehabilitation. Neural Plast. 2019;2019.

32. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. Brain [Internet]. 2011;134(6):1591–609. Available from: https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/awr039

33. Murphy TH, Corbett D. Plasticity during stroke recovery: From synapse to behaviour. Nat Rev Neurosci [Internet]. 2009;10(12):861–72. Available from: http://dx.doi.org/10.1038/nrn2735

34. Cramer SC, Bastings EP. Mapping clinically relevant plasticity after stroke. Neuropharmacology. 2000;39(5):842–51.

35. Sotelo C. Viewing the brain through the master hand of Ramon y Cajal. Nat Rev Neurosci [Internet]. 2003 Jan;4(1):71–7. Available from: http://www.nature.com/articles/nrn1010

36. Seitz RJ, Matyas TA, Carey LM. Neural plasticity as a basis for motor learning and

neurorehabilitation. Brain Impair. 2008;9(2):103–13.

37. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. J Speech, Lang Hear Res. 2008;51(1):225–39.

38. Wieloch T, Nikolich K. Mechanisms of neural plasticity following brain injury. Curr Opin Neurobiol. 2006;16(3):258–64.

39. Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. Muscle and Nerve. 2001;24(8):1000–19.

40. Takeuchi N, Izumi SI. Maladaptive plasticity for motor recovery after stroke: Mechanisms and approaches. Neural Plast. 2012;2012.

41. Carey L. Neuroplasticity and learning lead a new era in stroke rehabiliation. Int J Ther Rehabil [Internet]. 2007 Jun;14(6):250–1. Available from: http://www.magonlinelibrary.com/doi/10.12968/ijtr.2007.14.6.23893

42. Carey LM, Seitz RJ. Functional Neuroimaging in Stroke Recovery and Neurorehabilitation: Conceptual Issues and Perspectives. Int J Stroke [Internet]. 2007 Nov 23;2(4):245–64. Available from: http://journals.sagepub.com/doi/10.1111/j.1747-4949.2007.00164.x

43. Schaechter JD. Motor rehabilitation and brain plasticity after hemiparetic stroke. Prog Neurobiol. 2004;73(1):61–72.

44. Carey L, Blennerhassett J, Cadilhac D, Douglas J. Stroke rehabilitation: Multidisciplinary perspectives. Brain Impair. 2008;9(2):95–6.

45. Brewer L, Horgan F, Hickey A, Williams D. Review Stroke rehabilitation: recent advances and future therapies. Q J Med [Internet]. 2012; Available from: https://academic.oup.com/qjmed/article-abstract/106/1/11/1532273

46. Nudo RJ. Plasticity. NeuroRX [Internet]. 2006 Oct;3(4):420–7. Available from: http://physicstoday.scitation.org/doi/10.1063/1.3067168

47. Liepert J, Miltner WHR, Bauder H, Sommer M, Dettmers C, Taub E, et al. Motor cortex plasticity during constraint,induced movement therapy in stroke patients. Neurosci Lett. 1998;250(1):5–8.

48. Calautti C, Baron J-CC. Functional neuroimaging studies of motor recovery after stroke in adults: A review. Stroke [Internet]. 2003;34(6):1553–66. Available from: https://www.ahajournals.org/doi/10.1161/01.STR.0000071761.36075.A6

49. Liepert J, Bauder H, Miltner WHR, Taub E, Weiller C. Treatment-Induced Cortical Reorganization After Stroke in Humans. Stroke [Internet]. 2000 Jun;31(6):1210–6. Available from: https://www.ahajournals.org/doi/10.1161/01.STR.31.6.1210

50. Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain [Internet]. 2002;125(12):2731–42. Available from: https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/awg289

51. Van Peppen RPS, Kwakkel G, Wood-Dauphinee S, Hendriks HJM, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: What's the evidence? Clin Rehabil. 2004;18(8):833–62.

52. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. What Is the Evidence for Physical Therapy Poststroke? A Systematic Review and Meta-Analysis. Quinn TJ, editor. PLoS One [Internet]. 2014;9(2):e87987. Available from: www.pedro.org.au

53. Perez MA, Lungholt BKS, Nyborg K, Nielsen JB. Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. Exp Brain Res.

2004;159(2):197–205.

54. Pomeroy V, Tallis R. Restoring movement and functional ability after stroke: Now and the future. Physiotherapy. 2002;88(1):3–17.

55. Kwakkel G. Impact of intensity of practice after stroke: Issues for consideration. Disabil Rehabil. 2006;28(13–14):823–30.

56. Cauraugh JH, Summers JJ. Neural plasticity and bilateral movements: A rehabilitation approach for chronic stroke. Prog Neurobiol. 2005;75(5):309–20.

57. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. Stroke. 2006;37(9):2348–53.

58. Maier M, Ballester BR, Verschure PFMJ. Principles of Neurorehabilitation After Stroke Based on Motor Learning and Brain Plasticity Mechanisms. Front Syst Neurosci [Internet]. 2019 Dec 17;13. Available from: www.frontiersin.org

59. Bernhardt J, Hayward KS, Dancause N, Lannin NA, Ward NS, Nudo RJ, et al. A stroke recovery trial development framework: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2019;14(8):792–802.

60. Gowland C. Recovery of motor function following stroke: Profile and predictors. Physiother Canada [Internet]. 1982 Mar;34(2):77–84. Available from: https://utpjournals.press/doi/10.3138/ptc.34.2.077

61. Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst GJ. Predicting disability in stroke - A critical review of the literature. Age Ageing. 1996;25(6):479–89.

62. Bach-y-Rita P, Bach-y-Rita EW. Biological and psychosocial factors in recovery from brain damage in humans. Can J Psychol. 1990;44(2):148–65.

63. Kotila M, Waltimo O, Niemi ML, Laaksonen R, Lempinen M. The profile of recovery

from stroke and factors influencing outcome. Stroke. 1984;15(6):1039–44.

64. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke.Outcome Assessment and Sample Size Requirements Pamela. Stroke. 1992;23:1084–9.

65. Olsen TS. Improvement of Function and Motor Impairment After Stroke. Neurorehabil Neural Repair [Internet]. 1989 Jan 1;3(4):187–92. Available from: https://www.taylorfrancis.com/books/9781317971542

66. Hendricks HT, Van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: A systematic review of the literature. Arch Phys Med Rehabil. 2002;83(11):1629–37.

67. Lang CE, Lohse KR, Birkenmeier RL. Dose and timing in neurorehabilitation. Curr Opin Neurol [Internet]. 2015 Dec;28(6):549–55. Available from: https://journals.lww.com/00019052-201512000-00002

68. Schneider EJ, Lannin NA, Ada L, Schmidt J. Increasing the amount of usual rehabilitation improves activity after stroke: a systematic review. J Physiother [Internet]. 2016;62(4):182–7. Available from: http://dx.doi.org/10.1016/j.jphys.2016.08.006

69. Duncan PW, Horner RD, Reker DM, Samsa GP, Hoenig H, Hamilton B, et al. Adherence to Postacute Rehabilitation Guidelines Is Associated With Functional Recovery in Stroke. Stroke [Internet]. 2002;33(1):167–78. Available from: http://ahajournals.org

70. Ballester BR, Maier M, Duff A, Cameirão M, Bermúdez S, Duarte E, et al. A critical time window for recovery extends beyond one-year post-stroke. J Neurophysiol. 2019;122(1):350–7.

71. Teasell R, Mehta S, Pereira S, McIntyre A, Janzen S, Allen L, et al. Time to rethink

long-term rehabilitation management of stroke patients. Top Stroke Rehabil. 2012;19(6):457–62.

72. Korner-Bitensky N. When does stroke rehabilitation end? Int J Stroke. 2013;8(1):8–10.

73. Paolucci S, Antonucci G, Grasso MG, Morelli D, Troisi E, Cairo P, et al. Early versus delayed inpatient stroke rehabilitation: A matched comparison conducted in Italy. Arch Phys Med Rehabil. 2000;81(6):695–700.

74. Maulden SA, Gassaway J, Horn SD, Smout RJ, DeJong G. Timing of initiation of rehabilitation after stroke. Arch Phys Med Rehabil. 2005;86(12 SUPPL.):34–40.

75. Horn SD, DeJong G, Smout RJ, Gassaway J, James R, Conroy B. Stroke rehabilitation patients, practice, and outcomes: Is earlier and more aggressive therapy better? Arch Phys Med Rehabil. 2005;86(12 SUPPL.):101–14.

76. Biernaskie J, Chernenko G, Corbett D. Efficacy of Rehabilitative Experience Declines with Time after Focal Ischemic Brain Injury. J Neurosci. 2004;24(5):1245–54.

77. Kozlowski DA, James DC, Schallert T. Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions. J Neurosci. 1996;16(15):4776–86.

78. Corbett D, Carmichael ST, Murphy TH, Jones TA, Schwab ME, Jolkkonen J, et al. Enhancing the alignment of the preclinical and clinical stroke recovery research pipeline: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable translational working group. Int J Stroke [Internet]. 2017 Jul 12;12(5):462–71. Available from: http://journals.sagepub.com/doi/10.1177/1747493017711814

79. Langhorne P, Collier JM, Bate PJ, Thuy MNT, Bernhardt J. Very early versus delayed mobilisation after stroke. Cochrane Database Syst Rev. 2018;2018(10).

80. Brock KA, Vale SJ, Cotton SM. The Effect of the Introduction of a Case-Mix-Based

Funding Model of Rehabilitation for Severe Stroke: An Australian Experience. Arch Phys Med Rehabil. 2007;88(7):827–32.

81. Ween JE, Mernoff ST, Alexander MP. Recovery Rates after Stroke and Their Impact on Outcome Prediction. Neurorehabil Neural Repair. 2000;14(3):229–35.

82. Teasell R, Pereira S, Cotoi A. Chapter 22: The rehabilitation of severe stroke. Evidence-Based Rev Stroke Rehabil [Internet]. 2018;1–23. Available from: www.ebrsr.com

83. Teasell RW, Foley NC, Bhogal SK, Chakravertty R, Bluvol A. A Rehabilitation Program for Patients Recovering from Severe Stroke. Can J Neurol Sci / J Can des Sci Neurol [Internet]. 2005 May 2;32(4):512–7. Available from: https://www.cambridge.org/core/product/identifier/S0317167100004534/type/journal_article

84. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and Time Course of Recovery in Stroke. Part II: Time Course of Recovery. The Copenhagen Stroke Study. Anal Psicol. 1995;33(2):165–77.

85. Kwakkel G, Wagenaar RC, Twisk JWR, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral- artery stroke: a randomised trial. 1999;354:191–6.

86. Lohse KR, Lang CE, Boyd LA. Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation. Stroke. 2014;45(7):2053–8.

87. Jette AM. The importance of dose of a rehabilitation intervention. Phys Ther. 2017;97(11):1043.

88. Hornby T, Straube D, Kinnaird C, Holleran C, Echauz A, Rodriguez K, et al. Importance of specificity, amount, and intensity of locomotor training to improve

ambulatory function in patients poststroke. Top Stroke Rehabil. 2011;18(4):293–307.

89. Dalton E, Churilov L, Lannin NA, Corbett D, Hayward KS. Dose Articulation in Preclinical and Clinical Stroke Recovery: Refining a Discovery Research Pipeline and Presenting a Scoping Review Protocol. Front Neurol. 2019;10(November).

90. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. J Neurophysiol. 1998;80(6):3321–5.

91. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: What can be learned from animal models? Neurorehabil Neural Repair. 2012;26(8):923–31.

92. Nudo RJ. Recovery after brain injury: mechanisms and principles. Front Hum Neurosci [Internet]. 2013;7(December):1–14. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2013.00887/abstract

93. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural Substrates for the Effects of Rehabilitative Training on Motor Recovery After Ischemic Infarct. Science (80-) [Internet]. 1996 Jun 21;272(5269):1791–4. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.272.5269.1791

94. MacLellan CL, Keough MB, Granter-Button S, Chernenko GA, Butt S, Corbett D. A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. Neurorehabil Neural Repair. 2011;25(8):740–8.

95. Di Lauro A, Pellegrino L, Savastano G, Ferraro C, Fusco M, Balzarano F, et al. A randomized trial on the efficacy of intensive rehabilitation in the acute phase of ischemic stroke. J Neurol. 2003;250(10):1206–8.

96. Cooke E V, Mares K, Clark A, Tallis RC, Pomeroy VM. The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: a systematic

review and meta-analysis. BMC Med [Internet]. 2010 Dec 13 [cited 2017 Nov 10];8(1):60. Available from: https://bmcmedicine.biomedcentral.com/track/pdf/10.1186/1741-7015-8-60?site=bmcmedicine.biomedcentral.com

97. Johansson BB. Brain Plasticity and Stroke Rehabilitation The Willis Lecture. 2003;31:223–30.

98. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, et al. Very early mobilization after stroke fast-tracks return to walking: Further results from the phase II AVERT randomized controlled trial. Stroke. 2011;42(1):153–8.

99. Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, Collier J, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): A randomised controlled trial. Lancet [Internet]. 2015;386(9988):46–55. Available from: http://dx.doi.org/10.1016/S0140-6736(15)60690-0

100. Page SJ. Intensity versus task-specificity after stroke: How important is intensity? Am J Phys Med Rehabil. 2003;82(9):730–2.

101. Bohannon RW, Morton MG, Wikholm JB. Importance of four variables of walking to patients with stroke. Int J Rehabil Res [Internet]. 1991 Sep;14(3):246–50. Available from: http://journals.lww.com/00004356-199109000-00010

102. Richards CL, Malouin F, Wood-Dauphinee S, Williams JI, Bouchard JP, Brunet D. Task-specific physical therapy for optimization of gait recovery in acute stroke patients. Arch Phys Med Rehabil. 1993;74(6):612–20.

103. Thieme H, Morkisch N, Mehrholz J, Pohl M, Behrens J, Borgetto B, et al. Mirror therapy for improving motor function after stroke. Cochrane Database Syst Rev [Internet]. 2018 Jul 11;11(7). Available from:

http://doi.wiley.com/10.1002/14651858.CD008449.pub3

104. Dobkin BH. Strategies for stroke rehabilitation. Lancet Neurol. 2004;3(9):528–36.

105. Langhorne P, Bernhardt J, Kwakkel G. Stroke Care 2 Stroke rehabilitation [Internet]. Vol. 377, The Lancet. 2011 [cited 2018 Oct 1]. Available from: http://www.ebrsr.com

106. Li Y-CC, Wu C-YY, Hsieh Y-WW, Lin K-CC, Yao G, Chen C-LL, et al. The Priming Effects of Mirror Visual Feedback on Bilateral Task Practice: A Randomized Controlled Study. Occup Ther Int [Internet]. 2019 [cited 2020 Sep 7];2019. Available from: https://doi.org/10.1155/2019/3180306

107. Pomeroy V, Aglioti SM, Mark VW, McFarland D, Stinear C, Wolf SL, et al. Neurological Principles and Rehabilitation of Action Disorders. Neurorehabil Neural Repair [Internet]. 2011 Jun 25;25(5_suppl):33S-43S. Available from: http://journals.sagepub.com/doi/10.1177/1545968311410942

108. Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. Brain. 2008;131(5):1381–90.

109. Stoykov ME, Madhavan S. Motor Priming in Neurorehabilitation. J Neurol Phys Ther [Internet]. 2015 Jan;39(1):33–42. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4270918/pdf/nihms637165.pdf

110. Schacter DL, Buckner RL. Priming and the Brain. Neuron [Internet]. 1998 Feb;20(2):185–95. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0896627300804481

111. Ng SS, Hui-Chan CW. Contribution of ankle dorsiflexor strength to walking endurance in people with spastic hemiplegia after stroke. Arch Phys Med Rehabil. 2012;93(6):1046–51.

112. Thilmann AF, Fellows SJ, Ross HF. Biomechanical changes at the ankle joint after stroke. J Neurol Neurosurg Psychiatry [Internet]. 1991;54(2):134–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2019838

113. Dobkin BH. Training and exercise to drive poststroke recovery. Nat Clin Pract Neurol [Internet]. 2008 Feb;4(2):76–85. Available from: http://www.nature.com/articles/ncpneuro0709

114. Nadeau SE, Wu SS, Dobkin BH, Azen SP, Rose DK, Tilson JK, et al. Effects of Task-Specific and Impairment-Based Training Compared With Usual Care on Functional Walking Ability After Inpatient Stroke Rehabilitation. Neurorehabil Neural Repair [Internet]. 2013 May 15;27(4):370–80. Available from: http://journals.sagepub.com/doi/10.1177/1545968313481284

115. Ng SSM, Hui-Chan CWY. Ankle dorsiflexion, not plantarflexion strength , predicts the functional mobility of people with spastic Hemiplegia. J Rehabil Med. 2013;45(6):541–5.

116. Ramachandran VS, Rodgers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. Proc R Soc B Biol Sci. 1996;263(1369):377–86.

117. McCabe CS, Haigh RC, Ring EFJ, Halligan PW, Wall PD, Blake DR. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology. 2003;42(1):97–101.

118. McCabe CS, Haigh RC, Blake DR. Mirror visual feedback for the treatment of complex regional pain syndrome (Type 1). Curr Pain Headache Rep. 2008;12(2):103–7.

119. Lamont K, Chin M, Kogan M. Mirror box therapy seeing is believing. Explor J Sci Heal. 2011;7(6):369–72.

120. Michielsen ME, Selles RW, van der Geest JN, Eckhardt M, Yavuzer G, Stam HJ, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: A phase II randomized controlled trial. Neurorehabil Neural Repair [Internet]. 2011;25(3):223–33. Available from: http://nnr.sagepub.com

121. Sütbeyaz S, Yavuzer G, Sezer N, Koseoglu BF. Mirror Therapy Enhances Lower-Extremity Motor Recovery and Motor Functioning After Stroke: A Randomized Controlled Trial. Arch Phys Med Rehabil [Internet]. 2007 May;88(5):555–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003999307001712

122. Pandian JD, Arora R, Kaur P, Sharma D, Vishwambaran DK, Arima H. Mirror Therapy in Unilateral Neglect After Stroke (MUST trial). Neurology [Internet]. 2014 Sep 9;83(11):1012 LP – 1017. Available from: http://n.neurology.org/content/83/11/1012.abstract

123. Coleman ER, Moudgal R, Lang K, Hyacinth HI, Awosika OO, Kissela BM, et al. Early Rehabilitation After Stroke: a Narrative Review. [cited 2018 Oct 23]; Available from: https://www-ncbi-nlm-nih-gov.ueaezproxy.uea.ac.uk:2443/pmc/articles/PMC5802378/pdf/nihms938255.pdf

124. Arya KN. Underlying neural mechanisms of mirror therapy: Implications for motor rehabilitation in stroke. Neurol India. 2016;64(1):38–44.

125. Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain. 2009;132(7):1693–710.

126. Deconinck FJA, Smorenburg ARP, Benham A, Ledebt A, Feltham MG, Savelsbergh GJP. Reflections on Mirror Therapy. Neurorehabil Neural Repair [Internet]. 2015;29(4):349–61. Available from: http://journals.sagepub.com/doi/10.1177/1545968314546134

127. Buccino G, Solodkin A, Small SL. Functions of the Mirror Neuron System : Implications for neurorehabilitaion. Rehabilitation. 2006;19(1):55–63.

128. Carvalho D, Teixeira S, Lucas M, Yuan T-F, Chaves F, Peressutti C, et al. The mirror neuron system in post-stroke rehabilitation [Internet]. Vol. 6, International Archives of Medicine. 2013 [cited 2018 Sep 10]. Available from: http://www.intarchmed.com/content/6/1/41

129. Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H. Mirror Therapy Promotes Recovery From Severe. Neurorehabil Neural Repair. 2009;23(Cd):209–17.

130. Stevens JA, Stoykov MEP. Using Motor Imagery in the Rehabilitation of Hemiparesis. Arch Phys Med Rehabil [Internet]. 2003;84(7):1090–2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S000399930300042X

131. Grèzes J, Decety J. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: A meta-analysis. Hum Brain Mapp. 2000;12(1):1–19.

132. Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G. Cortical mechanisms of human imitation. Science (80-). 1999;286(5449):2526–8.

133. Pomeroy VM, Clark CA, Miller JSG, Baron JC, Markus HS, Tallis RC. The potential for utilizing the “mirror neurone system” to enhance recovery of the severely affected upper limb early after stroke: A review and hypothesis. Neurorehabil Neural Repair. 2005;19(1):4–13.

134. di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: a neurophysiological study. Exp Brain Res. 1992;91(1):176–80.

135. Rizzolatti G, Fogassi L, Gallese V. Motor and cognitive functions of the ventral premotor cortex. Curr Opin Neurobiol. 2002;12(2):149–54.

136. Krams M, Rushworth MFS, Deiber MP, Frackowiak RSJ, Passingham RE. The

preparation, execution and suppression of copied movements in the human brain. Exp Brain Res. 1998;120(3):386–98.

137. Bhasin A, Padma Srivastava M V., Kumaran SS, Bhatia R, Mohanty S. Neural interface of mirror therapy in chronic stroke patients: A functional magnetic resonance imaging study. Neurol India. 2012;60(6):570–6.

138. Ezendam DD, Bongers RM, Jannink MJA. Systematic review of the effectiveness of mirror therapy in upper extremity function. Disabil Rehabil. 2009;31(26):1–15.

139. Carr LJ, Harrison LM, Stephens JA. Evidence for bilateral innervation of certain homologous motoneurone pools in man. J Physiol. 1994;475(2):217–27.

140. Staudt M, Grodd W, Gerloff C, Erb M, Stitz J, Krägeloh-Mann I. Two types of ipsilateral reorganization in congenital hemiparesis: A TMS and fMRI study. Brain. 2002;125(10):2222–37.

141. Schwerin S, Dewald JPA, Haztl M, Jovanovich S, Nickeas M, MacKinnon C. Ipsilateral versus contralateral cortical motor projections to a shoulder adductor in chronic hemiparetic stroke: implications for the expression of arm synergies. Exp Brain Res. 2008;185(3):509–19.

142. Benecke R, Meyer B-U, Freund H-J. Reorganisation of descending motor pathways in patients after hemispherectomy and severe hemispheric lesions demonstrated by magnetic brain stimulation. Exp Brain Res [Internet]. 1991 Jan;83(2):419–26. Available from: http://link.springer.com/10.1007/BF00231167

143. Hamzei F, Erath G, Kücking U, Weiller C, Rijntjes M. Anatomy of brain lesions after stroke predicts effectiveness of mirror therapy. Eur J Neurosci [Internet]. 2020 Sep 25;52(6):3628–41. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ejn.14698

144. Reissig P, Garry MI, Summers JJ, Hinder MR. Visual feedback-related changes in ipsilateral cortical excitability during unimanual movement: Implications for mirror therapy. Neuropsychol Rehabil. 2014;24(6):936–57.

145. Läppchen CH, Ringer T, Blessin J, Seidel G, Grieshammer S, Lange R, et al. Optical illusion alters M1 excitability after mirror therapy: A TMS study. J Neurophysiol. 2012;108(10):2857–61.

146. Hamzei F, Läppchen CH, Glauche V, Mader I, Rijntjes M, Weiller C. Functional Plasticity Induced by Mirror Training. Neurorehabil Neural Repair [Internet]. 2012 Jun 13;26(5):484–96. Available from: http://journals.sagepub.com/doi/10.1177/1545968311427917

147. Bello UM, Kranz GS, Winser SJ, Chan CCHH. Neural Processes Underlying Mirror-Induced Visual Illusion: An Activation Likelihood Estimation Meta-Analysis. Front Hum Neurosci [Internet]. 2020 Jul 31;14(July):1–12. Available from: https://www.frontiersin.org/article/10.3389/fnhum.2020.00276/full

148. Saleh S, Adamovich S V., Tunik E. Mirrored Feedback in Chronic Stroke. Neurorehabil Neural Repair [Internet]. 2014 May 26;28(4):344–54. Available from: http://journals.sagepub.com/doi/10.1177/1545968313513074

149. Garry MI, Loftus A, Summers JJ. Mirror, mirror on the wall: Viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability. Exp Brain Res. 2005;163(1):118–22.

150. Novaes MM, Palhano-Fontes F, Peres A, Mazzetto-Betti K, Pelicioni M, Andrade KC, et al. Neurofunctional changes after a single mirror therapy intervention in chronic ischemic stroke. Int J Neurosci [Internet]. 2018;128(10):966–74. Available from: https://www.tandfonline.com/doi/full/10.1080/00207454.2018.1447571

151. Yarossi M, Manuweera T, Adamovich S V., Tunik E. The Effects of Mirror Feedback during Target Directed Movements on Ipsilateral Corticospinal Excitability. Front Hum Neurosci [Internet]. 2017;11(May):1–12. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00242/full

152. Adamovich SV, August K, Merians A, Tunik E. A virtual reality-based system integrated with fmri to study neural mechanisms of action observation-execution: A proof of concept study. Restor Neurol Neurosci. 2009;27(3):209–23.

153. Saleh S, Yarossi M, Manuweera T, Adamovich S, Tunik E. Network interactions underlying mirror feedback in stroke: A dynamic causal modeling study. NeuroImage Clin. 2017;13:46–54.

154. Michielsen M, Smits M, Ribbers G, Stam H, van der Geest J, Bussmann J SR. The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in patients with stroke. J Neurol Neurosurg Psychiatry. 2011;82(4):393–8.

155. Matthys K, Smits M, Van der Geest JN, Van der Lugt A, Seurinck R, Stam HJ, et al. Mirror-Induced Visual Illusion of Hand Movements: A Functional Magnetic Resonance Imaging Study. Arch Phys Med Rehabil [Internet]. 2009;90(4):675–81. Available from: http://dx.doi.org/10.1016/j.apmr.2008.09.571

156. Marshall RS, Zarahn E, Alon L, Minzer B, Lazar RM, Krakauer JW. Early imaging correlates of subsequent motor recovery after stroke. Ann Neurol [Internet]. 2009 May;65(5):596–602. Available from: http://doi.wiley.com/10.1002/ana.21636

157. Hadoush H, Mano H, Sunagawa T, Nakanishi K, Ochi M. Optimization of mirror therapy to excite ipsilateral primary motor cortex. NeuroRehabilitation. 2013;32(3):617–24.

158. Rossiter HE, Borrelli MR, Borchert RJ, Bradbury D, Ward NS. Cortical Mechanisms

of Mirror Therapy After Stroke. Neurorehabil Neural Repair [Internet]. 2015;29(5):444–52. Available from: http://journals.sagepub.com/doi/10.1177/1545968314554622

159. Guo F, Xu Q, Abo Salem HM, Yao Y, Lou J, Huang X. The neuronal correlates of mirror therapy: A functional magnetic resonance imaging study on mirror-induced visual illusions of ankle movements. Brain Res [Internet]. 2016 May;1639:186–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006899316301184

160. Lee H-M, Li P-C, Fan S-C. Delayed mirror visual feedback presented using a novel mirror therapy system enhances cortical activation in healthy adults. J Neuroeng Rehabil [Internet]. 2015 Dec 11;12(1):56. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498534/pdf/12984_2015_Article_53.pdf

161. Brunetti M, Morkisch N, Fritzsch C, Mehnert J, Steinbrink J, Niedeggen M, et al. Potential determinants of efficacy of mirror therapy in stroke patients – A pilot study. Restor Neurol Neurosci [Internet]. 2015 Aug 19;33(4):421–34. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4923713/pdf/rnn-33-4-rnn140421.pdf

162. Hung GKN, Li CTL, Yiu AM, Fong KNK. Systematic Review: Effectiveness of Mirror Therapy for Lower Extremity Post-Stroke. Hong Kong J Occup Ther [Internet]. 2015 Dec 1;26(1):51–9. Available from: http://journals.sagepub.com/doi/10.1016/j.hkjot.2015.12.003

163. Rothgangel AS, Braun SM, Beurskens AJ, Seitz RJ, Wade DT. The clinical aspects of mirror therapy in rehabilitation. Int J Rehabil Res [Internet]. 2011 Mar;34(1):1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21326041

164. Morkisch N, Thieme H, Dohle C. How to perform mirror therapy after stroke?

Evidence from a meta-analysis. Restor Neurol Neurosci. 2019;37:421–35.

165. Louie DR, Lim SB, Eng JJ. The Efficacy of Lower Extremity Mirror Therapy for Improving Balance, Gait, and Motor Function Poststroke: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis [Internet]. 2019 Jan;28(1):107–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30314760

166. Broderick P, Horgan F, Blake C, Ehrensberger M, Simpson D, Monaghan K. Mirror therapy for improving lower limb motor function and mobility after stroke: A systematic review and meta-analysis. Gait Posture [Internet]. 2018 Jun;63:208–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29775908

167. Li Y, Wei Q, Gou W, He C. Effects of mirror therapy on walking ability, balance and lower limb motor recovery after stroke: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil [Internet]. 2018 Aug 12;32(8):1007–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29644880

168. Yang Y, Zhao Q, Zhang Y, Wu Q, Jiang X, Cheng G. Effect of Mirror Therapy on Recovery of Stroke Survivors: A Systematic Review and Network Meta-analysis. Neuroscience [Internet]. 2018 Oct;390:318–36. Available from: https://doi.org/10.1016/j.neuroscience.2018.06.044

169. Crosby LD, Marrocco S, Brown J, Patterson KK. A novel bilateral lower extremity mirror therapy intervention for individuals with stroke. Heliyon [Internet]. 2016;2(12):e00208. Available from: http://dx.doi.org/10.1016/j.heliyon.2016.e002082405-8440/

170. Salem HMA, Huang X. The Effects of Mirror Therapy on Clinical Improvement in Hemiplegic Lower Extremity Rehabilitation in Subjects with Chronic Stroke. Int J Biomed Biol Eng [Internet]. 2015;9(2):163–6. Available from:

http://waset.org/publications/10000591

171. Xu Q, Guo F, Salem HMAA, Chen H, Huang X. Effects of mirror therapy combined with neuromuscular electrical stimulation on motor recovery of lower limbs and walking ability of patients with stroke: a randomized controlled study. Clin Rehabil [Internet]. 2017;31(12):1583–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28459163

172. Lee HJ, Kim YM, Lee DK. The effects of action observation training and mirror therapy on gait and balance in stroke patients. J Phys Ther Sci [Internet]. 2017;29(3):523–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5361025/pdf/jpts-29-523.pdf

173. Mohan U, Babu SK, Kumar KV, Suresh B V, Misri ZK, Chakrapani M. Effectiveness of mirror therapy on lower extremity motor recovery, balance and mobility in patients with acute stroke: A randomized sham-controlled pilot trial. Ann Indian Acad Neurol [Internet]. 2013;16(4):634. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/583/CN-01092583/frame.html%5Cnhttp://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/335/CN-00915335/frame.html

174. Donetto S, Pierri P, Tsianakas V, Robert G. Experiencebased co-design and healthcare improvement: Realizing participatory design in the public sector. Des J. 2015;18(2):227–48.

175. Trischler J, Pervan SJ, Kelly SJ, Scott DR. The Value of Codesign: The Effect of Customer Involvement in Service Design Teams. J Serv Res. 2018;21(1):75–100.

176. Robert G, Cornwell J, Locock L, Purushotham A, Sturmey G, Gager M. Patients and staff as codesigners of healthcare services. BMJ [Internet]. 2015;350(February):g7714.

Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.g7714

177. Bernhardt J, Borschmann KN, Kwakkel G, Burridge JH, Eng JJ, Walker MF, et al. Setting the scene for the Second Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2019;14(5):450–6.

178. Eng JJ, Bird M-L, Godecke E, Hoffmann TC, Laurin C, Olaoye OA, et al. Moving Stroke Rehabilitation Research Evidence into Clinical Practice: Consensus-Based Core Recommendations From the Stroke Recovery and Rehabilitation Roundtable. Neurorehabil Neural Repair [Internet]. 2019 Nov 29;33(11):935–42. Available from: https://doi.org/10.1177/1545968319886485

179. Fischer G. Meta — Design : Beyond User-Centered and Participatory Design. InProceedings HCI Int. 2003;22–7.

180. Howard Z, Somerville MM. A comparative study of two design charrettes: implications for codesign and participatory action research. CoDesign [Internet]. 2014 Jan 2;10(1):46–62. Available from: http://www.tandfonline.com/doi/abs/10.1080/15710882.2014.881883

181. Gulliksen J, Göransson B, Boivie I, Blomkvist S, Persson J, Cajander Å. Key principles for user-centred systems design. Behav Inf Technol [Internet]. 2003 Nov;22(6):397–409. Available from: http://acsd.hci.uu.se

182. Pea RD. User Centered System Design: New Perspectives on Human-Computer Interaction [Internet]. Vol. 3, Journal educational computing research. 1987. 129–134 p. Available from: https://telearn.archives-ouvertes.fr/hal-00190545/document

183. Jankowski N, Schönijahn L, Kreitlow A, Götze E, Wahl M. A user-centered design approach in the development of rehabilitation devices after stroke. Int Conf Rehabil Robot. 2017;965–70.

184. Mountain G, Wilson S, Eccleston C, Mawson S, Hammerton J, Ware T, et al. Developing and testing a telerehabilitation system for people following stroke: issues of usability. J Eng Des [Internet]. 2010 Jun 21;21(2–3):223–36. Available from: https://www.tandfonline.com/doi/full/10.1080/09544820903333792

185. Hancock NJ, Pomeroy VM, Dorer C, Jarritt P, Kennedy N, Mares K, et al. An action plan for production of the next generation of movement rehabilitation technologies. Synapse, Journal of the Association of Chartered Physiotherapists in Neurology. 2018.

186. Lu EC, Wang R, Huq R, Gardner D, Karam P, Zabjek K, et al. Development of a robotic device for upper limb stroke rehabilitation: A user-centered design approach. Paladyn, J Behav Robot [Internet]. 2011 Jan 1;2(4):176–84. Available from: http://www.degruyter.com/view/j/pjbr.2011.2.issue-4/s13230-012-0009-0/s13230-012-0009-0.xml

187. Scrivener K, Sherrington C, Schurr K. Exercise dose and mobility outcome in a comprehensive stroke unit : Description and prediction from a prospective cohort study. J Rehabil Med. 2012;44(10):824–9.

188. English C, Veerbeek J. Is more physiotherapy better after stroke? Int J Stroke. 2015;10(4):465–6.

189. Cooke E V, Tallis RC, Clark A, Pomeroy VM. Efficacy of Functional Strength Training on Restoration of Lower-Limb Motor Function Early After Stroke: Phase I Randomized Controlled Trial. Neurorehabil Neural Repair [Internet]. 2010 Jan 24;24(1):88–96. Available from: http://journals.sagepub.com/doi/10.1177/1545968309343216

190. Borschmann K, Hayward KS, Raffelt A, Churilov L, Kramer S, Bernhardt J. Rationale for Intervention and Dose Is Lacking in Stroke Recovery Trials: A Systematic Review.

Stroke Res Treat [Internet]. 2018 Oct 30;2018:1–9. Available from: https://doi.org/10.1155/2018/8087372

191. Piantadosi S. Translational clinical trials: an entropy-based approach to sample size. Clin trials [Internet]. 2005;2(1 82-1 92). Available from: www.SCT1ournal.com

192. Bretz F, Dette H, Pinheiro JC. Practical considerations for optimal designs in clinical dose finding studies. Stat Med. 2010;29(7–8):731–42.

193. Lang CE, Strube MJ, Bland MD, Waddell KJ, Cherry-Allen KM, Nudo RJ, et al. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. Ann Neurol. 2016;80(3):342–54.

194. Dobkin BH. Progressive staging of pilot studies to improve phase III trials for motor interventions. Neurorehabil Neural Repair. 2009;23(3):197–206.

195. Dent SF, Eisenhauer EA. Review Phase I trial design: Are new methodologies being put into practice? Vol. 7, Annals of Oncology. Kluwer Academic Publishers; 1996.

196. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ [Internet]. 2008 Sep 29;a1655. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.a1655

197. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new Medical Research Council guidance. Int J Nurs Stud [Internet]. 2013 May;50(5):587–92. Available from: http://dx.doi.org/10.1016/j.ijnurstu.2012.09.010

198. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: Update of Medical Research Council guidance. *BMJ* 2021; 374: n2061.

https://dx.doi.org/10.1136/bmj.n2061

199. O'Cathain A, Croot L, Duncan E, et al. Guidance on how to develop complex interventions to improve health and healthcare. *BMJ Open*. 2019;9:e029954. Available from: doi: 10.1136/bmjopen-2019-029954

200. McBride KA, MacMillan F, George ES, Steiner GZ. The Use of Mixed Methods in Research. In: Handbook of Research Methods in Health Social Sciences [Internet]. Singapore: Springer Singapore; 2019. p. 695–713. Available from: http://link.springer.com/10.1007/978-981-10-5251-4_97

201. Shorten A, Smith J. Mixed methods research: expanding the evidence base. Evid Based Nurs [Internet]. 2017 Jul;20(3):74–5. Available from: http://ebn.bmj.com/lookup/doi/10.1136/eb-2017-102699

202. Creswell J, Pioano Clark V. Introducing a mixed method design [Internet]. Designing and conducting mixed methods research. 2007. 58–89 p. Available from: https://www.sagepub.com/sites/default/files/upm-binaries/10982_Chapter_4.pdf

203. Tariq S, Woodman J. Using mixed methods in health research. JRSM Short Rep [Internet]. 2013 Jun 1;4(6). Available from: http://journals.sagepub.com/doi/10.1177/2042533313479197

204. O'Cathain A, Murphy E, Nicholl J. Why, and how, mixed methods research is undertaken in health services research in England: a mixed methods study. BMC Health Serv Res [Internet]. 2007;7(1):85. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-7-85

205. Johnstone PL. Mixed Methods, Mixed Methodology Health Services Research in Practice. Qual Health Res [Internet]. 2004 Feb;14(2):259–71. Available from: http://journals.sagepub.com/doi/10.1177/1049732303260610

206. Doyle L, Brady A-M, Byrne G. An overview of mixed methods research. J Res Nurs [Internet]. 2009 Mar 1;14(2):175–85. Available from: http://journals.sagepub.com/doi/10.1177/1744987108093962

207. Curry LA, Nembhard IM, Bradley EH. Qualitative and Mixed Methods Provide Unique Contributions to Outcomes Research. Circulation [Internet]. 2009;119(10):1442–52. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.107.742775

208. Tsay JS, Winstein CJ. Five Features to Look for in Early-Phase Clinical Intervention Studies. Neurorehabil Neural Repair. 2020;

209. Morgan DL. Practical strategies for combining qualitative and quantitative methods: Applications to health research. Qual Health Res. 1998;8(3):362–76.

210. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. Int J Stroke. 2017;12(5):444–50.

211. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. 2008. 81–94 p.

212. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7).

213. Sterne J, Savović J, Page M, Elbers R, Blencowe N, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ [Internet]. 2019;366(14898). Available from: http://www.bristol.ac.uk/media-library/sites/social-community-

medicine/images/centres/cresyda/RoB2-0_indiv_main_guidance.pdf

214. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJH. Meta-analyses in mental health research - A practical guide. Vol. 15, World Psychiatry. 2016. 245–258 p.

215. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ [Internet]. 2014 Mar 7;348(mar07 3):g1687–g1687. Available from: https://www.bmj.com/content/bmj/348/bmj.g1687.full.pdf

216. Boland, A., Cherry G, Dickson R eds. Doing a systematic review: A student's guide. 2017. 148 p.

217. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties. Neurorehabil Neural Repair [Internet]. 2002 Sep 30;16(3):232–40. Available from: http://journals.sagepub.com/doi/10.1177/154596802401105171

218. Turns LJ, Neptune RR, Kautz SA. Relationships Between Muscle Activity and Anteroposterior Ground Reaction Forces in Hemiparetic Walking. Arch Phys Med Rehabil. 2007;88(9):1127–35.

219. Rech KD, Salazar AP, Marchese RR, Schifino G, Cimolin V, Pagnussat AS. Fugl-Meyer Assessment Scores Are Related With Kinematic Measures in People with Chronic Hemiparesis after Stroke. J Stroke Cerebrovasc Dis [Internet]. 2020 Jan;29(1):104463. Available from: https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104463

220. Song F, Hooper, Loke Y. Publication bias: what is it? How do we measure it? How do we avoid it? Open Access J Clin Trials [Internet]. 2013 Jul;5(1):71. Available from:

http://www.dovepress.com/publication-bias-what-is-it-how-do-we-measure-it-how-do-we-avoid-it-peer-reviewed-article-OAJCT

221. De S, Chopra C, Mehta DD, Mehndiratta MM. Comparison between Mirror Therapy and Mental Imagery in Improving Ankle Motor Recovery in Sub Acute Stroke Patients. Indian J Physiother Occup Ther - An Int J. 2017;11(3):169.

222. May HI, Özdolap Å, Mengi A, Sarikaya S. The effect of mirror therapy on lower extremity motor function and ambulation in post-stroke patients: A prospective, randomized-controlled study. Turkish J Phys Med Rehabil. 2020;66(2):154–60.

223. Bhoraniya S, Mishra D, Parikh S. The effect of mirror therapy on the gait of chronic stroke patients: A randomized controlled trial. Natl J Physiol Pharm Pharmacol [Internet]. 2018;8(9):1321. Available from: www.njppp.com

224. Wang H, Zhao Z, Jiang P, Li X, Lin Q, Wu Q. Effect and mechanism of mirror therapy on rehabilitation of lower limb motor function in patients with stroke hemiplegia. Biomed Res [Internet]. 2017;28(22). Available from: www.biomedres.info

225. Ji S-G, Cha H-G, Kim M-K, Lee C-R. The Effect of Mirror Therapy Integrating Functional Electrical Stimulation on the Gait of Stroke Patients. J Phys Ther Sci [Internet]. 2014 Apr;26(4):497–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3996407/pdf/jpts-26-497.pdf

226. Kim M-K, Choe Y-W, Shin Y-J, Peng C, Choi E-H. Effect of mirror use on lower extremity muscle strength of patients with chronic stroke. J Phys Ther Sci [Internet]. 2018 Feb;30(2):213–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5851349/pdf/jpts-30-213.pdf

227. Cha HG, Kim M-K. Therapeutic Efficacy of Low Frequency Transcranial Magnetic Stimulation in Conjunction with Mirror Therapy for Sub-acute Stroke Patients. J Magn

[Internet]. 2015 Mar 31;20(1):52–6. Available from: http://koreascience.or.kr/journal/view.jsp?kj=E1MGAB&py=2015&vnc=v20n1&sp=52

228. Cha H-G, Kim M-K. The Effects of Repetitive Transcranial Magnetic Stimulation Integrated Mirror Therapy on the Gait of Chronic Stroke Patients. J Magn [Internet]. 2015 Jun 30;20(2):133–7. Available from: http://koreascience.or.kr/journal/view.jsp?kj=E1MGAB&py=2015&vnc=v20n2&sp=133

229. Shabaani Mehr M, Khaleghdoost Mohammadi T, Jafroudi S, Kazemnezhad Leyli E, Majd Teimoori Z. The Effect of Mirror Therapy on the Walking Ability of Patients After Stroke. J Holist Nurs Midwifery. 2019 Oct 30;200–9.

230. Kawakami K, Miyasaka H, Nonoyama S, Hayashi K, Tonogai Y, Tanino G, et al. Randomized controlled comparative study on effect of training to improve lower limb motor paralysis in convalescent patients with post-stroke hemiplegia. J Phys Ther Sci [Internet]. 2015;27(9):2947–50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4616132/pdf/jpts-27-2947.pdf

231. Simpson D, Ehrensberger M, Horgan F, Blake C, Roberts D, Broderick P, et al. Unilateral dorsiflexor strengthening with mirror therapy to improve motor function after stroke: A pilot randomized study. Physiother Res Int. 2019 Oct 1;24(4).

232. Broderick P, Horgan F, Blake C, Ehrensberger M, Simpson D, Monaghan K. Mirror therapy and treadmill training for patients with chronic stroke: a pilot randomized controlled trial. Top Stroke Rehabil. 2019 Apr 3;26(3):163–72.

233. Kim M-K, Shin Y-J, Choi E-H. Effect of Mirror Therapy Combined with Lower Extremity Muscle Strength Exercise on Gait and Balance of Patients with Chronic

Stroke. J Korean Soc Phys Med. 2018;13(1):81–8.

234. Arya KN, Pandian S, Kumar V. Effect of activity-based mirror therapy on lower limb motor-recovery and gait in stroke: A randomised controlled trial. Neuropsychol Rehabil [Internet]. 2017 Sep 14 [cited 2018 Apr 23];29(8):1193–210. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28949281

235. Ji SG, Kim MK. The effects of mirror therapy on the gait of subacute stroke patients: a randomized controlled trial. Clin Rehabil [Internet]. 2015 Apr 14;29(4):348–54. Available from: http://journals.sagepub.com/doi/10.1177/0269215514542356

236. In T-S, Cha Y-R, Jung J-H, Jung K-S. Effects of visual feedback with a mirror on balance ability in patients with stroke. J Phys Ther Sci [Internet]. 2016;28(1):181–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755999/pdf/jpts-28-181.pdf

237. Montori VM, Smieja M, Guyatt GH. Publication Bias: A Brief Review for Clinicians. Mayo Clin Proc [Internet]. 2000 Dec;75(12):1284–8. Available from: http://dx.doi.org/10.4065/75.12.1284

238. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ [Internet]. 2011 Jul 22;343(jul22 1):d4002–d4002. Available from: http://www.bmj.com/content/342/bmj.d4002/suppl/DC1

239. Pan SL, Wu SC, Wu TH, Lee TK, Chen T. Location and size of infarct on functional outcome of noncardioembolic ischemic stroke. Disabil Rehabil. 2006;28(16):977–83.

240. Chen CL, Tang FT, Chen HC, Chung CY, Wong MK. Brain lesion size and location: Effects on motor recovery and functional outcome in stroke patients. Arch Phys Med

Rehabil. 2000;81(4):447–52.

241. Feys H, Hetebrij J, Wilms G, Dom R, De Weerdt W. Predicting arm recovery following stroke: Value of site of lesion. Acta Neurol Scand. 2000;102(6):371–7.

242. Walker MF, Hoffmann TC, Brady MC, Dean CM, Eng JJ, Farrin AJ, et al. Improving the development, monitoring and reporting of stroke rehabilitation research: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. Int J Stroke [Internet]. 2017 Jul 12 [cited 2018 Oct 2];12(5):472–9. Available from: https://uk.sagepub.com/en-gb/eur/journals-permissions.

243. Winstein C, Requejo P. Innovative Technologies for Rehabilitation and Health Promotion: What Is the Evidence? Phys Ther [Internet]. 2015;95(3):294–8. Available from: https://academic.oup.com/ptj/article-lookup/doi/10.2522/ptj.2015.95.2.294

244. Chun MH, Harty C, Schweber L. Comparative study of user-centred design approaches. Proc 31st Annu Assoc Res Constr Manag Conf ARCOM 2015. 2015;(September):1125–34.

245. The Academy of Medical Sciences. Our data-driven future in healthcare.People and partnerships at the heart of health related technologies [Internet]. 2018. Available from: www.acmedsci.ac.uk

246. Wong LP. Focus group discussion: A tool for health and medical research. Singapore Med J. 2008;49(3):256–60.

247. Kitzinger J. Introducing focus groups. BMJ [Internet]. 1995;311:299–302. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2550365/pdf/bmj00603-0031.pdf

248. Morgan DL. Focus groups and social interaction. 2nd ed. The SAGE Handbook of Interview Research: The Complexity of the Craft. 2012. 161–176 p.

249. Ryan KE, Gandha T, Culbertson MJ, Carlson C. Focus Group Evidence. Am J Eval [Internet]. 2014 Sep 3;35(3):328–45. Available from: http://journals.sagepub.com/doi/10.1177/1098214013508300

250. Madden D, Cadet-James Y, Atkinson I, Watkin Lui F. Probes and prototypes: a participatory action research approach to codesign. CoDesign [Internet]. 2014 Jan 2 [cited 2018 Jan 8];10(1):31–45. Available from: http://www.tandfonline.com/doi/abs/10.1080/15710882.2014.881884

251. Staniszewska S, Brett J, Simera I, Seers K, Mockford C, Goodlad S, et al. GRIPP2 reporting checklists: Tools to improve reporting of patient and public involvement in research. BMJ. 2017;358.

252. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. Adm Policy Ment Heal Ment Heal Serv Res [Internet]. 2015 Sep 6;42(5):533–44. Available from: http://link.springer.com/10.1007/s10488-013-0528-y

253. Plummer P. Focus group methodology. Part 1: Design considerations. Int J Ther Rehabil [Internet]. 2017 Jul 2;24(7):297–301. Available from: http://www.magonlinelibrary.com/doi/10.12968/ijtr.2017.24.7.297

254. Korstjens I, Moser A. Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing. Eur J Gen Pract [Internet]. 2018 Jan 1;24(1):120–4. Available from: https://doi.org/10.1080/13814788.2017.1375092

255. Onwuegbuzie AJ, Dickinson WB, Leech NL, Zoran AG. A Qualitative Framework for Collecting and Analyzing Data in Focus Group Research. Int J Qual Methods [Internet]. 2009 Sep 1;8(3):1–21. Available from:

http://ejournals.library.ualberta.ca/index.php/IJQM/article/view/4554

256. Krueger R a, Casey M a. Designing and conducting focus group interviews. Soc Anal Sel Tools … [Internet]. 2001;36(October):4–23. Available from: http://web.worldbank.org/archive/website01028/WEB/IMAGES/SDP_36.PDF#page=10

257. Guest G, Namey E, McKenna K. How Many Focus Groups Are Enough? Building an Evidence Base for Nonprobability Sample Sizes. Field methods. 2017;29(1):3–22.

258. Braun V, Clarke V. using thematic analysis in psychology. Qual Res Psychol [Internet]. 2006 [cited 2018 Jun 29];3(2):77–101. Available from: http://eprints.uwe.ac.uk/11735

259. Moser A, Korstjens I. Series: Practical guidance to qualitative research. Part 3: Sampling, data collection and analysis. Eur J Gen Pract [Internet]. 2018 Jan 1 [cited 2019 Sep 5];24(1):9–18. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=igen20

260. Plummer P. Focus group methodology. Part 2: Considerations for analysis. Int J Ther Rehabil [Internet]. 2017;24(7):297–301. Available from: https://www-magonlinelibrary-com.ueaezproxy.uea.ac.uk:2443/doi/pdfplus/10.12968/ijtr.2017.24.8.345

261. Albers GW, Bogousslavsky J, Bozik MA, Brass LM, Broderick JP, Fisher M, et al. Recommendations for clinical trial evaluation of acute stroke therapies. Stroke. 2001;32(7):1598–606.

262. Scmidt R. Dose-finding studies in clinical drug development. Eur J Clin Pharmacol [Internet]. 1988;34(1):15–9. Available from: http://link.springer.com/10.1007/BF01061410

263. Cook N, Hansen AR, Siu LL, Abdul Razak AR. Early phase clinical trials to identify optimal dosing and safety. Mol Oncol [Internet]. 2015 May 1;9(5):997–1007. Available from: http://dx.doi.org/10.1016/j.molonc.2014.07.025

264. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Stat Med. 2014;33(10):1646–61.

265. Colucci E, Clark A, Lang CE, Pomeroy VM. A rule-based, dose-finding design for use in stroke rehabilitation research: Methodological development. Physiotherapy (United Kingdom) [Internet]. 2017; Available from: http://dx.doi.org/10.1016/j.physio.2016.10.393

266. Dite W, Langford ZN, Cumming TB, Churilov L, Blennerhassett JM, Bernhardt J. A Phase 1 exercise dose escalation study for stroke survivors with impaired walking. Int J Stroke. 2015;10(7):1051–6.

267. Penel N, Isambert N, Leblond P, Ferte C, Duhamel A, Bonneterre J. Classical 3+3 design versus “accelerated titration designs”: Analysis of 270 phase 1 trials investigating anti-cancer agents. Invest New Drugs. 2009;27(6):552–6.

268. Boxall L, Hemsley A, White N. Exploring recruitment issues in stroke research: A qualitative study of nurse researchers’ experiences. Nurse Res. 2016;23(5):8–14.

269. Ferreira IS, Pinto CB, Saleh Velez FG, Leffa DT, Vulcano de Toledo Piza P, Fregni F. Recruitment challenges in stroke neurorecovery clinical trials. Contemp Clin Trials Commun [Internet]. 2019 Sep;15:100404. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2451865418301546

270. Penel N, Kramar A. What does a modified-Fibonacci dose-escalation actually correspond to? BMC Med Res Methodol [Internet]. 2012 Dec 23;12(1):103. Available from: http://www.biomedcentral.com/1471-2288/12/103

271. de Sousa DG, Harvey LA, Dorsch S, Varettas B, Jamieson S, Murphy A, et al. Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke: a randomised trial. J Physiother [Internet]. 2019;65(3):152–8. Available from: https://doi.org/10.1016/j.jphys.2019.05.007

272. Tighiouart M, Rogatko A. Number of Patients per Cohort and Sample Size Considerations Using Dose Escalation with Overdose Control. J Probab Stat [Internet]. 2012;2012:1–16. Available from: http://www.hindawi.com/journals/jps/2012/692725/

273. Bretz F, Hsu J, Pinheiro J, Liu Y. Dose finding - A challenge in statistics. Biometrical J. 2008;50(4):480–504.

274. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, et al. Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. Int J Stroke [Internet]. 2017 Jul 12;12(5):451–61. Available from: http://journals.sagepub.com/doi/10.1177/1747493017711813

275. Fayazi M, Dehkordi SN, Dadgoo M, Salehi M. Test-retest reliability of Motricity Index strength assessments for lower extremity in post stroke hemiparesis. Med J Islam Repub Iran [Internet]. 2012;26(1):27–30. Available from: http://mjiri.iums.ac.ir/article-1-481-en.pdf

276. Summan R, Pierce SG, Macleod CN, Dobie G, Gears T, Lester W, et al. Spatial calibration of large volume photogrammetry based metrology systems. Measurement [Internet]. 2015 May;68:189–200. Available from: http://dx.doi.org/10.1016/j.measurement.2015.02.054

277. Kerr A, Clark A, Cooke E V., Rowe P, Pomeroy VM. Functional strength training and

movement performance therapy produce analogous improvement in sit-to-stand early after stroke: Early-phase randomised controlled trial. Physiother (United Kingdom). 2016;(2016).

278. Meldrum D, Shouldice C, Conroy R, Jones K, Forward M. Test-retest reliability of three dimensional gait analysis: Including a novel approach to visualising agreement of gait cycle waveforms with Bland and Altman plots. Gait Posture [Internet]. 2014;39(1):265–71. Available from: http://dx.doi.org/10.1016/j.gaitpost.2013.07.130

279. Silva A, Sousa ASP, Pinheiro R, Ferraz J, Tavares JMRS, Santos R, et al. Activation timing of soleus and tibialis anterior muscles during sit-to-stand and stand-to-sit in post-stroke vs. healthy subjects. Somatosens Mot Res [Internet]. 2013;30(1):48–55. Available from: http://www.tandfonline.com/doi/full/10.3109/08990220.2012.754755

280. Stegeman D, Hermens H. Standards for surface electromyography: The European project Surface EMG for non-invasive assessment of muscles (SENIAM). Enschede Roessingh Res Dev [Internet]. 2007;108–2. Available from: http://www.seniam.org/%5Cnhttp://www.med.uni-jena.de/motorik/pdf/stegeman.pdf

281. Burke D. Clinical uses of H reflexes of upper and lower limb muscles. Clin Neurophysiol Pract [Internet]. 2016;1:9–17. Available from: http://dx.doi.org/10.1016/j.cnp.2016.02.003

282. Palmieri RM, Ingersoll CD, Hoffman MA. The Hoffmann reflex: Methodologic considerations and applications for use in sports medicine and athletic training research [Internet]. Vol. 39, Journal of Athletic Training. Association, Inc; 2004. Available from: www.journalofathletictraining.org

283. Knikou M. The H-reflex as a probe: Pathways and pitfalls. J Neurosci Methods [Internet]. 2008 Jun;171(1):1–12. Available from:

https://linkinghub.elsevier.com/retrieve/pii/S0165027008001192

284. van de Ruit M, Grey MJ. The TMS Motor Map Does Not Change Following a Single Session of Mirror Training Either with Or without Motor Imagery. Front Hum Neurosci [Internet]. 2017 Dec 12;11(December):1–12. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00601/full

285. Cho SH, Lee JH. Comparison of the amplitudes of the H-reflex of post-stroke hemiplegia patients and normal adults during walking. J Phys Ther Sci. 2013;25(6):729–32.

286. Mar Cortes, MD1, Randie M Black-Schaffer, MD2, and Dylan J Edwards P, Kinam Park. Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: an overview for neurorehabilitation clinicians. Bone [Internet]. 2008;23(1):1–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

287. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol [Internet]. 2009;120(12):2008–39. Available from: http://dx.doi.org/10.1016/j.clinph.2009.08.016

288. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol [Internet]. 2015 Jun;126(6):1071–107. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1388245715000711

289. Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical

guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. Clin Neurophysiol [Internet]. 2012 May;123(5):858–82. Available from: https://ac.els-cdn.com/S1388245712000569/1-s2.0-S1388245712000569-main.pdf?_tid=9947511d-5352-4b3e-a26c-a9ecc95089ba&acdnat=1543509548_039decc6874246b514f57dca73641f49

290. Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol [Internet]. 2001 Apr;112(4):720. Available from: https://ac.els-cdn.com/S1388245700005186/1-s2.0-S1388245700005186-main.pdf?_tid=b7b8f599-dc58-4af4-a124-3d6611d0cafc&acdnat=1543513327_9a36b762ba3363a25369133c424eae07

291. van de Ruit M, Pearson T, Grey MJ. Novel tools for rapid online data acquisition of the TMS stimulus-response curve. Brain Stimul [Internet]. 2019 Jan;12(1):192–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1935861X18303176

292. Gugino LD, Rafael Romero J, Aglio L, Titone D, Ramirez M, Pascual-Leone A, et al. Transcranial magnetic stimulation coregistered with MRI: A comparison of a guided versus blind stimulation technique and its effect on evoked compound muscle action potentials. Clin Neurophysiol. 2001 Oct 1;112(10):1781–92.

293. McCabe C. Mirror visual feedback therapy. a practical approach. J Hand Ther [Internet]. 2011;24(2):170–9. Available from: http://dx.doi.org/10.1016/j.jht.2010.08.003

294. Holleran CL, Rodriguez KS, Echauz A, Leech KA, Hornby TG. Potential Contributions of Training Intensity on Locomotor Performance in Individuals with Chronic Stroke. J Neurol Phys Ther. 2015;39(2):95–102.

295. Hunter SM, Hammett L, Ball S, Smith N, Anderson C, Clark A, et al. Dose–Response

Study of Mobilisation and Tactile Stimulation Therapy for the Upper Extremity Early After Stroke. Neurorehabil Neural Repair [Internet]. 2011 May 31;25(4):314–22. Available from: http://nnr.sagepub.com

296. Pereira LC, Botelho AC, Martins EF. Relationships between body symmetry during weight-bearing and functional reach among chronic hemiparetic patients. Rev Bras Fisioter. 2010;14(3):229–66.

297. Kugler C, Altenhner T, Lochner P, Ferbert A. Does age influence early recovery from ischemic stroke? J Neurol [Internet]. 2003 Jun 1;250(6):676–81. Available from: http://link.springer.com/10.1007/s00415-003-1054-8

298. Bagg S, Pombo AP, Hopman W. Effect of Age on Functional Outcomes After Stroke Rehabilitation. Stroke [Internet]. 2002 Jan;33(1):179–85. Available from: https://www.ahajournals.org/doi/10.1161/hs0102.101224

299. Dorsch S, Elkins MR. Repetitions and dose in stroke rehabilitation. J Physiother [Internet]. 2020 Oct;66(4):211–2. Available from: https://doi.org/10.1016/j.jphys.2020.04.001

300. Cheng P-T, Chen C-L, Wang C-M, Hong W-H. Leg Muscle Activation Patterns of Sit-to-Stand Movement in Stroke Patients. Am J Phys Med Rehabil [Internet]. 2004;83(1):10–6. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002060-200401000-00002

301. Zehr EP. Considerations for use of the Hoffmann reflex in exercise studies. Eur J Appl Physiol. 2002;86(6):455–68.

302. Hunter SM, Johansen-Berg H, Ward N, Kennedy NC, Chandler E, Weir CJ, et al. Functional Strength Training and Movement Performance Therapy for Upper Limb

Recovery Early Poststroke—Efficacy, Neural Correlates, Predictive Markers, and Cost-Effectiveness: FAST-INdiCATE Trial. Front Neurol [Internet]. 2018;8(January):1–24. Available from: http://journal.frontiersin.org/article/10.3389/fneur.2017.00733/full

303. Boyd LA, Hayward KS, Ward NS, Stinear CM, Rosso C, Fisher RJ, et al. Biomarkers of stroke recovery: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. Int J Stroke [Internet]. 2017 Jul 12;12(5):480–93. Available from: http://journals.sagepub.com/doi/10.1177/1747493017714176

Appendices

Appendices I – systematic review relevant documents

a. **Prisma reporting guideline that been used in this study** (212)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

b. Terms used in some of the databases

For example the following terms in Medline (OVID) were used

1. (Stroke or cva or poststroke or post stroke or cerebrovasc* or cerebral vascular).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. (Cerebral or cerebellar or brain* or vertebrobasilar or intracran* or intracerebral).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. (Infarct* or ischemi* or ischaemi* or thrombo* or emboli* or apoplexy* or occlus*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

4. 2 and 3

5. (cerebr* or brain* or subarachnoid or intracranial).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. (Haemorrhage or haemorrhage or haematoma or hematoma or bleed*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. 5 and 6

8. (hempar* or paretic or paresis or hemipleg* or brain injur*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9. Brain injuries/ or brain injury, chronic/

10. Cerebrovascular Disorders.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

11. Hemiplegia.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12. Gait Disorders, Neurologic/

13. exp hemiplegia/ or exp paresis/

14. 8 or 9 or 10 or 11 or 12 or 13

15. 1 or 4 or 7 or 8 or 9 or 10 or 11 or 12 or 13

16. exp lower extremity/

17. (lower limb* or lower extremit* or buttock* or foot or feet or hip or hips or knee or knees or leg or legs or thigh* or ankle* or heel* or toe or toes).tw.

18. 16 or 17

19. Illusions/

20. (mirror* or visual*).tw.

21. (visual adj5 (reflection or illusion or feedback or therapy)).tw.

22. ((limb* or leg) adj5 (reflect or reflection or illusion)).tw.

23. (mirror* or mirror therapy or mirror visual feedback or MVF or mirror training or mirror illusion* or mirror box*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

24. 19 or 20 or 21 or 22 or 23

25. 15 and 18 and 24

26. 15 and 18

27. 19 or 20 or 21 or 22

28. 26 and 27

29. 23 and 28

CINHAL via ebsco

S48	**S40 AND S44 AND S46 AND S47**	**758**
S47	S25 OR S28 OR S37	Display
S46	S44 OR S45	Display
S45	mirror* OR mirror therapy OR mirror visual feedback OR MVF OR mirror training OR mirror illusion* OR mirror box*	Display
S44	S41 OR S42 OR S43	Display
S43	reflect or reflection or illusion or visual feedback	Display
S42	mirror* or visual*	Display
S41	illusion	Display
S40	S38 OR S39	Display
S39	lower limb* or lower extremit* or buttock* or foot or feet or hip or hips or knee or knees or leg or legs or thigh* or ankle* or heel* or toe or toes	Display
S38	lower extremity	Display
S37	S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	Display
S36	Cerebrovascular accident	Display
S35	Hemiplegia	Display
S34	Exp hemiplegia/ or exp paresis	Display
S33	Gait Disorders, Neurologic/	Display
S32	Brain injuries/or brain injury, chronic/	Display
S31	hempar* or paretic or paresis or hemipleg* or brain injur*	Display
S30	Haemorrhage or haemorrhage or haematoma or hematoma or bleed*	Display
S29	cerebr* or brain* or subarachnoid or intracranial	Display
S28	S26 AND S27	Display
S27	Infarct* or ischemi* or ischaemi* or thrombo* or emboli* or apoplexy* or occlus*	Display
S26	Cerebral or cerebellar or brain* or vertebrobasilar or intracran* or intracerebral	Display
S25	Stroke or cva or poststroke or post stroke or cerebrovasc* or cerebral vascular	Display
S24	S16 AND S20 AND S22 AND S23	758
S23	S1 OR S4 OR S13	343,846
S22	S20 OR S21	176,464
S21	mirror* OR mirror therapy OR mirror visual feedback OR MVF OR mirror training OR mirror illusion* OR mirror box*	5,366
S20	S17 OR S18 OR S19	176,437
S19	reflect or reflection or illusion or visual feedback	77,190
S18	mirror* or visual*	103,842
S17	illusion	1,467
S16	S14 OR S15	201,082

S15	lower limb* or lower extremit* or buttock* or foot or feet or hip or hips or knee or knees or leg or legs or thigh* or ankle* or heel* or toe or toes	201,082
S14	lower extremity	25,339
S13	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	309,129
S12	Cerebrovascular accident	48,858
S11	Hemiplegia	6,169
S10	Exp hemiplegia/ or exp paresis	1
S9	Gait Disorders, Neurologic/	1,998
S8	Brain injuries/or brain injury, chronic/	3,138
S7	hempar* or paretic or paresis or hemipleg* or brain injur*	42,463
S6	Haemorrhage or haemorrhage or haematoma or hematoma or bleed*	74,926
S5	cerebr* or brain* or subarachnoid or intracranial	221,725
S4	S2 AND S3	39,971
S3	Infarct* or ischemi* or ischaemi* or thrombo* or emboli* or apoplexy* or occlus*	220,914
S2	Cerebral or cerebellar or brain* or vertebrobasilar or intracran* or intracerebral	208,163
S1	Stroke or cva or poststroke or post stroke or cerebrovasc* or cerebral vascular	109,738

c. Included studies with study ID and references

unique ID	Study ID	full article details
A1	Sütbeyaz-2007	Sütbeyaz S, Yavuzer G, Sezer N, Koseoglu BF. Mirror therapy enhances lower-extremity motor recovery and motor functioning after stroke: a randomized controlled trial. Archives Of Physical Medicine And Rehabilitation. 2007;88(5):555-9.
A2	Abo Salem-2015	Abo Salem HM, Huang X. The effects of mirror therapy on clinical improvement in hemiplegic lower extremity rehabilitation in subjects with chronic stroke. International Journal of Medical, Health, Biomedical, Bioengineering and Pharmaceutical Engineering 2015;9(2):163-166. 2015.
A3	Arya-2017	Arya KN, Pandian S, Kumar V. Effect of activity-based mirror therapy on lower limb motor-recovery and gait in stroke: A randomised controlled trial. Neuropsychological Rehabilitation. 2017:1-18.
A4	De-2017	De S, Chopra C, Mehta DM, Mehndiratta MM. Comparison between Mirror Therapy and Mental Imagery in Improving Ankle Motor Recovery in Sub Acute Stroke Patients. Indian Journal of Physiotherapy & Occupational Therapy. 2017;11(3):169-72.
A5	Lee-2017	Ho Jeong LEE, Young Mi KIM, Dong Kyu LEE. The effects of action observation training and mirror therapy on gait and balance in stroke patients. Journal of Physical Therapy Science. 2017;29(3):523-6.
A6	Mohan-2013	Mohan U, Babu SK, Kumar KV, Suresh BV, Misri ZK, Chakrapani M. Effectiveness of mirror therapy on lower extremity motor recovery, balance and mobility in patients with acute stroke: A randomized sham-controlled pilot trial. Annals of Indian Academy of Neurology. 2013;16(4):634-9.
A7	Bhoraniya-2018	Bhoraniya SH, Mishra DG, Parikh SM. The effect of mirror therapy on the gait of chronic stroke patients: A randomized controlled trial. National Journal of Physiology, Pharmacy and Pharmacology. 2018;8(9):1321-5.
A8	Xu-2017	Xu Q, Guo F, Salem HMA, Chen H, Huang X. Effects of mirror therapy combined with neuromuscular electrical stimulation on motor recovery of lower limbs and walking ability of patients with stroke: a randomized controlled study [with consumer summary]. Clinical Rehabilitation 2017 Dec;31(12):1583-1591. 2017.
A9	wang-2017	Wang H, Zhao Z, Jiang P, Li X, Lin Q, Wu Q. Effect and mechanism of mirror therapy on rehabilitation of lower limb motor function in patients with stroke hemiplegia. Biomedical Research (India). 2017;28(22):10165-70.
A10	Ji-2014	Ji SG, Cha HG, Kim MK, Lee CR. The effect of mirror therapy integrating functional electrical stimulation on the gait of stroke patients. Journal of physical therapy science. 2014;26(4):497-9.
A11	Ji-2015	Ji SG, Kim MK. The effects of mirror therapy on the gait of subacute stroke patients: a randomized controlled trial. Clinical rehabilitation. 2015;29(4):348-54.
A12	Kim-2018	Kim MK, Choe YW, Shin YJ, Peng C, Choi EH. Effect of mirror use on lower extremity muscle strength of patients with chronic stroke. Journal of physical therapy science. 2018;30(2):213-5.
A13	cha-2015	Cha HG, Kim MK. Therapeutic efficacy of low frequency transcranial magnetic stimulation in conjunction with mirror therapy for sub-acute stroke patients. J Magn 2015;20:52-56
A14	Cha (b)-2015	Cha HG, Kim MK. The effects of repetitive transcranial magnetic stimulation integrated mirror therapy on the gait of chronic stroke patients. Journal of Magnetics. 2015 Jun;20(2):133-7.
A15	simpson-2019	Simpson D, Ehrensberger M, HorganF, et al. Unilateral dorsiflexor strengthening with mirror ther-apy to improve motor function after stroke: A pilot randomizedstudy.Physiother Res Int. 2019

A16	Boderick-2018	P. Broderick, F. Horgan, C. Blake, M. Ehrensberger, D. Simpson & K. Monaghan (2019) Mirror therapy and treadmill training for patients with chronic stroke: a pilot randomized controlled trial,Topics in Stroke Rehabilitation, 26:3, 163-172, DOI: 10.1080/10749357.2018.1556504
A17	MEHER-2019	Shabaani Mehr, M., Khaleghdoost Mohammadi, T., Jafroudi, S., Kazemnezhad Leyli, E. and Majd Teimoori, Z., 2019. The Effect of Mirror Therapy on the Walking Ability of Patients After Stroke. *Journal of Holistic Nursing And Midwifery*, *29*(4), pp.200-209.
A18	KIM &SHIN - 2018	Kim M-K, Shin Y-J, Choi E-H. Effect of Mirror Therapy Combined with Lower Extremity Muscle Strength Exercise on Gait and Balance of Patients with Chronic Stroke. J Korean Soc Phys Med. 2018;13(1):81–8.
A19	Kawakami-2015	Kawakami K, miyasaKa H, nonoyama S, HayasHi K, Tonogai yusuKe, Tanino G, et al. Randomized controlled comparative study on effect of training to improve lower limb motor paralysis in convalescent patients with post-stroke hemiplegia . Vol. 27, Journal of physical therapy science. 2015 Sep.
A20	May	May HI, Özdolap Å, Mengi A, Sarikaya S. The effect of mirror therapy on lower extremity motor function and ambulation in post-stroke patients: A prospective, randomized-controlled study. Turkish J Phys Med Rehabil. 2020;66(2):154–60

d. Risk of bias tables for each included study as retrieved from ROB2 tool (213)

Unique ID	A1	**Study ID**	sutbeyaz-2007	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
Bias arising from the randomization process **Bias due to deviations from intended interventions**	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	
	2.1.Were participants aware of their assigned intervention during the trial?			Y	
Bias due to deviations from intended interventions **Bias due to missing outcome data**	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the			NA	

	group to which they were randomized?		
	Risk of bias judgement	**Low**	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
Bias due to missing outcome data **Bias in measurement of the outcome**	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Some concerns**	
	4.1 Was the method of measuring the outcome inappropriate?	PN	
Bias in measurement of the outcome **Bias in selection of the reported result**	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
Bias in selection of the reported result **Overall bias**	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Low**	
	Risk of bias judgement	**Some concerns**	

Unique ID	A2	**Study ID**	abo salem-2015	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PN	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**High**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A3	**Study ID**	ARYA-2017	**Assessor**	SB
Reference		**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PN	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**High**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	A4	**Study ID**	DE-2017	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			NI	
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PY	
	Risk of bias judgement			**High**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement		
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	NI	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A5	**Study ID**	lee-2017	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			NI	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			NI	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	

	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	A6	**Study ID**	Mohan-2013	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			NI	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PY	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	A7	**Study ID**	Bhoraniya-2018	**Assessor**	SB
Reference		**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NI	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NI	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			NI	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PN	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A8	**Study ID**	Xu-20187	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			NI	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PY	
	Risk of bias judgement			**Some concerns**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	A9	**Study ID**	wang-2017	**Assessor**	
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			Y	
	Risk of bias judgement			**High**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	NI	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A10	**Study ID**	Ji-2014	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PY	
	Risk of bias judgement			**High**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	NI	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A11	**Study ID**	Ji-2015	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PY	
	Risk of bias judgement			**Some concerns**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	NI	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple analyses of the data?	PY	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	A12	**Study ID**	Kim-2018	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			NI	
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			NI	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			NI	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NI	
	Risk of bias judgement			**High**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	NI	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PY	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A13	**Study ID**	cha-2015	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			N	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**High**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			Y	
	Risk of bias judgement			**Some concerns**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PY	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A14	**Study ID**	cha (B)-2015	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Journal article(s) with results of the trial
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			NI	
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			NI	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			NI	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NI	
	Risk of bias judgement			**High**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A15	**Study ID**	simpson_2019	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PY	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			PY	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			N	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			Y	
	Risk of bias judgement			**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			PN	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	

	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	A16	**Study ID**	Boderick_2018	**Assessor**	
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			Y	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			PY	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			PN	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			PY	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			PY	

	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	A17	**Study ID**	mehr_2019	**Assessor**	SB
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**High**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PY	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			PY	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			N	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NI	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PY	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A18	**Study ID**	KIM,shin&choi-2018	**Assessor**	SB
Reference		**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PN	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple analyses of the data?	PY	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	A19	**Study ID**	kawakami-2018	**Assessor**	SB
Reference		**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PN	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	
	Risk of bias judgement			**High**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PN	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PY	
	Risk of bias judgement			**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			N	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			PN	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	A20	**Study ID**	May	**Assessor**	sb
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	
Outcome		**Results**		**Weight**	1
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PY	
	Risk of bias judgement			**High**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	

	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

e. Template for intervention description and replication (TIDieR) checklist and guide (215)***used to evaluate the quality reporting in the current literature***

Item No	Item
1. Brief name	Provide the name or a phrase that describes the intervention.
2. Why	Describe any rationale, theory, intervention or goal of the elements essential to the intervention.
3. What (materials)	Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where this can be accessed (for example, online appendix, URL).
4. What (procedure)	describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.
5. Who provided	for each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given.
6. How	describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.
7. Where	describe the type (s) of location (s) where the intervention occurred, including any necessary infrastructure or relevant features.
8. When and how much	describe the number of times the intervention was delivered and over what period of time, including the number of sessions, their schedule, and their duration, intensity or dose.
9. Tailoring	if the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.
10. Modification	if the intervention was modified during the course of the study, describe the changes (what, why, when, and how).
11. How well (planned)	if the intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.
12. How well (actual)	if intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

f. How to identify Severity of paresis in this review

Study name (ID)	Severity motor impairment	How I judge severity level, which motor impairment used for categorisation of severity
Sütbeyaz-2007 (A1)	▪ Mean Brunnstrom was 2.4 (SD 0.7) for experimental and 2.5 (SD 1.0) for control	▪ Stated in paper "score between 1and 3 on Brunnstrom stage of recovery",and without volitional ankle dorsiflexion ▪ So this mean they had **severe paresis**
Abo Salem-2015 (A2)	▪ Mean Brunnstrom was 3.1 (SD 1.21) for experimental and 2.8 (SD 1.15) for control.	▪ Not stated in the paper about the "level of severity" however, mentioned the baseline characteristics of the participants the Brunnstrom stage of recovery for experimental group was mean of 3.1 that mean ▪ **The BSR for control group = 2.8** ▪ **Therefore the mean for the entire group was 2.95** ▪ **severe paresis**
Arya-2017 (A3)	BRS MT mean 3.16 (SD1.12) CONTROL mean 3.18 (SD1.31) FMA-LE mean 19.13 (SD 6.03) for experimental and 22.06 (7.38) for control	▪ **stated that the baseline of the participants for Brunnstrom stage of recovery mean=** 3.16 (1.12) **- so classified as moderate**
DE -2017 (A4)	No baseline values provided ▪ Brunnstrom recovery stage 2 and above but no further detail provided	▪ This study **excluded** from the analysis because of insufficient reporting for outcome values.
Lee-2017 (A5)	No impairment measure	▪ **Excluded** from analysis because not mention any motor impairment measures for participant at their baseline
Mohan-2013 (A6)	▪ Brunnstrom stage at baseline ▪ Experimental=3(12.99) ▪ Control= 2.2(22.9) ▪ ▪ FMA for experimental = 19.36 (4.11) and for control = 11.36 (6.73) Spasticity for experimental = 4.64 (1.5) and for control = 4.0 (1.84)	▪ BSS stage 2 or more ▪ According to FMA ▪ severe paresis
Bhoraniya-2018 (A7)	▪ No impairment measure	▪ **Excluded** from analysis because not mention any motor impairment measure for participants at their baseline
XU-2017(A8)	▪ Brunnstrom stage for experimental = 2.35 (0.57) and for control = 2.35 (0.57)	▪ MAS BETWEEN 1 AND 4 ▪ BUT BBS for baseline measure among mirror therapy group was 2.35 (0.57) ▪ **SEVERE paresis**
Wang-2017 (A9)	▪ Brunnstrom stage for experimental = 2.50 (1.10) and for control = 2.61 (1.14)	BSS FROM I –IV That means from 1 to 4 From severe to moderated paresis however from BBS before treatment was 2.50(1.10) Reported as **SEVERE**
JI-2014 (A10)	▪ Not measured	▪ **Excluded** from analysis because not mention any motor impairment measure for participant at their baseline
Ji-2015(A11)	Not measured	▪ **Excluded** from analysis because not mention any motor impairment measure for participant at their baseline

KIM-2018 (A12)	▪ **Brunnstrom stage for experimental = mean 3.3 (SD 0.48) and for control = mean 3.1 (SD 0.73**)	▪ from BBS at baseline from 3 to 4 ▪ **Moderate paresis.**
Cha (A13)	Not reported	**Excluded** from analysis because not mention any motor impairment measure for participant at their baseline
Cha (A14)	Not reported	**Excluded** from analysis because not mention any motor impairment measure for participant at their baseline
Simpson A(15)	Not measured BRS OR FMA	**excluded as they did not measure BRS or FMA for LL**
Broderick A16	▪ FMA MT=mean 23.53(SD 6.12) CONTROL=mean 22.53 (SD 7.58)	• **According to FMA** • **MT=mean 23.53(SD 6.12)** • **CONTROL=mean 22.53 (SD 7.58)** • **moderate paresis**
Mehr A 17	▪ mention few details	▪ **Stated "BBS score of 1 to 3 "** ▪ **It could be Severe paresis;** mathematical **expectation that the mean will be 2.9 or below. But as all participants scored 3 then severe is misclassification**
Kim,2018 (A18)	Brunnstrom stage of recovery Stage 2 Control=20% Experimental I=0% Stage 3 Control=50% Experimental I=70% Stage 4 Control=30% Experimental I=30% ▪	▪ Stated BBS 1-4 ▪ Mathematical expectation from majority of participant in mirror therapy group is stage 3 &4 = **Moderate** ▪ **Moderate paresis**
Kawakami - A19	▪ Not measured BRS OR FMA for LL.	▪ **Excluded as they did not reported BRS OR FMA LL at the baseline.**
May 2020	▪ BSS at baseline control group= mean 2.4 (SD 1.1) ▪ Mirror group= mean 2.4 (SD 1.1)	▪ **For BBS score 2.4 consider severe**

g. Email to include Kawakmi et al study after disagreements between assessors to include in the study

Warning: This email is from outside the UEA system. Do not click on links or attachments unless you expect them from the sender and know the content is safe.

Dear Dr. Sara bajuaifer,

Thank you for your email.

I will answer your question.

In ankle dorsiflexion, the dorsiflexion motion was performed on the paralyzed side at the same time as the ankle dorsiflexion motion on the non-paralyzed side.

It is a simple, dorsiflexion motion of the ankle joint.

During the exercise, the subjects watched the movement of the non-paralyzed side of the foot in the mirror.

In addition, the therapist pressed on the patient's paralyzed heel to hold the leg in place.

This movement was performed for four sets of 50 movements, in a rhythm that was comfortable for the patient.

Best regards.

Kenji Kawakami

Fujita Health University, Nanakuri Memorial Hospital

----- Original Message -----
From: Sarah Bajuaifer (HSC - Postgraduate Researcher) <S.Bajuaifer@uea.ac.uk>
To: "kawakamikenji07n@yahoo.co.jp" <kawakamikenji07n@yahoo.co.jp>
Date: 2020/7/7, Tue 06:24
Subject: lower limb study

Dear Mr Kawakami,

We are researcher at University of East Anglia doing our researcher on lower limb mirror therapy, we want to include you study (Randomized controlled comparative study on effect of training to improve lower limb motor paralysis in convalescent patients with post-stroke hemiplegia), we notice in the method that you used the motor imagery with mirror therapy in hip and knee exercise but its unclear for ankle exercise,

If you can please clarify for us if the ankle exercise is with motor imagery or no?

Thank you very much for your time

Kind regards,

Sarah

Sent from Mail for Windows 10

h. Studies exclude at the stage of screening titles and abstract

DGRW-update: Neurology - From empirical strategies towards evidence based interventions. [German]. Rehabilitation. 2011;50(6):354-62.

Al Sayegb S, Filen T, Johansson M, Sandstrom S, Stiewe G, Butler S. Mirror therapy for complex regional pain syndrome (CRPS)-A literature review and an illustrative case report. Scandinavian Journal of Pain. 2013;4(4):200-7.

Almeida P, Santos AR, Caseiro P, Poco R, Guimaraes R. Physiotherapy and mobility, self-care and domestic life independency of stroke patients-systematic review. Physiotherapy (United Kingdom). 2011;1):eS59.

Amasyali SY, Yaliman A. Comparison of the effects of mirror therapy and electromyography-triggered neuromuscular stimulation on hand functions in stroke patients: a pilot study. International Journal Of Rehabilitation Research Internationale Zeitschrift Fur Rehabilitationsforschung Revue Internationale De Recherches De Readaptation. 2016;39(4):302-7.

Anonymous. 31st Annual Congress of the French Society of Physical and Rehabilitation Medicine. Annals of Physical and Rehabilitation Medicine Conference: 31st Annual Congress of the French Society of Physical and Rehabilitation Medicine France. 2016;59(Supplement).

Arya KN, Pandian S. Effect of task-based mirror therapy on motor recovery of the upper extremity in chronic stroke patients: a pilot study. Topics In Stroke Rehabilitation. 2013;20(3):210-7.

Arya KN, Pandian S. Inadvertent recovery in communication deficits following the upper limb mirror therapy in stroke: A case report. Journal Of Bodywork And Movement Therapies. 2014;18(4):566-8.

Auld ML, Russo R, Moseley GL, Johnston LM. Determination of interventions for upper extremity tactile impairment in children with cerebral palsy: a systematic review. Developmental Medicine And Child Neurology. 2014;56(9):815-32.

Avanzino L, Raffo A, Pelosin E, Ogliastro C, Marchese R, Ruggeri P, et al. Training based on mirror visual feedback influences transcallosal communication. The European journal of neuroscience. 2014;40(3):2581-8.

Baskaya MC, Ercalik C, Karatas Kir O, Ercalik T, Tuncer T. The efficacy of mirror therapy in patients with adhesive capsulitis: a randomized, prospective, controlled study. Journal of Back and Musculoskeletal Rehabilitation 2018 Jul 20:Epub ahead of print. 2018.

Bondoc S, Booth J, Budde G, Caruso K, DeSousa M, Earl B, et al. Mirror Therapy and Task-Oriented Training for People With a Paretic Upper Extremity. The American Journal Of Occupational Therapy: Official Publication Of The American Occupational Therapy Association. 2018;72(2):7202205080p1-p8.

Brewer L, Horgan F, Hickey A, Williams D. Stroke rehabilitation: Recent advances and future therapies. Qjm. 2013;106(1):11-25.

Broderick P, Horgan F, Blake C, Ehrensberger M, Simpson D, Monaghan K. Mirror therapy for improving lower limb motor function and mobility after stroke: A systematic review and meta-analysis. Gait & posture. 2018;63:208-20.

Broderick PM, Horgan FP, Blake CP, Hickey PMB, O'Reilly JBPT, Ehrensberger MBA, et al. Mirror therapy and treadmill training for a patient with chronic stroke: A case report. Physiotherapy Theory And Practice. 2018:1-11.

Cacchio A, De Blasis E, De Blasis V, Santilli V, Spacca G. Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. Neurorehabilitation and Neural Repair. 2009;23(8):792-9.

Cha H-G, Oh D-W. Effects of mirror therapy integrated with task-oriented exercise on the balance function of patients with poststroke hemiparesis: a randomized-controlled pilot trial. International Journal Of Rehabilitation Research Internationale Zeitschrift Fur Rehabilitationsforschung Revue Internationale De Recherches De Readaptation. 2016;39(1):70-6.

Cho H-S, Cha H-G. Effect of mirror therapy with tDCS on functional recovery of the upper extremity of stroke patients. Journal Of Physical Therapy Science. 2015;27(4):1045-7.

Christakou A. Motor control and motor learning: Rehabilitation instruments and techniques. [Greek]. Epitheorese Klinikes Farmakologias kai Farmakokinetikes. 2013;31(3):234-42.

Coleman ER, Moudgal R, Lang K, Hyacinth HI, Awosika OO, Kissela BM, et al. Early Rehabilitation After Stroke: a Narrative Review. Current Atherosclerosis Reports. 2017;19(12):59-.

Crosby LD, Marrocco S, Brown J, Patterson K. Mirror therapy for the lower-extremities post-stroke: A case series. Archives of Physical Medicine and Rehabilitation. 2014;95 (10):e23.

Crosby LD, Marrocco S, Brown J, Patterson KK. A novel bilateral lower extremity mirror therapy intervention for individuals with stroke. Heliyon. 2016;2(12):e00208.

D'Agata F, Peila E, Cicerale A, Caglio MM, Caroppo P, Vighetti S, et al. Cognitive and Neurophysiological Effects of Non-invasive Brain Stimulation in Stroke Patients after Motor Rehabilitation. Frontiers in behavioral neuroscience. 2016;10:135.

Da-Silva RH, Moore SA, Price CI. Self-directed therapy programmes for arm rehabilitation after stroke: a systematic review. Clinical Rehabilitation. 2018;32(8):1022-36.

de Almeida Oliveira R, Cintia Dos Santos Vieira P, Rodrigues Martinho Fernandes LF, Patrizzi LJ, Ferreira de Oliveira S, Pascucci Sande de Souza LA. Mental practice and mirror therapy associated with conventional physical therapy training on the hemiparetic upper limb in poststroke rehabilitation: a preliminary study. Topics In Stroke Rehabilitation. 2014;21(6):484-94.

Doyle S, Bennett S, Fasoli SE, McKenna KT. Interventions for sensory impairment in the upper limb after stroke. The Cochrane Database Of Systematic Reviews. 2010(6):CD006331.

Ezendam D, Bongers RM, Jannink MJA. Systematic review of the effectiveness of mirror therapy in upper extremity function. Disability And Rehabilitation. 2009;31(26):2135-49.

Fuentes MA, Borrego A, Latorre J, Colomer C, Alcañiz M, Sánchez-Ledesma MJ, et al. Combined Transcranial Direct Current Stimulation and Virtual Reality-Based Paradigm for Upper Limb Rehabilitation in Individuals with Restricted Movements. A Feasibility Study with a Chronic Stroke Survivor with Severe Hemiparesis. Journal Of Medical Systems. 2018;42(5):87-.

Georgiades A, Sherwood A, Gullette EC, Babyak MA, Hinderliter A, Waugh R, et al. Effects of exercise and weight loss on mental stress-induced cardiovascular responses in individuals with high blood pressure. Hypertension 2000 Aug;36(2):171-176. 2000.

Guo F, Xu Q, Abo Salem HM, Yao Y, Lou J, Huang X. The neuronal correlates of mirror therapy: A functional magnetic resonance imaging study on mirror-induced visual illusions of ankle movements. Brain research. 2016;1639:186-93.

Gurbuz N, Afsar SI, Ayaş S, Cosar SNS. Effect of mirror therapy on upper extremity motor function in stroke patients: a randomized controlled trial. Journal Of Physical Therapy Science. 2016;28(9):2501-6.

Gygax MJ, Schneider P, Newman CJ. Mirror therapy in children with hemiplegia: a pilot study. Developmental Medicine And Child Neurology. 2011;53(5):473-6.

Hassan A, Josephs KA. Alien Hand Syndrome. Current Neurology and Neuroscience Reports. 2016;16 (8) (no pagination)(73).

Hlebs S. The effects and underlying mechanisms of mirror therapy - Literature review. Zdravniski Vestnik. 2013;82(6):410-8.

Horne M, Thomas N, McCabe C, Selles R, Vail A, Tyrrell P, et al. Patient-directed therapy during in-patient stroke rehabilitation: stroke survivors' views of feasibility and acceptability. Disability and rehabilitation. 2015;37(25):2344-9.

Hung GKN, Li CTL, Yiu AM, Fong KNK. Systematic Review: Effectiveness of Mirror Therapy for Lower Extremity Post-Stroke. Hong Kong Journal of Occupational Therapy. 2015;26(2):51-9.

Invernizzi M, Negrini S, Carda S, Lanzotti L, Cisari C, Baricich A. The value of adding mirror therapy for upper limb motor recovery of subacute stroke patients: a randomized controlled trial. European Journal Of Physical And Rehabilitation Medicine. 2013;49(3):311-7.

Ju Y, Yoon I-J. The effects of modified constraint-induced movement therapy and mirror therapy on upper extremity function and its influence on activities of daily living. Journal Of Physical Therapy Science. 2018;30(1):77-81.

Kang YJ, Park HK, Kim HJ, Lim T, Ku J, Cho S, et al. Upper extremity rehabilitation of stroke: facilitation of corticospinal excitability using virtual mirror paradigm. Journal Of Neuroengineering And Rehabilitation. 2012;9:71-.

Kawakami K, Miyasaka H, Nonoyama S, Hayashi K, Tonogai Y, Tanino G, et al. Randomized controlled comparative study on effect of training to improve lower limb motor paralysis in convalescent patients with post-stroke hemiplegia. Journal of physical therapy science. 2015;27(9):2947-50.

Kim H, Lee G, Song C. Effect of functional electrical stimulation with mirror therapy on upper extremity motor function in poststroke patients. Journal Of Stroke And Cerebrovascular Diseases: The Official Journal Of National Stroke Association. 2014;23(4):655-61.

Kim H, Shim J. Investigation of the effects of mirror therapy on the upper extremity functions of stroke patients using the manual function test. Journal Of Physical Therapy Science. 2015;27(1):227-9.

Kim JH, Lee B-H. Mirror therapy combined with biofeedback functional electrical stimulation for motor recovery of upper extremities after stroke: a pilot randomized controlled trial. Occupational Therapy International. 2015;22(2):51-60.

Kim K, Lee S, Kim D, Lee K, Kim Y. Effects of mirror therapy combined with motor tasks on upper extremity function and activities daily living of stroke patients. Journal Of Physical Therapy Science. 2016;28(2):483-7.

Kuhl N, Prowell K, Russell M. Rehabilitation of stroke recovery complicated by alien limb syndrome. Archives of Physical Medicine and Rehabilitation. 2017;98 (10):e100.

Laffont I, Galano E, Mottet D, Perrey S, Pelissier J, Froger J. How does BCI integrate our current strategies for rehabilitation after brain injury. Annals of Physical and Rehabilitation Medicine. 2013;1):e378-e9.

Lee D, Lee M, Lee K, Song C. Asymmetric training using virtual reality reflection equipment and the enhancement of upper limb function in stroke patients: a randomized controlled trial. Journal Of Stroke And Cerebrovascular Diseases: The Official Journal Of National Stroke Association. 2014;23(6):1319-26.

Lee MM, Cho H-Y, Song CH. The mirror therapy program enhances upper-limb motor recovery and motor function in acute stroke patients. American Journal Of Physical Medicine & Rehabilitation. 2012;91(8):689-96.

Lee Y-Y, Hsieh Y-W, Wu C-Y, Lin K-C, Chen C-K. Proximal Fugl-Meyer Assessment Scores Predict Clinically Important Upper Limb Improvement After 3 Stroke Rehabilitative Interventions. Archives Of Physical Medicine And Rehabilitation. 2015;96(12):2137-44.

Li LSW. Stroke rehabilitation. Journal of the Neurological Sciences. 2015;1):e460-e1.

Li Y, Wei Q, Gou W, He C. Effects of mirror therapy on walking ability, balance and lower limb motor recovery after stroke: a systematic review and meta-analysis of randomized controlled trials. Clinical rehabilitation. 2018;32(8):1007-21.

Liepert J. Evidence-based therapies for upper extremity dysfunction. Current Opinion In Neurology. 2010;23(6):678-82.

Liepert J. Evidence-based methods in motor rehabilitation. [German]. Journal fur Neurologie, Neurochirurgie und Psychiatrie. 2010;11(1):5-10.

Louie DR, Lim SB, Eng JJ. The Efficacy of Lower Extremity Mirror Therapy for Improving Balance, Gait, and Motor Function Poststroke: A Systematic Review and Meta-Analysis. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2018.

Medeiros Freitas AC, Pimenta Bezerra LA, Alves de Oliveira PC, Medeiros Freitas L, Rodrigues da Silva S, de Medeiros Cirne GN, et al. Avaliação da eficácia da terapia de espelho na Síndrome de Pusher e da heminegligência em pacientes pós-acidente vascular encefálico. Fisioterapia Brasil. 2017;18(3):362-8.

Mirela Cristina L, Matei D, Ignat B, Popescu CD. Mirror therapy enhances upper extremity motor recovery in stroke patients. Acta Neurologica Belgica. 2015;115(4):597-603.

Miryutova NF, Chistyakova VA, Vorob'eva VA, Zaitsev AA. [The comprehensive step-by-step rehabilitation of the patients after acute disturbances of the cerebral circulation]. Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury. 2017;94(2):4-11.

Margrett, C. M. *et al.* (2019) 'A Comparative Study on Mirror Therapy and Motor Imagery on Improving Gait in Post Stroke Subjects', *Indian Journal of Physiotherapy and Occupational Therapy - An International Journal*, 13(2), p. 23. doi: 10.5958/0973-5674.2019.00039.x.

Nam HS, Koh S, Beom J, Kim YJ, Park JW, Koh ES, et al. Recovery of Proprioception in the Upper Extremity by Robotic Mirror Therapy: a Clinical Pilot Study for Proof of Concept. Journal Of Korean Medical Science. 2017;32(10):1568-75.

Nilsen DM, DiRusso T. Using mirror therapy in the home environment: a case report. The American Journal Of Occupational Therapy: Official Publication Of The American Occupational Therapy Association. 2014;68(3):e84-e9.

Nilsen DM, Gillen G, Geller D, Hreha K, Osei E, Saleem GT. Effectiveness of interventions to improve occupational performance of people with motor impairments after stroke: an evidence-based review. The American journal of occupational therapy : official publication of the American Occupational Therapy Association. 2015;69(1):6901180030p1-9.

Opara JA. Post-stroke rehablitation. European Journal of Neurology. 2015;1):897.

Oujamaa L, Relave I, Froger J, Mottet D, Pelissier JY. Rehabilitation of arm function after stroke. Literature review. Annals Of Physical And Rehabilitation Medicine. 2009;52(3):269-93.

Paik Y-R, Lee J-H, Lee D-H, Park H-S, Oh D-H. Effect of mirror therapy and electrical stimulation on upper extremity function in stroke with hemiplegic patient: a pilot study. Journal Of Physical Therapy Science. 2017;29(12):2085-6.

Park Y, Chang M, Kim K-M, An D-H. The effects of mirror therapy with tasks on upper extremity function and self-care in stroke patients. Journal Of Physical Therapy Science. 2015;27(5):1499-501.

Paulino RH, Casarin Pastor FA. FEEDBACK VISUAL COM ESPELHO EM MEMBRO INFERIOR PARÉTICO APÓS ACIDENTE VASCULAR ENCEFÁLICO: Estudo De Casos. Revista Inspirar Movimento & Saude. 2014;6(5):1-5.

Pérez-Cruzado D, Merchán-Baeza JA, González-Sánchez M, Cuesta-Vargas AI. Systematic review of mirror therapy compared with conventional rehabilitation in upper extremity function in stroke survivors. Australian Occupational Therapy Journal. 2017;64(2):91-112.

Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. The Cochrane Database Of Systematic Reviews. 2014(11):CD010820.

Pulyk OR, Hyryavets MV. Treatment for patients with neglekt after ischemic stroke. Wiadomosci lekarskie (Warsaw, Poland : 1960). 2018;71(2 pt 1):326-8.

Radajewska A, Opara JA, Kucio C, Błaszczyszyn M, Mehlich K, Szczygiel J. The effects of mirror therapy on arm and hand function in subacute stroke in patients. International Journal Of Rehabilitation Research Internationale Zeitschrift Fur Rehabilitationsforschung Revue Internationale De Recherches De Readaptation. 2013;36(3):268-74.

Rothgangel AS, Braun SM, Beurskens AJ, Seitz RJ, Wade DT. The clinical aspects of mirror therapy in rehabilitation: a systematic review of the literature. International Journal of Rehabilitation Research. 2011;34(1):1-13.

Sakzewski L, Ziviani J, Boyd RN. Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis. Pediatrics. 2014;133(1):e175-e204.

Samuelkamaleshkumar S, Reethajanetsureka S, Pauljebaraj P, Benshamir B, Padankatti SM, David JA. Mirror therapy enhances motor performance in the paretic upper limb after stroke: a pilot randomized controlled trial. Archives Of Physical Medicine And Rehabilitation. 2014;95(11):2000-5.

Santamato A, Panza F, Filoni S, Ranieri M, Solfrizzi V, Frisardi V, et al. Effect of botulinum toxin type A, motor imagery and motor observation on motor function of hemiparetic upper limb after stroke. Brain Injury. 2010;24(9):1108-12.

Sathian K, Greenspan AI, Wolf SL. Doing it with mirrors: a case study of a novel approach to neurorehabilitation. Neurorehabilitation And Neural Repair. 2000;14(1):73-6.

Sayegh SA, Filén T, Johansson M, Sandström S, Stiewe G, Butler S. Mirror therapy for Complex Regional Pain Syndrome (CRPS)-A literature review and an illustrative case report. Scandinavian Journal Of Pain. 2013;4(4):200-7.

Schick T, Schlake H-P, Kallusky J, Hohlfeld G, Steinmetz M, Tripp F, et al. Synergy effects of combined multichannel EMG-triggered electrical stimulation and mirror therapy in subacute stroke patients with severe or very severe arm/hand paresis. Restorative Neurology And Neuroscience. 2017;35(3):319-32.

Schupp W. DGRW-update: Neurology - from empirical strategies towards evidence based interventions. Rehabilitation (Stuttg). 2011;50(6):354-62.

Schuster-Amft C, Henneke A, Hartog-Keisker B, Holper L, Siekierka E, Chevrier E, et al. Intensive virtual reality-based training for upper limb motor function in chronic stroke: a feasibility study using a single case experimental design and fMRI. Disability And Rehabilitation Assistive Technology. 2015;10(5):385-92.

Selles RW, Michielsen ME, Bussmann JBJ, Stam HJ, Hurkmans HL, Heijnen I, et al. Effects of a mirror-induced visual illusion on a reaching task in stroke patients: implications for mirror therapy training. Neurorehabilitation And Neural Repair. 2014;28(7):652-9.

Stoykov ME, Corcos DM. A review of bilateral training for upper extremity hemiparesis. Occupational Therapy International. 2009;16(3-4):190-203.

Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. [German]. Neurologie und Rehabilitation. 2013;19(2):103-17.

Thieme H, Morkisch N, Mehrholz J, Pohl M, Behrens J, Borgetto B, et al. Mirror therapy for improving motor function after stroke. The Cochrane Database Of Systematic Reviews. 2018;7:CD008449.

Thieme H, Morkisch N, Rietz C, Dohle C, Borgetto B. The Efficacy of Movement Representation Techniques for Treatment of Limb Pain--A Systematic Review and Meta-Analysis. The Journal Of Pain: Official Journal Of The American Pain Society. 2016;17(2):167-80.

Tung ML, Murphy IC, Griffin SC, Alphonso AL, Hussey-Anderson L, Hughes KE, et al. Observation of limb movements reduces phantom limb pain in bilateral amputees. Annals of Clinical and Translational Neurology 2014 Sep;1(9):633-638. 2014.

Tyson S, Thomas N, Wilkinson J, Vail A, Walsh C, McCabe C, et al. The effects of patient-directed mirror therapy on upper limb impairments and activity. International Journal of Stroke. 2014;4):16-7.

Wang W, Ma YW, Yang W. Mirror therapy on upper extremity function in patients with cerebral apoplexy hemiplegia and hand function. [Chinese]. Journal of Dalian Medical University. 2013;35(6):600-2.

Wilson CS, Smith D, Stockley R, Holmes PS. Do physiotherapists and occupational therapists use cognitive therapies during stroke rehabilitation? International Journal of Stroke. 2012;2):64-5.

Yang YR, Chen YH, Chang HC, Chan RC, Wei SH, Wang RY. Effects of interactive visual feedback training on post-stroke pusher syndrome: a pilot randomized controlled study. Clinical rehabilitation. 2015;29(10):987-93.

Yavuzer G, Selles R, Sezer N, Sütbeyaz S, Bussmann JB, Köseoğlu F, et al. Mirror therapy improves hand function in subacute stroke: a randomized controlled trial. Archives Of Physical Medicine And Rehabilitation. 2008;89(3):393-8.

Yeldan I, Huseyınsınoglu BE, Akıncı B, Tarakcı E, Baybas S, Ozdıncler AR. The effects of very early mirror therapy on functional improvement of the upper extremity in acute stroke patients. Journal Of Physical Therapy Science. 2015;27(11):3519-24.

Yi L, Qingchuan W, Wei G, Chengqi H. Effects of mirror therapy on walking ability, balance and lower limb motor recovery after stroke: a systematic review and meta-analysis of randomized controlled trials. Clinical Rehabilitation. 2018;32(8):1007-21.

Zeng W, Guo Y, Wu G, Liu X, Fang Q. Mirror therapy for motor function of the upper extremity in patients with stroke: A meta-analysis. Journal Of Rehabilitation Medicine. 2018;50(1):8-15.

Zhu L, Jia XH, Liu L, Wang SY, Yang SR, Song WQ. (Efficacy of movement imagination on rehabilitation of hand function in patients with post-stroke hemiplegia) [Chinese - simplified characters]. Chinese Journal of Cerebrovascular Diseases 2009 Sep 18;6(9):451-455,460. 2009.

Appendices II user design relevant documents (study II)

Research approval study information and consent

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Sarah Bajuaifer
HSC

Research & Innovation Services
Floor 1, The Registry
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ

Email: fmh.ethics@uea.ac.uk

Web: www.uea.ac.uk/researchandenterprise

23.08.18

Dear Sarah,

Title: The usability and feasibility of a novel mirror therapy device for lower limb stroke
Reference: 2017/18 - 117

Thank you for your e-mail dated 10.08.18 notifying us of the amendments you would like to make to your above proposal in line with the recommendations from your first letter. These have been considered and we can now confirm that your application have been approved.

Please could you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance and also that any adverse events which occur during your project are reported to the Committee.

Approval by the FMH-REC should not be taken as evidence that your study is compliant with GDPR and the Data Protection Act 2018. If you need guidance on how to make your study GDPR compliant, please contact your institution's Data Protection Officer.

Please can you also arrange to send us a report once your project is completed.

Yours sincerely,

Professor M J Wilkinson
Chair
FMH Research Ethics Committee

University of East Anglia

Appendix G II: Consent form

Date of visit |__|__|-|__|__|-|__|__|__|__| (DD-MM-YYYY)

Participant Identification Number: | |

Title of project: "The usability and feasibility of a novel mirror therapy device for lower limb stroke."

Researcher: Sarah Bajuaifer (PhD student) s.bajuaifer@uea.ac.uk

Primary supervisor: professor. Valerie Pomeroy V.pomeroy@uea.ac.uk

Secondary supervisor: Dr. Michael Grey M.grey@uea.ac.uk

Name of Participant: _____

Please initial box

I have read and understood the participant information sheet (PIS Version 2 , 31 July 2018)	
I understand that I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	
I understand that my participation is voluntary and that I am free to withdraw at any time until the point that the data are analysed without giving any reason.	
I also agree to complete a survey asking for: my demographic information (e.g., age, sex) experiences with the tool and further views on the mirror therapy.	
I understand that the focus groups discussions will be audio recorded. Only the researcher will have access to the recordings. The recordings will be anonymised when analysed.	
I understand that I will be asked to view the mirror box and explore it.	
I understand that while information gained during the study may be published, I will not be identified and all data will remain confidential.	
I agree to anonymised quotes being used in publications and presentations.	
I agree to take part in the study.	

One original copy of this form should be completed. The original should be stored in the investigator site file. Photocopies should be made of the original and given to the participant

Name of participant	Date	Signature
Researcher	Date	Signature
(Person taking consent)	(In full, i.e. 01 January 2017	

Appendix G (I)

Consent form

Date of visit |__|__|-|__|__|-|__|__|__|__| (DD-MM-YYYY)

Participant Identification Number: | |

Title of project: "The usability and feasibility of a novel mirror therapy device for lower limb stroke."

Researcher: Sarah Bajuaifer (PhD student) s.bajuaifer@uea.ac.uk

Primary supervisor: Professor Valerie Pomeroy V.pomeroy@uea.ac.uk

Secondary supervisor: Dr. Michael Grey M.grey@uea.ac.uk

Name of Participant: _____

I have read and understood the participant information package (PIS Version 2, 31 July 2018)

I have read and understood the participant information package

Please initial the box below (with thumb up and thumb down)

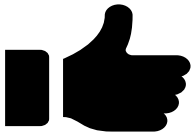
yes

No

I understand that I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily

I understand that I can ask questions

Please initial the box below (with thumb up and thumb down)



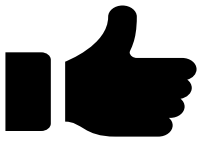
yes

No

I understand that my participation is voluntary and that I am free to withdraw at any time until the point that the data are analysed without giving any reason and without my medical care or legal rights being affected.

I understand that I can stop any time

Please initial the box below (with thumb up and thumb down)



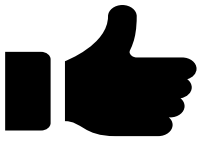
yes

No

I agree to also complete a survey asking for: my demographic information (e.g. age, address…..,) impact of stroke, experiences with the tool and further views on the mirror therapy equipment.

I'm happy to complete the survey

Please initial the box below (with thumb up and thumb down)



yes

No

I understand that the discussion will be audio recorded during the focus groups. Only the researcher will have the access to the recordings. The resultant recordings will be anonymised when analysed.

I agree to be audio recorded during the session

Please initial the box below (with thumb up and thumb down)

yes

No

I understand that I could be participating in focus groups at the University of East Anglia or my support group (stroke survivor) or my workplace (physiotherapist). I understand that I will be asked to view the mirror therapy equipment, try it out and explore its usability.

I agree to attend focus groups at the University of East Anglia, or my support group or my workplace to try the mirror therapy equipment and give my views regarding it.

Please initial the box below (with thumb up and thumb down)

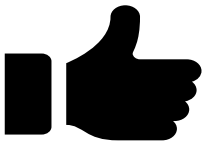
yes

No

I understand that while information gained during the study may be published, I will not be identified and all data will remain confidential.

I agree to anonymised quotes being used in publications and presentations.

Please initial the box below (with thumb up and thumb down)



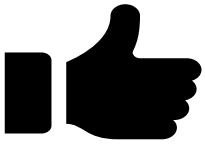
yes

No

We are conducting a second research study of how to use mirror therapy to improve lower limb recovery after stroke. If you are interested in learning more about this second study please let us know. If you express interest we will hold your contact details in a locked cabinet at UEA. We will contact you once either by phone or e-mail as soon as we finish this first study to see if you are interested in learning more about the second study. Your details would be protected by the **General Data Protection Regulation** (GDPR) and will not be shared with other parties. The data will not be kept if you're not interested or you withdraw from the first study at any point.

I agree to be contacted regarding other stroke related research for the University of East Anglia

Please initial the box below (with thumb up and thumb down)



yes

No

I agree to take part in the study.

Please initial the box below (with thumb up and thumb down)

yes

No

Name of participant	Date	Signature
Researcher (Person taking consent)	Date (In full, i.e. 01 January 2017	Signature

Participant information package/ Physiotherapist.

Project title: "The usability and feasibility of a novel mirror therapy device for lower limb stroke."

Researcher: Sarah Bajuaifer (s.bajuaifer@uea.ac.uk)

Primary supervisor: Professor. Valerie Pomeroy (V.pomeroy@uea.ac.uk)

Secondary supervisor: Dr. Michael Grey (M.grey@uea.ac.uk)

Researchers from the University of East Anglia (UEA) are gathering views about a new Rehabilitation tool, mirror therapy equipment, for stroke survivors. We would like to invite you to take part in our project. Your participation in this project is voluntary, and you are free to withdraw from the study at any time as detailed below.

If you **need more information about the study, please** ask the researchers at UEA who will be happy to answer your questions**. Their contact information is above.**

Thank you for reading this information and for considering taking part in this project.

What is the purpose of this project?

We intend to identify the best equipment setup to enable use mirror therapy for ankle dorsiflexion/plantar-flexion exercise in an upright sitting posture. We wish to seek your input about this process by asking you to participate in a focus group. This will allow us to change or adjust the apparatus according to users' feedback. We are seeking input from both stroke survivors and physiotherapists.

Am I eligible to take part in this project?

You're eligible to participate:

- If you are a qualified physiotherapist (Band 5 OR above).
- If you are currently involved in stroke rehabilitation or have previous experience in stroke rehabilitation
- If you would like to take part in this study.

Do I have to take part?

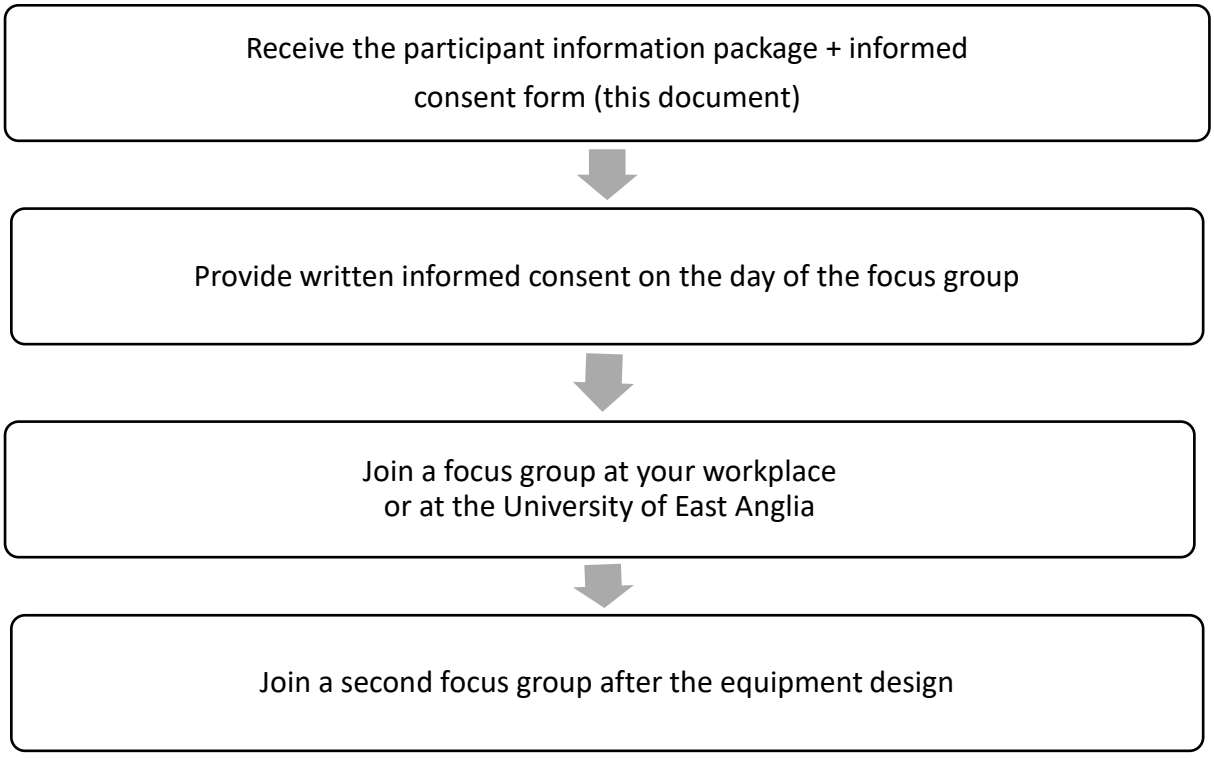
No. It is entirely up to you to decide. Your participation is voluntary. If you do take part, **you may withdraw at any time without giving a reason.**

If you do withdraw, we can only destroy your responses up until the point they are anonymised. After that point, it will not be possible to remove your data from the study.

What will happen to me if I take part?

If you are suitable and decide to take part, you will be asked to sign a consent form to show that you agree to take part.

What I will have to do??



What will happen to my information?

We will collect personal information such as your address, telephone number and/or email address so that we may arrange your appointment with us. Your contact details will be **stored separately from the anonymised data records and will not be associated with the results of the study in any way.**

You will be given a project number for the purpose of collecting and analysing data. This means you will remain anonymous. The data will be accessed only by authorised persons within the Research Team, who follow strict ethical protocols in the handling and storage of all project data and observe the **General Data Protection Regulation** (GDPR).

Will my taking part in this project be kept confidential?

The audio recordings of the focus groups will be transcribed by the researcher, and at this point, any information identifying you will be removed. **Your name will not be used in any records made in connection with the project.**

How will my information be stored?

Fully anonymised data will be stored securely in the lead researcher's office and on a password-protected computer during the project. Your contact details will be stored **in a locked file cabinet** in the researcher office and on **password-protected computer.**

After the project, these data will then be stored in a secure room, on a password-protected computer, at the **University of East Anglia for ten years**. All procedures for the handling, processing, storage, and destruction of data follow the requirements of the **General Data Protection Regulation** (GDPR).

What will happen to the results of the research project?

The results of the project will be used to **develop better mirror therapy equipment for the lower-limb.** The results of the study will be published in academic journals and presented at scientific conferences. The data will also be used within the researcher's PhD thesis. Participants **will not be identifiable in any publication**.

Are there any possible risks with this project?

There are no known risks to taking part in this project.

What are the possible benefits of taking part?

The data we obtain from your participation will give us **important insights that will be used to improve the rehabilitation tool** in the next stage of its development. We greatly appreciate the contribution of participants to this research and to future potential research, which, we hope, will benefit all stroke survivors.

What if there is a problem?

If you have **any complaints** about the way you have been dealt with or any harm is caused during the project **this will be addressed**.

You can contact the researchers at any point (whose information is at the beginning of this sheet). Or, you can contact the Director of Research at the School of Health Sciences at UEA:

Professor Valerie Pomeroy

School of Health Sciences. Queen's Building.

The University of East Anglia. Norwich NR4 7Tj.

Telephone: (01603) 591923. Email: v.pomeroy@uea.ac.uk

What if I no longer wish to continue with the project?

You have all the right to withdraw from the project without giving any reason up until the point your data is analysed. Should you wish to withdraw from the project, please contact either Sarah Bajuaifer (s.bajuaifer@uea.ac.uk) (TEL: +44 (0)) or Professor Valerie Pomeroy (contact details above).

Who has reviewed this project?

The Research Ethics Committee of the Faulty of Medicine and Health Sciences at the University of East Anglia (UEA) has reviewed and approved the project. The Research Ethics Committee is an independent group, which reviews research to protect the dignity, rights, safety, and well-being of participants and researchers.

Thank you very much for taking the time to read this leaflet. If you choose to participate, you will receive a copy of this participant information package and your signed informed consent form

Participant information package/stroke survivors.

Project title: "The usability and feasibility of a novel mirror therapy device for lower limb stroke."

Researcher: Sarah Bajuaifer (s.bajuaifer@uea.ac.uk)

Primary supervisor: Professor. Valerie Pomeroy (V.pomeroy@uea.ac.uk)

Secondary supervisor: Dr. Michael Grey (M.grey@uea.ac.uk)

Researchers from the University of East Anglia (UEA) are gathering views about a new rehabilitation tool for stroke survivors. We would like to invite you to take part in our project. Your participation in this project is voluntary, and you are free to withdraw from the study at any time as detailed below.

Please discuss the project with others (family, physiotherapist, etc.) if you would like to**.** If you **need more information about the study, please** ask the researchers at UEA who will be happy to answer your questions**. Their contact information is above.**

Thank you for reading this information and for considering taking part in this project.

What is the purpose of this project?

We intend to identify the best equipment setup to enable use the mirror therapy for ankle movement exercise in an upright sitting posture. We wish to seek your input about this process by asking you to participate in a focus group. This will allow us to change or adjust the apparatus and the set-up according to the user's feedback. We are seeking input from both stroke survivors and physiotherapists.

Am I eligible to take part in this project?

You are eligible to participate:

- If you have had a stroke, and you have been discharged from the NHS stroke rehabilitation service.
- If you are 18 years or older.
- If you are interested to take part in the study.

Do I have to take part?

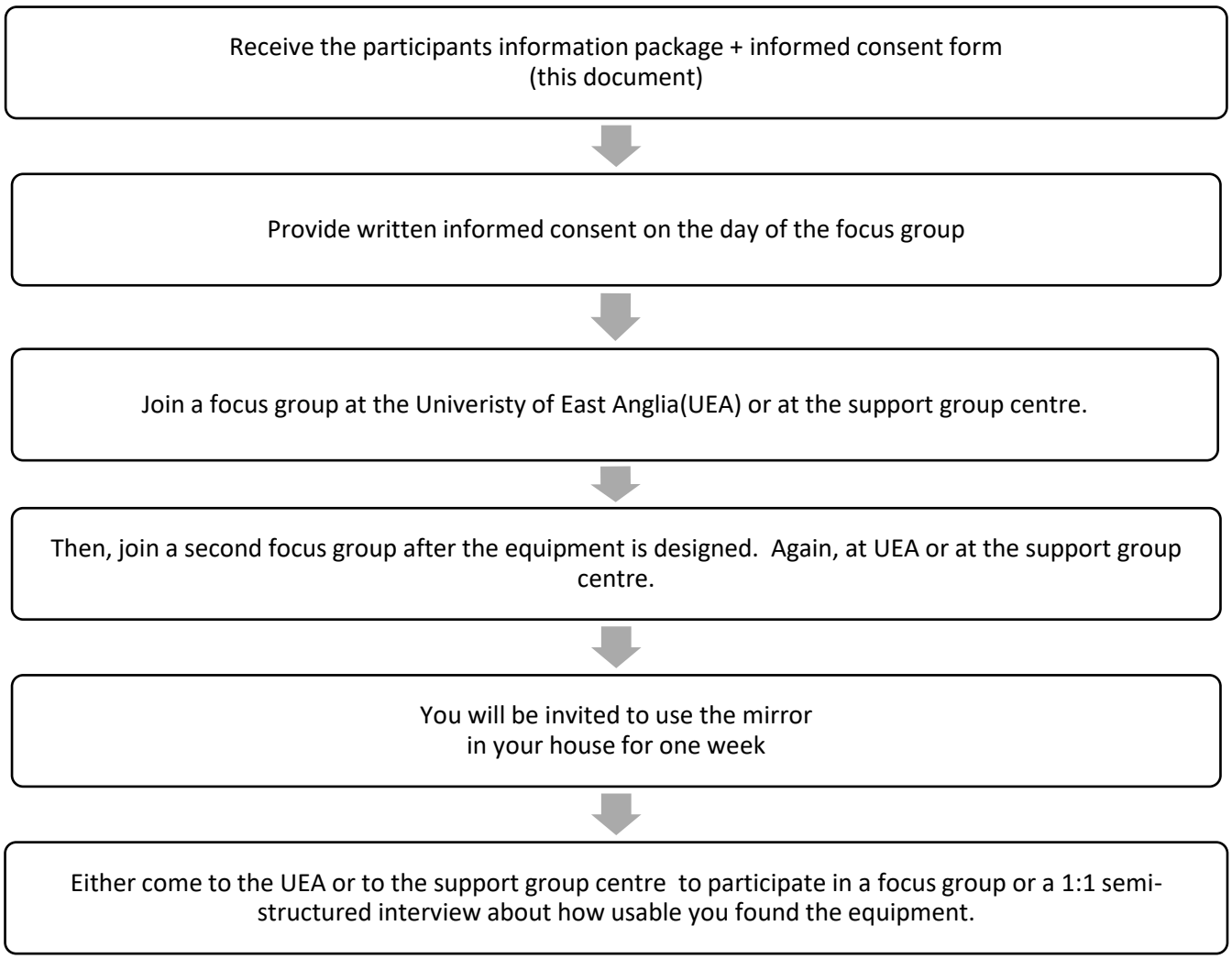
No. It is entirely up to you to decide. Your participation is voluntary. If you do take part, **you may withdraw at any time without giving a reason.**

If you do withdraw, we can only destroy your responses up until the point they are anonymised. After that point, it will not be possible to remove your data from the study. However, it will remain anomymised.

What will happen to me if I take part?

If you are suitable and decide to take part, you will be asked to sign a consent form to show that you agree to take part.

What will I have to do?



What will happen to my information?

The information we gather will include your age, sex and time since stroke. We will also record contact information including your address, telephone number and/or email address so that we may arrange your appointment with us. Your contact details will be **stored separately from the anonymised data records and will not be associated with the results of the study in any way.**

You will be given a project number for the purpose of collecting and analysing data. This means you **will remain anonymous**. The data will be accessed only by authorised persons within the Research Team, who will follow strict ethical protocols in the handling and storage of all project data and observe the **General Data Protection Regulation** (GDPR).

Will my taking part in this project be kept confidential?

The audio recordings of the focus groups will be transcribed by the researcher, and at this point, any information identifying you will be removed. **Your name will not be used in any records made in connection with the project.**

How will my information be stored?

Fully anonymised data will be **stored securely** in the lead researcher's office and on a

password-protected computer during the project. Your contact details will be stored **in a locked file cabinet** in the researcher office and on a **password-protected computer.**

After the project, these data will then be stored in a secure room, on a password protected computer, at the **University of East Anglia for ten years**. All procedures for the handling, processing, storage, and destruction of data follow the requirements of the **General Data Protection Regulation** (GDPR).

What will happen to the results of the research project?

The results of the project will be used to **develop better mirror therapy equipment for the lower-limb.** The results of the study will be published in academic journals and presented at scientific conferences. The data will also be used within the researcher's PhD thesis. Participants **will not be identifiable in any publication**.

Are there any possible risks with this project?

There are no known risks to taking part in this project.

What are the possible benefits of taking part?

The data we obtain from your participation will give us **important insights that will be used to improve the mirror therapy equipment** in the next stage of its development. We greatly appreciate the contribution of participants to this research and to future potential research, which, we hope, will benefit all stroke survivors.

What if there is a problem?

If you have **any complaints** about the way you have been dealt with or any harm is caused during the project **this will be addressed**.

You can contact the researchers at any point (whose information is at the beginning of this Sheet). Or, you can contact the Director of Research at the School of Health Sciences at UEA:

Professor Valerie Pomeroy

School of Health Sciences. Queen's Building.

The University of East Anglia. Norwich NR4 7Tj.

Telephone: (01603) 591923. Email: v.pomeroy@uea.ac.uk

What if I no longer wish to continue with the project?

You have the right to withdraw from the project without giving any reason up until the point your data is analysed. If you wish to withdraw from the project, please contact either Sarah Bajuaifer (s.bajuaifer@uea.ac.uk) (TEL: +44 (0)) or Professor Valerie Pomeroy (contact details above).

Who has reviewed this project?

The Research Ethics Committee of the Faculty of Medicine and Health Sciences at the University of East Anglia (UEA) has reviewed and approved the project. The Research Ethics Committee is an independent group, which reviews research to protect the dignity, rights, safety, and well-being of participants and researchers.

Thank you very much for taking the time to read this leaflet. If you choose to participate, you will receive a copy of this participant information package and the signed consent form.

Appendices III dose-finding relevant documents (study III)

Research governance, study information and consent

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Dose-Finding of lower limb mirror therapy after stroke.

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

(●) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(●) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Dose-Finding of lower limb mirror therapy after stroke.

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

(●) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(●) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

NHS
Health Research Authority

London – Stanmore Research Ethics Committee
Health Research Authority
Skipton House
80 London Road
London
SE1 6LH

Telephone: 020 7972 2561

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

23 April 2019

Mrs. Sarah Bajuaifer
University of East Anglia
Movement and Exercise Laboratory
Norwich research Park
Earlham Road
Norwich
NR4 7TJ

Dear Mrs Bajuaifer

Study title:	**Maximum tolerable dose per day to do lower limb mirror therapy with ankle exercise after stroke.**
REC reference:	**19/LO/0422**
IRAS project ID:	**255913**

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

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

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

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

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

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

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database 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).

Non-NHS sites

Research site	*Principal Investigator / Local Collaborator*
University of East Anglia, Movement and Exercise Physiology Laboratory	Mrs. Sarah Bajuaifer

The favourable opinion is subject to management permission or approval being obtained from the host organisation prior to the start of the study at the site concerned.

Approved documents

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

Document	*Version*	*Date*
Covering letter on headed paper [covering letter]	1	04 February 2019
Covering letter on headed paper [covering letter]	2	15 April 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [insurance]	1.0	11 February 2019
GP/consultant information sheets or letters [letter to GP]	1.0	07 February 2019
GP/consultant information sheets or letters [letter to GP]	2	15 April 2019
IRAS Application Form [IRAS_Form_12022019]		12 February 2019
IRAS Checklist XML [Checklist_15042019]		15 April 2019
Letters of invitation to participant [invitation letter to participants]	1.0	07 February 2019
Non-validated questionnaire [questions and demographics]	1.0	07 February 2019
Non-validated questionnaire [questions and demographics]	2	15 April 2019
Other [appendix]	1.0	07 February 2019
Other [sponser letter]	1.0	18 February 2019
Other [insurance 2]	1.0	18 February 2019
Other [funder letter]	1.0	19 February 2019
Other [appendix]	2	15 April 2019
Participant consent form [consent form]	1.0	07 February 2019
Participant consent form [consent form]	2	15 April 2019

Participant information sheet (PIS) [PIS]	1.0	07 February 2019
Participant information sheet (PIS) [PIS]	2	15 April 2019
Research protocol or project proposal [protocol]	1.0	07 February 2019
Research protocol or project proposal [protocol]	2	15 April 2019
Summary CV for Chief Investigator (CI) [CV for CI]	1	07 February 2019
Summary CV for student [student CV]	1	07 February 2019
Summary CV for supervisor (student research) [supervisor CV]	1	07 February 2019
Summary CV for supervisor (student research) [supervisor CV]	1	18 February 2019
Summary CV for supervisor (student research) [supervisor cv]	1.0	18 February 2019
Summary, synopsis or diagram (flowchart) of protocol in non technical language [summary]	1.0	07 February 2019

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/

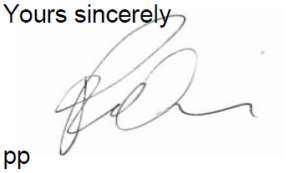
HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/LO/0422	Please quote this number on all correspondence

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

Yours sincerely



pp
Mrs Sunder Chita
Chair

Email:nrescommittee.london-stanmore@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Graham Horne*

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mrs. Sarah Bajuaifer
University of East Anglia, Movement and Exercise Laboratory
Norwich research park,Earlham Road
Norwich
NR4 7TJ

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

23 April 2019

Dear Mrs Bajuaifer

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Maximum tolerable dose per day to do lower limb mirror therapy with ankle exercise after stroke.**
IRAS project ID:	**255913**
REC reference:	**19/LO/0422**
Sponsor	**University of East Anglia**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

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

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **255913**. Please quote this on all correspondence.

Yours sincerely,
Andrea Bell

Approvals Specialist

Email: hra.approval@nhs.net

Copy to: *Mr Graham Horne*

NHS
Health Research Authority

London - Stanmore Research Ethics Committee

Ground Floor
NRES/HRA
80 London Road
London
SE1 6LH

25 October 2019

Mrs. Sarah Bajuaifer
The Queens Building- Norwich Research Park
School of Health Sciences- University of East Anglia
Norwich NR4 7TJ

Dear Mrs. Bajuaifer

Study title:	**Maximum tolerable dose per day to do lower limb mirror therapy with ankle exercise after stroke.**
REC reference:	**19/LO/0422**
Amendment number:	**3**
Amendment date:	**08 October 2019**
IRAS project ID:	**255913**

Thank you for submitting the above amendment, which was received on 17 October 2019. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC.

Documents received

The documents to be reviewed are as follows:

Document	*Version*	*Date*
GP/consultant information sheets or letters [letter to GP version 3.docx]	3	17 October 2019
Notice of Substantial Amendment (non-CTIMP) [AmendmentForm_ReadyForSubmission.pdf]	3	08 October 2019
Participant consent form [consent form version 3.docx]	3	17 October 2019
Participant consent form [consent to contact form.docx]	2	17 October 2019
Participant information sheet (PIS) [PIS VERSION 3.docx]	3	17 October 2019
Research protocol or project proposal [dose protocol version 3.docx]	3	17 October 2019

Notification of the Committee's decision

The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

R&D approval

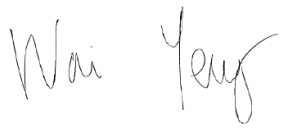
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval for the research.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/LO/0422:	**Please quote this number on all correspondence**

Yours sincerely



Wai Yeung
Approvals Administrator

Email: nrescommittee.london-stanmore@nhs.net

Copy to: *Mrs. Sarah Bajuaifer*

NHS
Health Research Authority

London - Stanmore Research Ethics Committee

Ground Floor
NRES/HRA
80 London Road
London
SE1 6LH

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

31 October 2019

Mrs. Sarah Bajuaifer
The Queens Building- Norwich Research Park
School of Health Sciences- University of East Anglia
Norwich NR4 7TJ

Dear Mrs. Bajuaifer

Study title:	**Maximum tolerable dose per day to do lower limb mirror therapy with ankle exercise after stroke.**
REC reference:	**19/LO/0422**
Amendment number:	**3**
Amendment date:	**08 October 2019**
IRAS project ID:	**255913**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [letter to GP version 3.docx]	3	17 October 2019
Notice of Substantial Amendment (non-CTIMP) [AmendmentForm_ReadyForSubmission.pdf]	3	08 October 2019
Participant consent form [consent form version 3.docx]	3	17 October 2019
Participant consent form [consent to contact form.docx]	2	17 October 2019
Participant information sheet (PIS) [PIS VERSION 3.docx]	3	17 October 2019
Research protocol or project proposal [dose protocol version 3.docx]	3	17 October 2019

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

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.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/LO/0422:	**Please quote this number on all correspondence**

Yours sincerely

PP - Mrs Sunder Chita
Chair

E-mail: nrescommittee.london-stanmore@nhs.net

Enclosures:	*List of names and professions of members who took part in the review*
Copy to:	*Mrs. Sarah Bajuaifer*

IRAS Project ID 255913. HRA Approval for the Amendment

nrescommittee.london-stanmore@nhs.net
Mon 11/25/2019 5:07 PM
To: Sarah Bajuaifer (HSC - Postgraduate Researcher); Graham Horne (RIN - Staff)

Dear Mrs. Bajuaifer,

IRAS Project ID:	255913
Short Study Title:	Dose-Finding of lower limb mirror therapy after stroke.
Amendment No./Sponsor Ref:	3
Amendment Date:	08 October 2019
Amendment Type:	Substantial Non-CTIMP

I am pleased to confirm **HRA and HCRW Approval** for the above referenced amendment.

You should implement this amendment at NHS organisations in England and Wales, in line with the conditions outlined in your categorisation email.

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 tle 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/.

Please contact hra.amendments@nhs.net for any queries relating to the assessment of this amendment.

Kind regards

Juliana Araujo
Approvals Specialist
Health Research Authority
Ground Floor | Skipton House | 80 London Road | London | SE1 6LH
E. hra.amendments@nhs.net
W. www.hra.nhs.uk

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University of East Anglia

Participant information sheet

Project title: “Dose-finding of lower limb mirror therapy after stroke.”

Researcher: Sarah Bajuaifer

Researchers from the University of East Anglia (UEA) are investigating a new rehabilitation therapy for stroke survivors. We would like to invite you to take part in our project**. Your participation in this project is voluntary, and you are free to withdraw from the study at any time as detailed below.**

You are free to discuss the project with others (for example your family, and/or physiotherapist) if you would like to**.** If you **need more information about the study before deciding whether to take part**, please ask the researchers at UEA who will be happy to answer your questions**. The researchers’ contact information is provided at the end of this information leaflet.**

Thank you for reading this information and for considering taking part in this project.

What is mirror therapy?

Mirror therapy produces the feeling that the weak limb is moving freely. A mirror is placed in front of, and between, your legs. You will sit so that the weaker leg is behind the mirror and the stronger leg is in front. The

weaker leg is covered so that you cannot see it. Then you move the foot of the stronger leg so that the toes come up from the floor and then back down again. You will be watching the reflection in the mirror. This produces the feeling that the weaker side is moving normally.

What is the purpose of this project?

There is some research evidence that mirror therapy might improve recovery after stroke but by how much is unknown. This study is the beginning of research to identify the best dose of mirror therapy. The purpose of this study is to find out what is the **maximum tolerable time** to do mirror therapy for **ankle exercise per day**. The study findings will provide some **guidance for the clinical setting** of the daily dose (time) for mirror therapy.

Am I eligible to take part in this project?

You are eligible to participate:

- If you have had a stroke that happened from at least six weeks ago.
- If you have been discharged from NHS stroke rehabilitation.
- If you are 18 years or older.
- If your have weakness in your leg following your stroke.
- If you are interested in taking part in the study.

Do I have to take part?

Your participation is voluntary . It is entirely up to you to decide. If you do take part, **you are free to withdraw at any time without giving a reason. Your decision will in no way affect any other parts of your treatment.**

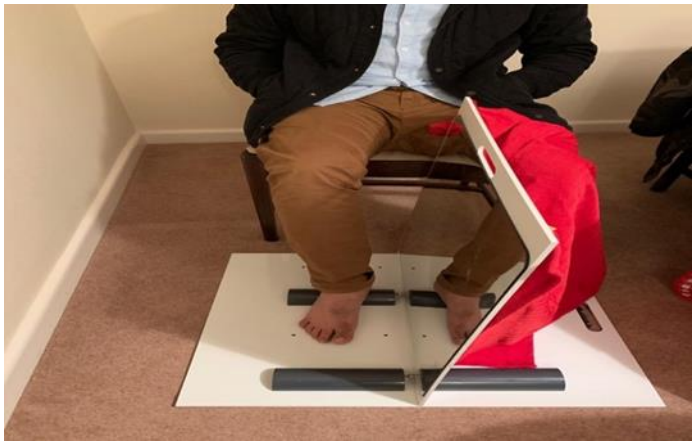
What will happen to me if I take part?

If you are suitable and have decided to take part, you will be asked to sign a consent form to show that you agree to take part. Also, we will contact your GP to check if there are any medical concerns that might prevent with you taking part in the study.

What will I have to do?

- You will give your **contact information (consent to be contacted)** to the clinical team/or gatekeeper of your support group.
- **The Researche**r will **contact you** to talk about the study.
- **The participant information sheet/consent** form will be **sent** to you according **to your preference (i.e. email or post).**
- **You will have up to seven days to** make your decision. If you decide to take part, you will sign a consent form. Then you will **come to** the **UEA MovExLab.**
- **At the lab visit,** you will undertake **baseline measures**. Then, we will set up the **mirror therapy** for you **and explain what you will do**. Please bring comfortable shorts and a t-shirt for wearing during the measures.

- **A Lower limb mirror box will be provided to you during the therapy (see picture at the end of this section).**
- You will be asked to do the **mirror therapy for two weeks at home**. The researcher will contact you during this time to check on your progress.
- **After the end of 14 days**, you will be asked to **come to** the UEA **MovExlab** for the **outcome measures**. Please bring comfortable shorts and a t-shirt for wearing during the measures.
- Your **travel expenses** to and from UEA will **be paid by the research team**.
- If you have a carer, he/she can attend the visit, help you with therapy and completion of the diary. The travel expenses of the carer will be covered as well.



The measures you will undertake before (baseline) and after doing the mirror therapy (outcome)

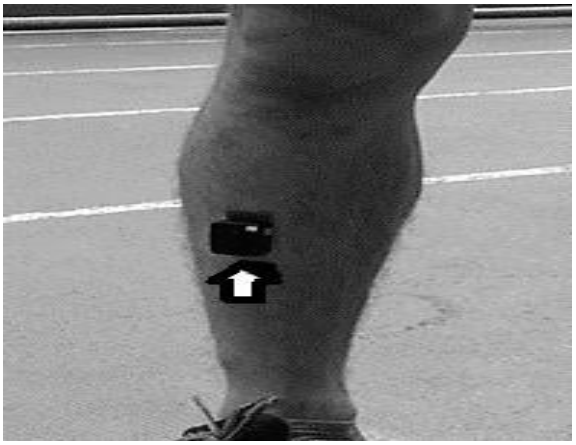
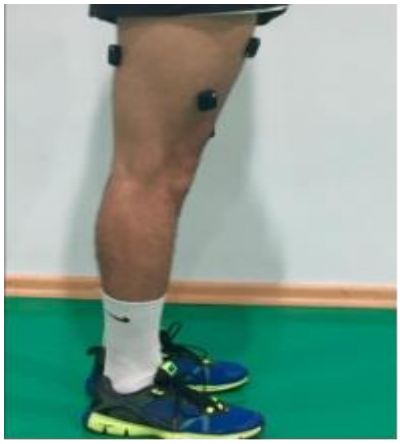
You will undertake the **baseline measures** on your first visit to the UEA MoveExLab. After you finish the baseline measures, the researchers will set up the mirror therapy for you and teach you how to do it. Then

you will do the mirror therapy for two weeks in your home. Then you will come back to the UEA MoveExLab to undertake the **outcome measures**.

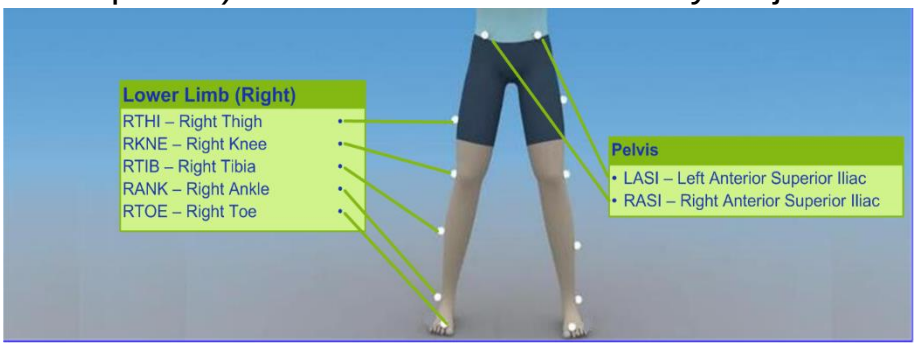
The **baseline and outcome measures are exactly the same** and will take **approximately 90 minutes**. The measures are **painless**.

You will change into your comfortable shorts and t-shirt. Then, we will take the following measures:

- **EMG** surface electrode will be placed on your lower limb muscles to measure muscle activity

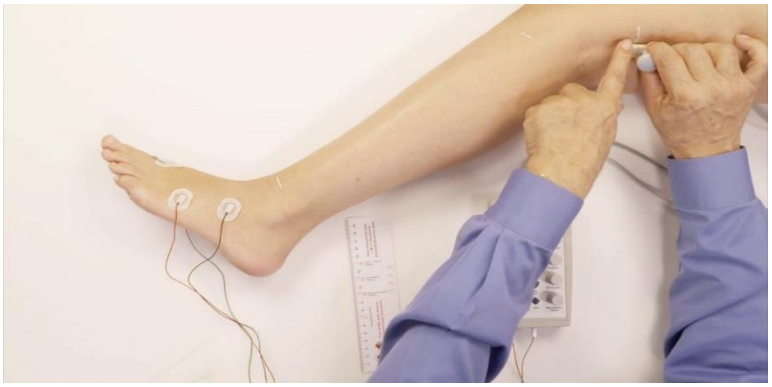
- **Reflective markers** will be placed on your lower limb (see picture below please) to record the movement of your joints.



Peripheral nerve stimulation (PNS)

Peripheral nerve stimulation involves electrically stimulating a nerve via surface electrodes which will be placed on your leg. It is a technique that has been in used clinically and in laboratories throughout the world for more than 200 years.

For this test, you will receive an electrical stimulation to your leg just below your knee. The stimulation will cause a small contraction of muscles in your leg. This type of stimulation has been compared to feeling a strong carpet shock (static electricity). PNS has no known risks.



Transcranial Magnetic Stimulation (TMS)

- This is an optional measure, before you undertake the TMS, a safety questionnaire will be completed by the team to assess your suitability for TMS.
- If you are not suitable for TMS or you decline to participate this measure will not be taken .

TMS is a method of stimulating the brain using an electromagnetic coil placed on the top of the head. It will allow us to assess the strength of the connection between your brain and muscles in your leg.

TMS produces a magnetic pulse that activates the nerves in your brain that control the leg. A brief stimulation of your brain will produce a small twitch in the muscles of your leg. We will use a range of pulse intensities

to investigate the strength of the connection between your brain and the leg muscle.

We will find the lowest intensity required to produce a noticeable muscle twitch. We then use this to determine the intensity required for the main experiment.

TMS has been used clinically for many years. It has been also used as a method of research for more than 30 years and is in use in hundreds of laboratories and clinics worldwide. However, there are some risks which are described below.

Induced currents

Because TMS uses a strong electromagnetic field, it can induced an electrical currents in electronics such as pacemakers or hearing aids. We train our staff in good laboratory practice to eliminate any related risk, and we carefully question all participants to make sure we exclude anyone with clinical implants such as pacemakers.

Headache

The most frequent adverse effect of TMS is mild headache. In our experience, this occurs in less than 5% of our participants. The headache is usually mild and typically lasts a few minutes. It can be treated with normal over-the-counter painkillers. There is no evidence that TMS leads to any change in frequency or severity of headaches.

Seizures

In a very few instances, TMS has been reported to induce brief seizures. The risk of a seizure is very low and has only been reported when using a different form of TMS procedures to those used in our laboratory. The incidence of seizure is estimated at less than 1 in 1000; we use well defined international safety guidelines and expect the incidence to be even lower than this figure.

What will happen to my information?

UEA is the sponsor for this study based in the United Kingdom. We will be using your information in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The UEA will keep, securely, the identifiable information about you for 12 months after the study has finished.

If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information at dataprotection@uea.ac.uk

Will my taking part in this project be kept confidential?

The UEA research team will keep your name, contact details and demographic information confidential and will not pass this information to other parties within or outside of the UEA. We will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. You will be given a project number for the purpose of collecting and analyzing data. This means **you will remain anonymous**. Certain individuals from the UEA research team and regulatory organizations may look at your research records to check the quality and accuracy of the research**.** The people who analyse the information will **not be able to identify you** and will not be able to find out your name or your contact details.

The UEA will keep identifiable information about you from this study for 12 months after the study has finished.

How will my information be stored?

Fully anonymised data will be **stored securely** in the lead researcher's office and on a **password-protected computer** during the project. Your contact details will be stored **in a locked file cabinet** in the researcher office and on a **password-protected computer.**

After the project has ended, these anonymised data will then be stored in a secure room, on a password protected computer, at the **University of East Anglia for ten years**. All procedures for the handling, processing, storage, and destruction of data follow the requirements of the **General Data Protection Regulation** (GDPR).

What will happen to the results of the research project?

The results of the study will be published in academic journals and presented at scientific conferences. The data will also be used within the Researcher's PhD thesis. Participants will **not be identifiable** in any publication. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Are there any possible risks with this project?

There could be a **small risk** of "overuse". This might be experienced as pain or fatigue after doing ankle dorsiflexion movements over a period of time. If you take part in TMS, you might experience a mild headache.

What if there is a problem?

If you have **any complaints** about the way you have been dealt with or any harm is caused during the project **this will be addressed**.

You can contact the researchers at any point (whose information is at the end of this Sheet). Or, you can contact the Primary Supervisor of this research who is also the Director of Research at the School of Health Sciences at UEA:

Professor Valerie Pomeroy

School of Health Sciences. Queen's Building.

The University of East Anglia. Norwich NR4 7Tj.

Telephone: (01603) 591923. Email: v.pomeroy@uea.ac.uk

What if I no longer wish to continue with the project?

You have the right to withdraw from the project without giving any reason up until the point that your data is analysed. If you wish to withdraw from the project, please contact either Sarah Bajuaifer or Professor Valerie Pomeroy (contact details below).

Who has reviewed this project?

The study has been reviewed by The Stanmore Research Ethics Committee. The RECs are independent groups, which review research to protect the dignity, rights, safety, and well-being of participants and researchers.

Contact information for the research team

Sarah Bajuaifer

The Queens Building

Researcher University of East Anglia S.bajuaifer@uea.ac.uk

Norwich, NR4 7TJ

Prof. Valerie Pomeroy

The Queens Building

Primary supervisor University of East Anglia V.pomeroy@uea.ac.uk

Norwich, NR4 7TJ

Dr. Michael Grey

Dr. Nicola Hancock

Thank you very much for taking the time to read this leaflet. If you choose to participate, you will receive a copy of your signed consent form to keep with this participant information package.

Appendix 5

Consent form

Date of visit |__|__|-|__|__|-|__|__|__|__| (DD-MM-YYYY)

Participant Identification Number: | |

Title of project: "Dose-finding for lower limb mirror therapy after stroke".

Researcher: Sarah Bajuaifer (PhD student) s.bajuaifer@uea.ac.uk

Primary supervisor: Professor Valerie Pomeroy V.pomeroy@uea.ac.uk

Secondary supervisor: Dr. Michael Grey M.grey@uea.ac.uk

Name of Participant: _____

NB. If the potential participant is unable to write, please find an independent witness who may complete this form as verbal consent is given by the potential participant. The independent witness should read each of the items to the potential participant and if the participant agrees, the independent witness should initial each of the boxes.

The purpose of the independent witness is to physically complete this consent form on the instruction of a participant in the instance that the participant cannot do so for him or herself due to a physical inability to hold and or use a pen, or in the instance in which attempting to do so would or appears to cause distress to the participant. The independent witness cannot provide consent on behalf of a participant.

An independent witness must:

· *Not be part of the research team*

· *Not be managed by a member of the research team*

One original copy of this form should be completed. The original should be stored in the investigator site file. A photocopies should be made of the original and given to the participant

I have read and understood the participant information package (PIS Version4)

I have read and understood the participant information package

Please initial the box below (with thumb or thumb down)

yes

No

I understand that I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily

I understand that I can ask questions

Please initial the box below (with thumb up or thumb down)

yes

No

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

I understand that I can stop any time

Please initial the box below (with thumb up or thumb down)

yes

No

I agree to also complete a survey asking for: my demographic information (e.g. age, address…..,) impact of stroke.

I'm happy to provide the information

Please initial the box below (with thumb up or thumb down)

yes

No

I understand that that the research team will need to contact my GP to inform them of my participation in the study.

I agree that my GP can be contacted.

Please initial the box below (with thumb up or thumb down)

yes

No

I understand that I will be attending the Movement and Exercise Laboratory at the University of East Anglia to do undertake the measures for the study.

I agree to attend the Movement and Exercise Laboratory at the University of East Anglia.

Please initial the box below (with thumb up or thumb down)

yes

No

I understand that while information gained during the study may be published, I will not be identified and all data will remain confidential.

I agree to anonymised quotes being used in publications and presentations.

Please initial the box below (with thumb up or thumb down)

yes

No

I agree to take part in the study.

Please initial the box below (with thumb up or thumb down)

yes

No

Name of participant	Date	Signature
Researcher (Person taking consent)	Date (In full, i.e. 01 January 2017	Signature
Witness name (if any)	Date	Signature

Appendix 6: **Letter** to GP

Date:

Dear Dr……

I am writing to you to inform you that your patient (name……), (DOB……) has consented to take part in a study that is currently underway at the University of East Anglia. The study iscalled: dose-finding for lower limb mirror therapy after stroke. We are aiming to recruit 40 participants who have had a stroke for 6 weeks or more . The intervention is performance of ankle exercise whilst seating and watching the reflection of the stronger foot in a mirror (mirror therapy). The mirror therapy intervention will be conducted for two weeks.

Please find a one-page summary of the protocol attached to this letter.

We would be grateful if you could let us know of any medical reason why your

patient (name) may not be included in this study. If we have not heard from you, then we will understand that (name) is medically fit to participate.

If you require any further information about the study, then please contact either myself (Sarah Bajuaifer) or Prof. Valerie Pomeroy.

Sarah Bajuaifer

S.bajuaifer@uea.ac.uk

01603593093

OR 075

Prof. Valerie Pomeroy

V.Pomeroy@uea.ac.uk

01603591923

You're sincerely

Sarah Bajuaifer

Daily record form

Date :

Date for first session:

Participants ID number:

Number of target minutes per day:…….

Number of achieved minutes per day:……

Did you completed the exercise in one session or did you have to split it in to many sessions per day:

No. of Sessions per day……. time for each session: ……...

How did you find the exercise?

☐ Difficult ☐ Annoying ☐ Easy

☐ Comfortable ☐ high intensity ☐ low intensity

☐ appropriate intensity ☐ Other (please specify……)

Did you notice any pain or discomfort from the exercise? ☐ Yes ☐ no

If yes, please specify ……

If you did not achieve the target minutes per day, choose one/or more of the following options why:

- ☐ I was bored
- ☐ I was tired
- ☐ I was busy
- ☐ I was sick
- ☐ Pain or discomfort in the foot or leg
- ☐ The number of minutes was too high
- ☐ I couldn't do it(please specify why: ……)
- ☐ Other (please specify:……..……..)

Any more comments?.....

Day	Number of session	Minutes per session	If not performer the target minutes, why?(please write the reason)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			

Day	Number of session	Minutes per session	If not performer the target minutes, why?(please write the reason)
Day 7			
Day 8			
Day 9			
Day 10			

Day	Number of session	Minutes per session	If not performer the target minutes, why?(please write the reason)
Day 11			
Day 12			
Day 13			
Day 14			

Safety screening for TMS

Transcranial Magnetic Stimulation† (TMS) Adult Safety Screen*

If you agree to take part in this study, please answer the following questions. The information you provide is for screening purposes only and will be kept completely confidential.

CIRCLE or CROSS OUT

Have you ever suffered from any neurological or psychiatric conditions?	YES / NO
If YES please give details (nature of condition, duration, current medication, etc)	
. . . . .	
Have you ever suffered from epilepsy, febrile convulsions in infancy or had recurrent fainting spells?	YES / NO
Does anyone in your immediate or distant family suffer from epilepsy?	YES / NO
If YES please state your relationship to the affected family member.	
. . . . .	
Do you suffer from migraine?	YES / NO
Have you ever undergone a neurosurgical procedure (including eye surgery)?	YES / NO
If YES please give details.	
Do you have an implanted device such as a cardiac pacemaker, medication pump or cochlear implant?.	YES / NO
Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork?.	YES / NO
Are you currently taking any medication (prescribed or unprescribed)?	YES / NO
If YES please give details.	
Are you currently undergoing anti - malarial treatment?	YES / NO
Have you ingested any alcohol in the last 24 hours?	YES / NO
Have you had any coffee or other sources of caffeine in the last hour?	YES / NO
Have you used recreational drugs in the last 24 hours?	YES / NO
Did you have very little sleep last night?	YES / NO
Have you already participated in a TMS experiment today?	YES / NO
Have you participated in more than one TMS experiment in the last 6 months?	YES / NO
Is there any chance that you could be pregnant?	YES / NO
Do you need further explanation of TMS and its associated risks?	YES / NO
Date of Birth _____/_____/_____	

Signed: .....Date: ….....

Name (in block letters): .....

† For use with single-pulse TMS, paired-pulse TMS, or repetitive TMS.

* Modified TASS based on Keel JC, July 2000.

Reason for Changing the markers

While performing the sit to stand task, it was difficult to capture the ASIS marker (1cm) especially for people with big belly and because we were dealing with stroke survivors it was difficult to ask them to repeat the task many times. It was essential to change the marker to bigger size (5cm) in order to have enough data across the frames, and to avoid the participant burden from repeating the task.

We didn't know if that will affect the accuracy for the data, an email were sent to Vicon Nexues Company and they response that; the changes will be small but they don't know how much. We ran a small test in the LAB to check the accuracy of the data. Sit to stand task were performed with small marker for LL then bigger marker were applied to ASIS and performed the same task again. Slight change to the joint angle within 3 degree were found. And because we will compare within subject pre and post the intervention, for accuracy of collected data we decided to use bigger marker for both sides of the ASIS.

Degrees in Sagittal Plane							
		Mean of Peak	STD of Peaks	Mean of Min	STD of Min	ROM	Over-estimation factor (%)
Left Ankle	Normal Markers	25.73	1.09	11.32	0.66	14.41	21.42
	Big Markers processed as Normal	22.64	2.70	8.61	1.83	14.03	0.65
	Big Markers processed as Big	22.73	2.71	8.70	1.83	14.03	21.35
Right Ankle	Normal Markers	21.63	0.82	8.83	0.51	12.80	22.37
	Big Markers processed as Normal	18.77	2.50	4.29	1.79	14.48	1.11

	Big Markers processed as Big	18.93	2.50	4.39	1.81	14.54	18.58
Left Knee	Normal Markers	94.27	1.35	3.49	0.95	90.78	7.50
	Big Markers processed as Normal	87.46	2.03	3.82	1.08	83.65	0.49
	Big Markers processed as Big	87.88	2.07	4.29	1.10	83.59	7.65
Right Knee	Normal Markers	90.45	0.87	5.63	0.23	84.82	7.57
	Big Markers processed as Normal	84.03	1.93	5.57	1.10	78.46	0.76
	Big Markers processed as Big	84.63	2.00	6.14	1.12	78.49	7.42
Left Hip	Normal Markers	77.54	1.90	-2.38	2.76	79.93	-8.11
	Big Markers processed as Normal	84.02	4.22	-4.09	1.52	88.11	0.37
	Big Markers processed as Big	84.35	4.18	-3.36	1.52	87.72	-7.76
Right Hip	Normal Markers	79.06	1.64	2.38	2.29	76.68	-8.37
	Big Markers processed as Normal	85.47	4.07	0.83	1.58	84.64	0.58
	Big Markers processed as Big	85.97	4.02	1.61	1.58	84.35	-8.19

Partner Organisations:
Health Research Authority, England
NIHR Clinical Research Network, England
NHS Research Scotland
NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	Dose-Finding of lower limb mirror therapy after stroke
IRAS Project ID:	255913
Sponsor Amendment Notification number:	2
Sponsor Amendment Notification date:	20-03-2020
Details of Chief Investigator:	
Name [first name and surname]	Sarah Bajuaifer
Address:	The Queens Building Postgraduate researcher office University of East Anglia
Postcode:	NR4 7TJ
Contact telephone number:	07549019007
Email address:	s.bajuaifer@uea.ac.uk
Details of Lead Sponsor:	
Name:	Graham Horne
Contact email address:	G.horne@uea.ac.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	England
If England led is the study going through CSP? *delete as appropriate*	Yes / No
Name of lead R&D office:	NHS SOUTH NORFOLK CCG

Partner Organisations:
Health Research Authority, England NIHR Clinical Research Network, England
NHS Research Scotland NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

2. Summary of amendment(s)

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

No.	**Brief description of amendment** *(please enter each separate amendment in a new row)*	**Amendment applies to** *(delete/ list as appropriate)*		**List relevant supporting document(s), including version numbers** *(please ensure all referenced supporting documents are submitted with this form)*		**R&D category of amendment** *(category A, B, C) For office use only*
		Nation	**Sites**	**Document**	**Version**	
1	Temporary study halt as safety measure for COVID19 from 16-03-2020 until further notice from UEA and the NHS.	England	All sites			
2	Update contact information for the researcher			Participant information sheet	4	
3	Update contact information for the researcher			GP letter	4	
4	For consistency with change in PIS version number will change the informed consent form (in the box that state PIS version number)			Informed consent form	4	

[Add further rows as required]

3. Declaration(s)

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator: .....

Print name: Sarah Bajuaifer

Date: 20/03/2020.....

Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative:

Print name: Graham Horne

Post: Project Officer

Organisation: University of East Anglia

Date: 20/03/2020

Partner Organisations:
Health Research Authority, England
NIHR Clinical Research Network, England
NHS Research Scotland
NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

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If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	Dose finding of lower limb mirror therapy after stroke
IRAS Project ID:	255913
Sponsor Amendment Notification number:	3
Sponsor Amendment Notification date:	24/09/2020
Details of Chief Investigator:	
Name [first name and surname]	Sarah Bajuaifer
Address:	The Queens Building Postgraduate researcher office University of East Anglia
Postcode:	NR4 7TJ
Contact telephone number:	07549019007
Email address:	s.bajuaifer@uea.ac.uk
Details of Lead Sponsor:	
Name:	University of East Anglia Polly Harrison
Contact email address:	researchsponsor@uea.ac.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	ENGLAND
If England led is the study going through CSP? *delete as appropriate*	
Name of lead R&D office:	NHS SOUTH NORFOLK CCG

Partner Organisations:
Health Research Authority, England NIHR Clinical Research Network, England
NHS Research Scotland NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

2. Summary of amendment(s)

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If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

No.	Brief description of amendment *(please enter each separate amendment in a new row)*	Amendment applies to *(delete/ list as appropriate)*		List relevant supporting document(s), including version numbers *(please ensure all referenced supporting documents are submitted with this form)*		R&D category of amendment *(category A, B, C) For office use only*
		Nation	Sites	Document	Version	
1	Re-start the study after COVID-19 halt	England	All			
		Northern Ireland				
		Scotland				
		Wales				
2	Due to COVID-19 situation and following UEA safety procedure, we will explain for the participants the safety procedure by providing them with participant information sheet paper and video to explain the safety process, this is not a study specific change, it is only to maximize safety for participants and researcher, and to follow UEA guideline.			COVID-19 participant information sheet-SB	1	
3						
4						
5						

[Add further rows as required]

Partner Organisations:
Health Research Authority, England
NHS Research Scotland
HSC Research & Development, Public Health Agency, Northern Ireland
NIHR Clinical Research Network, England
NISCHR Permissions Co-ordinating Unit, Wales

3. Declaration(s)

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator: 

Print name: Sarah Bajuaifer

Date: 24/09/2020

Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: 

Print name: Polly Harrison

Post: Contracts Officer

Organisation: University of East Anglia

Date: 01 October 2020

Partner Organisations:
Health Research Authority, England
NIHR Clinical Research Network, England
NHS Research Scotland
NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	Dose-Finding of lower limb mirror therapy after stroke
IRAS Project ID:	255913
Sponsor Amendment Notification number:	Non-substantial amendment 4
Sponsor Amendment Notification date:	11/01/2021
Details of Chief Investigator:	
Name [first name and surname]	Sarah Bajuaifer
Address:	The Queens Building Postgraduate researcher office University of East Anglia
Postcode:	NR4 7TJ
Contact telephone number:	07549019007
Email address:	s.bajuaifer@uea.ac.uk
Details of Lead Sponsor:	
Name:	University of East Anglia Polly Harrison
Contact email address:	researchsponsor@uea.ac.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	England
If England led is the study going through CSP? *delete as appropriate*	N/A
Name of lead R&D office:	NHS SOUTH NORFOLK CCG

Partner Organisations:
Health Research Authority, England NIHR Clinical Research Network, England
NHS Research Scotland NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

2. Summary of amendment(s)

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

No.	Brief description of amendment *(please enter each separate amendment in a new row)*	Amendment applies to *(delete/ list as appropriate)*		List relevant supporting document(s), including version numbers *(please ensure all referenced supporting documents are submitted with this form)*		R&D category of amendment *(category A, B, C) For office use only*
		Nation	Sites	Document	Version	
1	Pause recruitment due to Covid national lockdown	England				
2						
3						
4						
5						

[Add further rows as required]

Partner Organisations:
Health Research Authority, England
NIHR Clinical Research Network, England
NHS Research Scotland
NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

3. Declaration(s)

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator:

Print name: sarah Bajuaifer

Date: 11/01/2021

Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: .....

Print name: Polly Harrison

Post: Contracts Officer

Organisation: University of East Anglia

Date: 11 January 2021

MoveExLab COVID-19 Participant Information Sheet

Introduction

Following the COVID-19 pandemic, the way in which you participate in a research projects has changed. This document will inform you of the processes we have put in place to minimise the risk for you and ourselves. Please take your time to read this document carefully to ensure you fully understand its contents. Contact details are at the bottom of this document.

Section 1: Prior to your visit to the MoveExLab

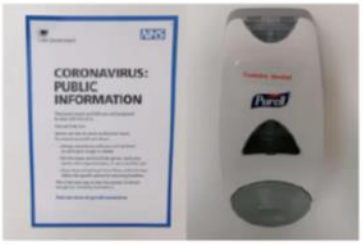
Before visiting the MoveExLab, you will be contacted by the lead researcher of the project to assess the likelihood that you have COVID-19 or have been possibly exposed to it. In the event that there is a high possibility of you having COVID-19 your visit to the MoveExLab may be postponed. You will also be asked to bring a face covering with you so that it can be worn upon your arrival.

Section 2: On the day of your visit and arriving at the MoveExLab

On the day of your MoveExLab visit, you will need to follow the directions provided to you and make your way to the back of the Norwich Medical School carpark. When you have arrived, you must contact the researcher by mobile telephone to notify them of your arrival. Please wait in your car until the lead researcher has come to meet you.

Section 3: Entering the Norwich Medical School Building and MoveExLab

Once greeted by the lead researcher you will be escorted into the Norwich Medical School and the MoveExLab. Social distancing of two metres will be maintained throughout this route. As you walk through a specially designed one-way route to the MoveExLab, you will be asked to sanitise your hands using one of the many dispensers that are positioned throughout the route.



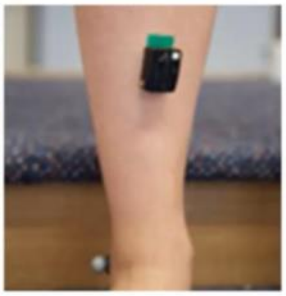
Once you have entered the MoveExLab you will be offered a range of additional Personal Protective Equipment (PPE) to wear if you want to. Hand washing practices will be implemented where necessary.

Section 4: Data Collection Process

You will be asked to change in your MoveExLab testing attire in a designated area. The testing attire will consist of either shorts or t-shirt depending on the research activities. The testing attire provided to you will have been washed in line with Government guidelines.

To reduce the number of people you have to come into contact with there will normally only be yourself and two other researchers in the MoveExLab at any one time. However, on occasions, there could be up to four researchers in the MoveExLab during your visit. The lead researcher will be in close proximity to you throughout most of the data collection process, but the other researchers will be in designated marked out (2m) areas where they will work away from you.

Where possible social distancing guidelines will be followed. For some parts of the data collection process the lead researcher will need to place markers and sensors on your skin meaning that the two metres social distancing rule cannot be maintained. The lead researcher will spend the minimal amount of time as possible doing this. To minimise the risk of infection both the lead researcher and you will be wearing PPE and hand washing practices will be implemented when skin-to-skin contact is made.



Section 6: Completion of data collection and leaving the MoveExLab

Once all the testing procedures are completed, you will change back into attire you arrived in. You will place the testing attire you have worn into the bag provided. You must continue to wear the PPE you have been provided with until you have left the MoveExLab and the Norwich Medical School Building. The lead researcher will take you back to your car using the one-way system that is in place.

Section 7: Post visit follow up.

Forty-eight hours after your visit to the MoveExLab, you will receive a phone call from the lead researcher to see if you have developed any COVID-19 systems.

Section 8: Contact Information

Please contact sarah bajuaifer email: S.bajuaifer@uea.ac.uk or phone number: 01603593093

Extension the study

Amendment Tool
v1.4 30 Nov 2020

For office use
QC: No

Section 1: Project information

Short project title*:	dose-finding of lower limb mirror therapy after stroke
IRAS project ID* (or REC reference if no IRAS project ID is available):	255913
Sponsor amendment reference number*:	Non-substantial amendment 5
Sponsor amendment date* (enter as DD/MM/YY):	10 February 2021
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	need to extend the ethical approval of the study for 12 months,as Covid-19 and lock downs impacted the data collection for the study (ethical approval end on 01/04/2021- extended to 01/04/2022)

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

Section 2: Summary of change(s)

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

Change 1	
Area of change (select)*:	Study Design

Specific change (select - only available when area of change is selected first)*:	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below
Further information (free text - note that this field will adapt to the amount of text entered):	Covid-19 and national lockdown had impacted the data collection, need to extend the approval period of the study for extra 12 months as this come to an end in 01/04/2021, this is in order to meet sample sizes and hence study aims. New end date(01/04/2022)

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	☑	☐	☐	☐
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	◉ All		○ Some	

Add another change: ☐

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

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

*Name [first name and surname]**:	Polly Harrison
*Email address**:	researchsponsor@uea.ac.uk

Lock for submission

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

Lock for submission

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

Section 4: Review bodies for the amendment

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

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

IRAS Project ID 255913. No objection to amendment-NCHC

Dear Mrs Bajuaifer,

IRAS Project ID:	255913
Short Study Title:	Dose-Finding of lower limb mirror therapy after stroke.
Amendment No./Sponsor Ref:	NSA 5
Amendment Date:	10 February 2021
Amendment Type:	Non Substantial Non-CTIMP

I am pleased to confirm **HRA and HCRW Approval** for the above referenced amendment.

Please note:

- The overall outcome for this study is Non-substantial, no study-wide review required, therefore, this was submitted incorrectly via the amendment portal. Please ensure future amendments are submitted following the correct procedures.

You should implement this amendment at NHS organisations in England and Wales, in line with the guidance in the amendment tool.

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/.

Please contact amendments@hra.nhs.uk for any queries relating to the assessment of this amendment.

Kind regards,

Natalie

Natalie Wilson
Approvals Manager
Health Research Authority

HRA | NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle-upon-Tyne | NE2 4NQ

E.amendments@hra.nhs.uk
W. www.hra.nhs.uk

Sign up to receive our newsletter HRA Latest.

IRAS Project ID 255913. No objection to amendment-NCHC

To: Sarah Bajdaifer (HSC - Postgraduate Researcher)
Cc: Valerie Pomeroy (HSC - Staff); Watts Joanna <Joanna.Watts@nchc.nhs.uk>; Howard Stephanie; RANDDOFFICE (NHS NORFOLK AND WAVENEY CCG) <nwccg.randdoffice@nhs.net>; Gilbert Louise

Dear Sarah,

Arrangements to support the below amendment in Norfolk Community and Health Care NHS Trust

Full Study Title: 2020GC05 (255913) Dose-finding of lower limb mirror therapy after stroke.

Type	Title	Date of Amendment	Date of HRA Approval	Summary of Amendment
Non-substantial amendment	NSA5	10/02/2021	16/02/2021 (study-wide review not required)	Extension of study end date by one year from 01/04/2021 to 04/01/2022.

We acknowledge receipt of this amendment for which **regulatory and HRA approvals are in place** and are happy for it to be implemented in **Norfolk Community and Health Care NHS Trust.** It is a sponsor responsibility to communicate the changes to sites.

Kind regards

Clare Symms
Senior Manager – Research and Finance
Norfolk and Suffolk Primary and Community Care Research Office

Helen Sutherland
Research Officer

Norfolk & Suffolk Primary & Community Care Research Office
NHS Norfolk and Waveney Clinical Commissioning Group
Lakeside 400, Old Chapel Way, Broadland Business Park, Thorpe St Andrew, Norwich, NR7 0WG

E-mail: helen.sutherland6@nhs.net
Team email: nwccg.randdoffice@nhs.net
R&D Finance email: nwccg.RandDFinance@nhs.net
Research Office Website: http://nspccro.nihr.ac.uk

Follow us on Twitter **@NHS_NSResearch**

CCG Website: www.norfolkandwaveneyccg.nhs.uk

Please note my working hours are normally Mon 13:00-17:00 and Wed-Fri 09.00-17.00

Partner Organisations:
Health Research Authority, England
NIHR Clinical Research Network, England
NHS Research Scotland
NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

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If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	Dose-Finding of lower limb mirror therapy after stroke
IRAS Project ID:	255913
Sponsor Amendment Notification number:	Non-substantial amendment 6
Sponsor Amendment Notification date:	11/05/2021
Details of Chief Investigator:	
Name [first name and surname]	Sarah Bajuaifer
Address:	The Queens Building Postgraduate researcher office University of East Anglia
Postcode:	NR4 7TJ
Contact telephone number:	07549019007
Email address:	s.bajuaifer@uea.ac.uk
Details of Lead Sponsor:	
Name:	University of East Anglia Polly Harrison
Contact email address:	researchsponsor@uea.ac.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	England
If England led is the study going through CSP? *delete as appropriate*	N/A
Name of lead R&D office:	NHS SOUTH NORFOLK CCG

2. Summary of amendment(s)

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

No.	Brief description of amendment *(please enter each separate amendment in a new row)*	Amendment applies to *(delete/ list as appropriate)*		List relevant supporting document(s), including version numbers *(please ensure all referenced supporting documents are submitted with this form)*		R&D category of amendment *(category A, B, C) For office use only*
		Nation	Sites	Document	Version	
1	Restart recruitment after Covid national lockdown on 17/05/2021	England				
2						
3						
4						
5						

[Add further rows as required]

Partner Organisations:
Health Research Authority, England NIHR Clinical Research Network, England
NHS Research Scotland NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

3. Declaration(s)

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator:

Print name: sarah Bajuaifer

Date: 11/05/2021

Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: .....

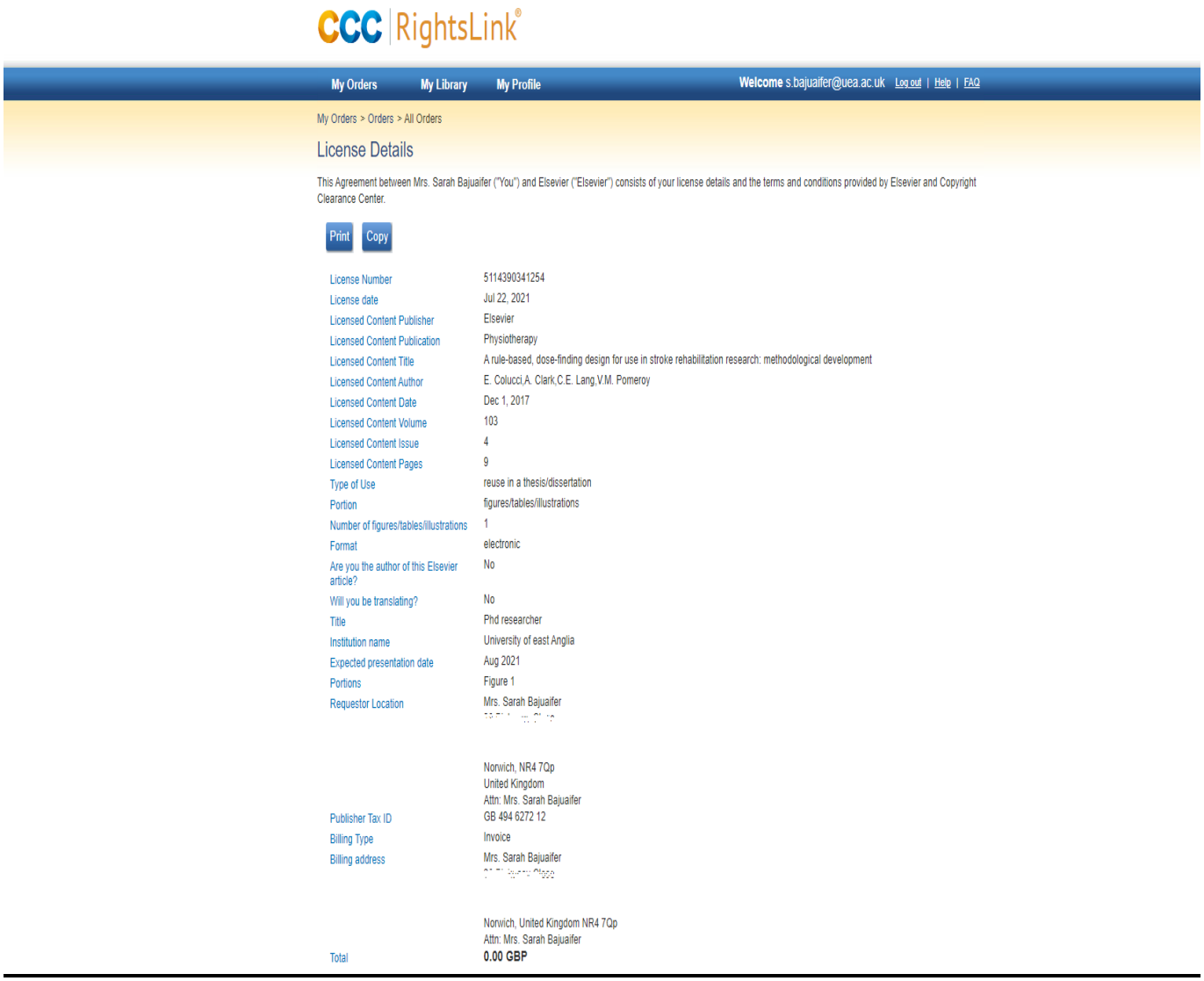
Print name: Polly Harrison

Post: Contracts Officer

Organisation: University of East Anglia

Date: 13 May 2021

Copy right permission to use Figure (4-1)



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