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Motor neuroprosthesis for promoting recovery of function after stroke (Review)

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TABLE OF CONTENTS

[Intervention Review]

Motor neuroprosthesis for promoting recovery of function after stroke

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ABSTRACT

Background

Motor neuroprosthesis (MN) involves electrical stimulation of neural structures by miniaturized devices to allow the performance of tasks in the natural environment in which people live (home and community context), as an orthosis. In this way, daily use of these devices could act as an environmental facilitator for increasing the activities and participation of people with stroke.

Objectives

To assess the effects of MN for improving independence in activities of daily living (ADL), activities involving limbs, participation scales of health-related quality of life (HRQoL), exercise capacity, balance, and adverse events in people after stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (searched 19 August 2019), the Cochrane Central Register of Controlled Trials (CENTRAL) (August 2019), MEDLINE (1946 to 16 August 2019), Embase (1980 to 19 August 2019), and five additional databases. We also searched trial registries, databases, and websites to identify additional relevant published, unpublished, and ongoing trials.

Selection criteria

Randomized controlled trials (RCTs) and randomized controlled cross-over trials comparing MN for improving activities and participation versus other assistive technology device or MN without electrical stimulus (stimulator is turned off), or no treatment, for people after stroke.

Data collection and analysis

Two review authors independently selected trials, extracted data, and assessed risk of bias of the included studies. Any disagreements were resolved through discussion with a third review author. We contacted trialists for additional information when necessary and performed all analyses using Review Manager 5. We used GRADE to assess the certainty of the evidence.

Main results

We included four RCTs involving a total of 831 participants who were more than three months poststroke. All RCTs were of MN that applied electrical stimuli to the peroneal nerve. All studies included conditioning protocols to adapt participants to MN use, after which participants used MN from up to eight hours per day to all-day use for ambulation in daily activities performed in the home or community context. All studies compared the use of MN versus another assistive device (ankle-foot orthosis [AFO]). There was a high risk of bias for at least one assessed domain in three of the four included studies.

No studies reported outcomes related to independence in ADL. There was low-certainty evidence that AFO was more beneficial than MN on activities involving limbs such as walking speed until six months of device use (mean difference (MD) −0.05 m/s, 95% confidence interval (CI) −0.10 to −0.00; P = 0.03; 605 participants; 2 studies; I^2 = 0%; low-certainty evidence); however, this difference was no longer present in our sensitivity analysis (MD −0.07 m/s, 95% CI −0.16 to 0.02; P = 0.13; 110 participants; 1 study; I^2 = 0%). There was low to moderate certainty that MN was no more beneficial than AFO on activities involving limbs such as walking speed between 6 and 12 months of device use (MD 0.00 m/s, 95% CI −0.05 to 0.05; P = 0.93; 713 participants; 3 studies; I^2 = 17%; low-certainty evidence), Timed Up and Go (MD 0.51 s, 95% CI −4.41 to 5.43; P = 0.84; 692 participants; 2 studies; I^2 = 0%; moderate-certainty evidence), and modified Emory Functional Ambulation Profile (MD 14.77 s, 95% CI −12.52 to 42.06; P = 0.29; 605 participants; 2 studies; I^2 = 0%; low-certainty evidence). There was no significant difference in walking speed when MN was delivered with surface or implantable electrodes (test for subgroup differences P = 0.09; I^2 = 65.1%).

For our secondary outcomes, there was very low to moderate certainty that MN was no more beneficial than another assistive device for participation scales of HRQoL (standardized mean difference 0.26, 95% CI −0.22 to 0.74; P = 0.28; 632 participants; 3 studies; I^2 = 77%; very low-certainty evidence), exercise capacity (MD −9.03 m, 95% CI −26.87 to 8.81; P = 0.32; 692 participants; 2 studies; I^2 = 0%; low-certainty evidence), and balance (MD −0.34, 95% CI −1.96 to 1.28; P = 0.68; 692 participants; 2 studies; I^2 = 0%; moderate-certainty evidence). Although there was low- to moderate-certainty evidence that the use of MN did not increase the number of serious adverse events related to intervention (risk ratio (RR) 0.35, 95% CI 0.04 to 3.33; P = 0.36; 692 participants; 2 studies; I^2 = 0%; low-certainty evidence) or number of falls (RR 1.20, 95% CI 0.92 to 1.55; P = 0.08; 802 participants; 3 studies; I^2 = 33%; moderate-certainty evidence), there was low-certainty evidence that the use of MN in people after stroke may increase the risk of participants dropping out during the intervention (RR 1.48, 95% CI 1.11 to 1.97; P = 0.007; 829 participants; 4 studies; I^2 = 0%).

Authors' conclusions

Current evidence indicates that MN is no more beneficial than another assistive technology device for improving activities involving limbs measured by Timed Up and Go, balance (moderate-certainty evidence), activities involving limbs measured by walking speed and modified Emory Functional Ambulation Profile, exercise capacity (low-certainty evidence), and participation scale of HRQoL (very low-certainty evidence). Evidence was insufficient to estimate the effect of MN on independence in ADL. In comparison to other assistive devices, MN does not appear to increase the number of falls (moderate-certainty evidence) or serious adverse events (low-certainty evidence), but may result in a higher number of dropouts during intervention period (low-certainty evidence).

PLAIN LANGUAGE SUMMARY

Motor neuroprosthesis for improving activities and participation of people in their natural environment after stroke

Review question

Is motor neuroprosthesis (MN) effective for improving activities and participation of people in their natural environment after stroke?

Background

Stroke survivors usually face long-term impairment, activity limitation, and reduced participation. MN consists of electronic devices that electrically stimulate a nervous system structure to help the performance of daily activities in the natural environment in which people live, as an orthosis (a device applied to a body segment to optimize position, or to limit or assist movement). However, the role of MN for improving activities and participation after stroke is unclear.

Study characteristics

We found four studies of MN involving a total of 831 participants who more than three months poststroke, with mean ages from 53 to 64 years. All participants were able to walk from less than 0.5 m/s to more than 0.7 or even 0.9 m/s. The included studies were published between 2007 and 2015 in the USA and the Netherlands. All included studies applied MN directed to a nerve in the leg (peroneal nerve) to promote the contraction of a muscle at the front of the leg, thus preventing the foot 'dropping' as the leg was swung forward while the participant walked. MN was used from up to eight hours per day to all-day use for walking about in the natural environment in which people live. Three studies used an MN device that interfaces with the nervous system through electrodes positioned over the skin in the projection of the peroneal nerve in the leg. Only one study used a implantable device whose electrical stimulus is released directly on the nerve by electrodes placed under the layer that surrounds the nerve. All studies compared MN versus ankle-foot orthosis (AFO), that is an assistive device usually made of a rigid material and placed externally on the lower leg to hold the foot and ankle to prevent the foot dropping.

Key results

There is limited evidence that people after stroke who receive MN as an orthosis for walking in the home or community context may not improve activities involving limbs such as walking speed between 6 and 12 months of device use (low-certainty evidence), Timed Up and Go (moderate-certainty evidence), and modified Emory Functional Ambulation Profile (low-certainty evidence); as well as participation scale of health-related quality of life (very low-certainty evidence), exercise capacity (low-certainty evidence), and balance (moderate-certainty evidence), compared with people after stroke who receive AFO. There was evidence of an effect that the control intervention (AFO) attained a higher walking speed after six months of device use (low-certainty evidence), but this evidence showed that the improvements were too small to indicate a meaningful change to patients, and when we excluded the study in which the people that assessed the outcomes were aware of the intervention details, this effect was no longer found. There was no difference in effects on walking speed between MN with surface versus MN with implantable electrodes. No study reported outcomes related to independence in activities of daily living.

The majority of studies reported adverse events such as falls and serious adverse events related to device use, which were found to be similar for MN and AFO use (moderate- and low-certainty evidence, respectively). One study considered serious adverse events related to device use as serious falls. More people who received MN withdrew from the studies than did people who received AFO (low-certainty evidence). The results of this review indicate that little is known about the effects of MN and that further information is required.

It is unknown if people less than three months poststroke could benefit from MN use as an assistive device to perform activities in daily life. The impact of MN applied to the upper limb or MN that uses brain or muscle signals to trigger the stimulation is unknown in people with stroke. We found no evidence evaluating the costs of delivering MN.

Certainty of the evidence

The certainty of the evidence ranged from moderate to very low.

Summary of findings for the main comparison. Motor neuroprosthesis compared to another assistive technology device for promoting recovery of function after stroke

Motor neuroprosthesis compared to another assistive technology device for promoting recovery of function after stroke

Patient or population: promoting recovery of function after stroke
Setting: home or community context
Intervention: motor neuroprosthesis
Comparison: another assistive technology device

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with another assistive technology device	Risk with motor neuroprosthesis				
Independence in activities of daily living		(No data)	-	-	No studies	Insufficient evidence	No trials measured this outcome.
Activities involving limbs	**Walking speed until 6 months of device use (m/s)** timed measures at the end of treatment	The mean walking speed in the control group was on average **0.58 m/s**.	**0.05 mean difference lower** (0.1 lower to 0) on intervention group	-	605 (2 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	Minimal important difference for comfortable walking speed in chronic stroke participant is 0.2 m/s (Hiengkaew 2012).
	Walking speed between 6 and 12 months of device use (m/s) timed measures at the end of treatment	The mean walking speed in the control group was on average **0.69 m/s**.	**0 mean difference** (0.05 lower to 0.05 higher)	-	713 (3 RCTs)	⊕⊕⊖⊖ **Low**[a,c]	Minimal important difference for comfortable walking speed in chronic stroke participant is 0.2 m/s (Hiengkaew 2012).
	TUG (s) timed measures at the end of treatment	The mean TUG in the control group was on average **27.57 s**.	**0.51 mean difference higher** (4.41 lower to 5.43 higher) on intervention group	-	692 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[d]	

	mEFAP (s) timed measures at the end of treatment	The mean mEFAP in the control group was on average **286.43 s**.	**14.77 mean difference higher** (12.52 lower to 42.06 higher) on intervention group	-	605 (2 RCTs)	⊕⊕⊖⊖ **Low**[a,e]	
Participation scales of HRQoL timed measures at the end of treatment		The mean participation scales of HRQoL in the control groups was **NA**.[d]	**0.26 standardized mean difference** (0.22 lower to 0.74 higher)	-	632 (3 RCTs)	⊕⊖⊖⊖ **Very low**[a,e,f]	Using Cohen's rules of thumb, 0.26 represents a small effect.
Exercise capacity: 6MWT (m) timed measures at the end of treatment		The mean 6MWT in the control group was on average **208.12 m**.	**9.03 mean difference lower** (26.87 lower to 8.81 higher) on intervention group	-	692 (2 RCTs)	⊕⊕⊖⊖ **Low**[a,e]	There are no accurate indices of minimal important difference for 6MWT in people poststroke whose gait speed was ≥ 0.40 m/s (Fulk 2018).
Balance: BBS timed measures at the end of treatment		The mean BBS in the control group was on average **44.15**.	**0.34 mean difference lower** (1.96 lower to 1.28 higher) on intervention group	-	692 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	Minimal detectable change for BBS in chronic stroke participant is 5 points (Hiengkaew 2012).
Adverse events	**Number of dropouts during the intervention period**	Study population **96 per 1000****	**142 per 1000**** (106 to 188)	**RR 1.48** (1.11 to 1.97)	829 (4 RCTs)	⊕⊕⊖⊖ **Low**[e,g]	
	Falls	Study population **296 per 1000****	**355 per 1000**** (272 to 459)	**RR 1.20** (0.92 to 1.55)	802 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[e,h]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**We used the median control group risk across studies.

6MWT: 6-minute walk test; **BBS**: Berg Balance Scale; **CI:** confidence interval; **HRQoL**: health-related quality of life; **mEFAP**: modified Emory Functional Ambulation Profile; **NA**: not applicable; **RCT:** randomized controlled trial; **RR:** risk ratio; **TUG**: Timed Up and Go test.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]The outcome assessors were not blinded in the larger study.
[b]The evidence of this effect is removed when sensitivity analysis is performed, suggesting some inconsistency in this finding.
[c]One study has high risk of bias for incomplete outcome data.
[d]No data can be provided due to the combination of different outcome measures for the same outcome in this analysis.
[e]Imprecise due to confidence intervals that included potential for important harm or benefit.
[f]Considerable heterogeneity between trials.
[g]As no study included motor neuroprosthesis (MN) directed to the upper limb, this effect addresses only lower limb MN and not the whole category of MN.
[h]Although two of the three studies were sponsored by the manufacturers, they clearly described fall events. There is no blinding of outcome assessment for the largest study, but this would seem not to interfere with this outcome.

BACKGROUND

Description of the condition

Among the cardiovascular diseases, hemorrhagic and ischemic strokes were considered to be the second and third most common causes of disability-adjusted life-years, respectively, in 2015 (Roth 2017). They present a higher prevalence among individuals aged 74 to 79 years (Roth 2017). Projections indicate that by 2030 there will be 70 million stroke survivors worldwide (Feigin 2014). The stroke survivors will face long-term impairment, activity limitation, and reduced participation that will impact not only on their own lives, but also on the lives of their families (Langhorne 2009). Among them, approximately one-third will have functional dependence during the first year after stroke (de Campos 2017). One of the important factors that contributes to being unable to live independently is motor impairment by hemiparesis, because it leads to difficulties in performing functional activities (Schiemanck 2006). Lower limb impairment typically affects the performance of gait, and it is common to observe foot drop when the individual tries to take a step with the paretic limb (Stein 2008). Upper limb impairment affects the interaction with objects in the environment, involving movements such as grasp, grip, pinch, and others (Lang 2013). In this scenario, the use of contextual factors, such as assistive technology devices (e.g. orthosis), work as a resource to facilitate the performance of daily activities and the recovery of motor function after stroke (Eng 2007).

Description of the intervention

The first application of electric current to nervous tissue in order to promote movement dates back to the experiment of Galvani in the 1790s (Cambridge 1977). Since then, there have been advances in the use of electrical stimulation of motor neurons to activate paralyzed or paretic muscles, and it is widely used in clinical rehabilitation (Sheffler 2007). This electrical stimulus applied to excite peripheral sensory and motor nerves is known as neuromuscular electrical stimulation (NMES) (Alon 2003b); when the aim is to employ this stimulus to achieve functional tasks, the term used is functional electrical stimulation (FES) (Sheffler 2007). FES is a routine therapeutic approach that physiotherapists use during stroke rehabilitation in a clinical setting to improve strength, upper extremity function, and gait, and to prevent hemiplegic shoulder subluxation (Auchstaetter 2016).

Due to technological advances, especially in electronics, electrical stimulation devices have become increasingly miniaturized and lightweight, and with more refined control and sensor configurations, they can be worn as an orthosis beyond the clinical setting (Melo 2015; Popović 2014). By integrating the electric stimulator with control algorithms and sensors, it is possible to determine the time of delivery of the electrical current in response to the sensor signals (Melo 2015). This integration was implemented for the first time in 1961 when Liberson applied electrical stimuli to the common peroneal nerve to activate the tibialis anterior muscle during the swing phase of gait. He used a heel switch as a sensor to control the timing of the stimulation. The train of stimuli was only released when the heel came off the ground at the end of the stance phase and ended when the heel contacted the ground again at the beginning of the stance phase (Liberson 1961). Since then, much progress has been made, with devices becoming portable, battery powered, and wireless, allowing them to be worn and implemented as an assistive technology device (e.g. an orthosis) that acts as an environmental facilitator for expanded capacity and performance in walking and moving and also carrying and handling objects (Bosch 2014; Cowan 2012). In addition to this direct effect on performance, the orthotic use of the electric current enables people with stroke to experience a greater amount of practice in their current environment. This orthotic use is often referred to as motor neuroprosthesis (MN), which is considered to be an electronic device that interfaces with the nervous system and attempts to restore functions, generally by electrical stimulation (Naik 2014; Ziat 2015).

The activation of neural structures to promote movement through electrical stimulation is used in both MN and FES, meaning there may be overlap between FES and MN concepts (Popović 2014). Although both MN and FES use electrical stimulation, MN has a system technology configuration that allows its use in the actual context in which people live (real-world setting). In this way MN allows the electrical stimulus to be used as an environmental facilitator (e.g. an orthosis) to achieve a greater level of practice, producing effects during the performance of functional abilities in the individual's current environment (Laufer 2009). Several studies and guidelines already consider comparisons of MN with other orthotic devices for decision-making purposes (Bethoux 2015; Bosch 2014; Kluding 2014; NICE 2009). We focused on this perspective within the scope of this review, that is that MN consists of a category that uses stimuli to allow the performance of tasks in the actual context in which a person lives, and is being used daily for increasing the activities and participation of people with stroke, while FES comprises the use of electrical stimulation to enhance function (Martin 2012; Sheffler 2007), and is especially used in the context of the clinical setting. Several Cochrane Reviews have already shown evidence of therapies for improving activities of daily living (ADL) such as virtual reality (Laver 2017), action observation (Borges 2018), and mirror therapy (Thieme 2018). Within the context of rehabilitation, these therapies may be additional and further enhanced by MN daily use.

In order to operate autonomously during the performance of functional activities, MN has a typical architecture composed of a network of sensors, control unit, and a stimulation unit (Melo 2015). The stimulation unit is responsible for generating the electric current that is delivered to the nervous system via electrodes placed in different locations, ranging from the skin surface to directly implanted into different areas of the nervous system (Collinger 2013). Regardless of the location of this interface in the nervous system, all devices that stimulate it electrically for the previously described purposes are considered to be MN. It is possible to use biological signals, such as electromyography, electroencephalography, and electroneurography signals, eye tracking, and voice control, or non-biological signals such as force/pressure and inertial sensors as an input to trigger the electrical stimulus to the desired motor function (Ambrosini 2014). Consequently, there is a need to translate and to adjust the command signal provided by sensors as an input to the stimulation unit, a function of the control unit (Horch 2004; Naik 2014). Besides the described requirements, the device needs to be portable, lightweight, autonomously controlled, and battery powered to be an assistive technology device (Melo 2015).

How the intervention might work

MN allows people with stroke to enhance the performance of functional activities in the home and community, including the

manipulation of objects with the paretic upper limb or gait activities with the paretic lower limb (Cowan 2012; Moss 2011; Sheffler 2009). The use of these assistive devices can lead people with stroke to benefit from their orthotic effect, reflecting the direct improvement in tasks while using the MN (Dunning 2015; Kottink 2004; Prenton 2016). Furthermore, the daily use of MN allows people with stroke to perform repetitive activities that lead to a longer-lasting improvement (as an effect of relearning) after the stimulation is turned off (Ambrosini 2011; Dunning 2015; Prenton 2016). This may be explained by plasticity mechanisms from peripheral effects in muscles and central effects from the central nervous system reorganization. It is hypothesized that these devices activate the motor-related areas of the cortex and their residual corticospinal pathways induce neural plasticity in people with stroke (Everaert 2010). Thus far, direct signs of brain injury repair after one year of using the MN in people with chronic stroke were seen by cortical metabolism improvement over the damaged motor areas, leading to recovery of near-to-normal brain metabolism (Thibaut 2017).

Why it is important to do this review

Some systematic reviews have been conducted on the topic of FES that considered devices with the architecture configuration of MN to promote recovery of function after stroke (Bolton 2004; Dunning 2015; Kottink 2004; Meilink 2008). Only one of these reviews considered daily use of MN devices in the home or community context as an assistive device; however, this review only analyzed surface MN directed to a specific part of the lower limb, without performing a meta-analysis (Dunning 2015). In order to determine the level of evidence of the effects of the daily use of the whole category of upper limb and lower limb MN for improving activities and participation in the natural environment in which people with stroke live, it was essential to conduct this high-quality systematic review.

Due to the wide variety of MN, there is a need to clarify which device has the best evidence for improving activity and participation after stroke, the best phase in which to use the device, the optimal frequency of use, and which target shows the best results. Moreover, to support clinical practice, healthcare managers, policymakers, and consumers, and the acceptability of using MN, costs, and benefits, must be considered. This review aimed to synthesize the evidence for the use of MN for improving activities and participation after stroke and hence to assist clinical decision-making.

OBJECTIVES

To assess the effects of motor neuroprosthesis (MN) for improving independence in activities of daily living (ADL), activities involving limbs, participation scales of health-related quality of life (HRQoL), exercise capacity, balance, and adverse events in people after stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to review published and unpublished randomized controlled trials (RCTs) and randomized controlled cross-over trials. For randomized controlled cross-over trials, we only analyzed the first period as a parallel-group trial. Cross-over trials were only eligible if comparison groups included placebo; the evaluation of outcomes was blinded to allocation; and a minimum period of follow-up was clearly described. Trials reported in abstract form were eligible for inclusion only when adequate information was provided in the abstract or was available from the trial authors. We excluded quasi-RCTs, that is trials in which the method of allocating participants to a treatment is not strictly random (e.g. by date of birth, hospital record number, or alternation). If we included a study that was described as randomized, but while assessing risk of bias we learned that it was a quasi-RCT, we excluded the data from this study from the analysis.

Types of participants

We included studies whose participants were clinically diagnosed with stroke, were over 18 years of age, of both sexes, at any stage of the disease. A diagnosis of stroke fulfills the clinical criteria of the World Health Organization (WHO); stroke is defined as a "neurological deficit of cerebrovascular cause that lasts more than 24 hours or leads to death within 24 hours" (WHO 1989). A diagnosis of stroke encompasses ischemic and hemorrhagic stroke (including subarachnoid, intraventricular, or intracerebral hemorrhage).

Types of interventions

This review included studies that used motor neuroprosthesis (MN) devices for improving activities and participation after stroke. Considering that this approach focuses on the use of MN as an orthosis, we only included studies that used MN in the home or community context and that fulfilled some device requirements, such as working autonomously, being battery powered to ensure its autonomy, and have stimulus triggered by a sensor. We also included studies that used implanted or superficial electrodes whose application is directed to upper or lower limbs, and studies that addressed hybrid MN, which combines an exoskeleton or a mechanical orthosis with an electrical stimulation device. We excluded studies that used sensory stimulation as transcutaneous electrical nerve stimulation (TENS).

We selected studies that included the following comparisons.

- MN with electrical stimulus versus no treatment.
- MN with electrical stimulus versus MN without electrical stimulus, where both groups used the device, but in one group the stimulator was turned off.
- MN versus another assistive technology device (e.g. foot drop stimulator versus ankle foot orthosis, electromyographic (EMG)-triggered stimulation versus hand orthosis, etc).

Types of outcome measures

We included outcome measures falling into the International Classification of Functioning, Disability and Health (ICF) categories for activity and participation (Brehm 2011; Mudge 2007; Sullivan 2013). According to the ICF, 'activity' corresponds to the execution of a task or action by an individual, while 'participation' means the involvement in a life situation (WHO 2001).

Primary outcomes

- Independence in ADL, e.g. Functional Independence Measure (FIM) (Hamilton 1994), Barthel Index (BI) (Quinn 2011), Motor Assessment Scale (MAS) (Dean 1992).

- Activities involving limbs, e.g. Jebsen Taylor Hand Function Test (Stern 1992), Wolf Motor Function Test (WMFT) (Wolf 2001), 9-Hole Peg Test (9HPT) (Heller 1987), Box & Blocks Test (BBT) (Mathiowetz 1985), Motor Activity Log (MAL) (Uswatte 2005), Timed Up and Go test (TUG) (Podsiadlo 1991), Rivermead Mobility Index (Collen 1991), Functional Ambulation Categories (FAC) (Holden 1984), Dynamic Gait Index (Jonsdottir 2007), modified Emory Functional Ambulation Profile (mEFAP) (Baer 2001; Wolf 1979), walking speed.

Secondary outcomes

- Participation scales of HRQoL, e.g. 36-Item Short Form Health Survey (SF-36) (Anderson 1996), Stroke Impact Scale (SIS) (Duncan 1999).
- Exercise capacity, e.g. 6-minute walk test (6MWT) (Seale 2006).
- Balance, e.g. Berg Balance Scale (BBS) and Functional Reach Test (FRT) (Berg 1992; Martins 2012).
- Adverse events, i.e. pain, skin irritation, dropouts, acceptance, number of falls.

Adverse events

To measure the acceptance of MN we considered the number of withdrawals or dropouts from the study due to any reason during the study period. We used the incidence of serious adverse events related to intervention and number of falls to investigate the safety of MN. We considered the number of falls due to the nature of the use of MN in the home or community context for walking activities.

Search methods for identification of studies

See the 'Specialized register' information at the Cochrane Stroke Group's website. We searched for trials in all languages and arranged for the translation of relevant articles when necessary.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (last searched 19 August 2019) and the following electronic bibliographic databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8 of 12, August 2019) in the Cochrane Library (searched 19 August 2019; Appendix 1)
- MEDLINE Ovid (1946 to 16 August 2019; Appendix 2)
- Embase Ovid (1980 to 2019 Week 33; searched 19 August 2019; Appendix 3)
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1982 to 19 August 2019; Appendix 4)
- AMED Ovid (Allied and Complementary Medicine Database; 1985 to 19 August 2019; Appendix 5)
- PEDro (Physiotherapy Evidence Database; www.pedro.org.au/; searched 19 August 2019; Appendix 6)
- REHABDATA (www.naric.com/?q=en/REHABDATA; searched 19 August 2019; Appendix 7);
- IEEE (Institute of Electrical and Electronics Engineers; www.ieee.org/; searched 19 August 2019; Appendix 8)

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialist and modified it for the other databases. The search strategy included Cochrane's highly sensitive search strategies for identification of RCTs, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011), and the Cochrane Stroke Group's search strategies for the identification of stroke studies in respective databases and other resources.

We also searched the following electronic registries, databases, and websites to identify additional relevant published, unpublished, and ongoing trials.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 19 August 2019; Appendix 9)
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/; searched 19 August 2019; Appendix 10)
- Stroke Trials Registry (www.strokecenter.org/trials/; searched 21 August 2019; Appendix 11)
- ISRCTN registry (www.isrctn.com/; searched 20 August 2019; Appendix 12)
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/; searched 20 August 2019; Appendix 13)
- Health Technology Assessment (HTA) database - Centre for Reviews and Dissemination, University of York (www.crd.york.ac.uk/PanHTA; searched 19 August 2019; Appendix 14)
- OAIster (oaister.worldcat.org/; searched 19 August 2019; Appendix 15)
- The Directory of Open Access Repositories – OpenDOAR (searched using CORE; searched 19 August 2019; Appendix 16)
- British Library Ethos (ethos.bl.uk/; searched 19 August 2019; Appendix 17)
- ProQuest Dissertations & Theses Global (www.proquest.com/products-services/pqdtglobal.html; 19 August 2019; Appendix 18)

Searching other resources

We contacted equipment manufacturers to ask for information about any relevant trials that address MN (Appendix 19). We contacted some original study authors for clarification and further data if trial reports were unclear. Additionally, we used Grey Matters: a practical tool for searching health-related grey literature checklist, published by the Canadian Agency for Drugs and Technologies in Health (CADTH) to conduct additional searches of grey literature (Grey Matters; www.cadth.ca/resources/finding-evidence/grey-matters; searched 19 August 2019; Appendix 20).

Data collection and analysis

Selection of studies

Two review authors (LM and IN) independently screened the titles and abstracts of the studies identified by the search and removed obviously irrelevant reports. We obtained the full-text of the remaining studies, and the same two review authors selected studies for inclusion according to the predefined inclusion criteria. In the case of any questions on methodology, we contacted the study authors for clarification to determine study eligibility. Two other review authors (VR or TS) evaluated any discrepancies as required and advised in case of disagreement. We recorded the reasons for exclusion and completed a PRISMA flow chart (Liberati 2009).

Data extraction and management

Two review authors (LM and IN) independently extracted data from the included studies and summarized trial details on a data extraction template in Covidence that was developed specifically for this review (Covidence). In the case of incomplete or unclear data, we contacted the study authors for clarification. Any disagreements were resolved by discussion or by involving a third review author (VR or TS). We extracted the following information according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

- General information: title of the review, study ID, and contact details.
- Methods: study design, instruments used, study duration, 'Risk of bias' criteria (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting), year of study.
- Participants: total number of participants, setting, age, sex, country, motor impairment, type of stroke, phase (acute, subacute, or chronic).
- Intervention: intervention details regarding time (number and duration of exposure, weeks of use, and in the case of follow-up, describe the duration), devices (type of electrode and sensor), and place of application (upper or lower limb); methods used in the control group.
- Outcomes: definition of primary and secondary outcome(s).
- Results: number of participants allocated to each group, number of withdrawals (by group, with reasons), adverse events, overall sample size and methods used to estimate statistical power (regarding the target number of participants to be recruited, the clinical difference to be detected, and the ability of the trial to detect this difference).
- Notes: contact with authors (information obtained or not), article in a language other than English, funding source and noteworthy conflicts of interest of study authors.

Assessment of risk of bias in included studies

Two review authors (LM and IN) independently assessed the risk of bias for each included study using the Cochrane 'Risk of bias' tool (Higgins 2011b). Any disagreements were resolved by discussion or by involving a third review author (VR or TS). We assessed risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We graded the risk of bias for each domain as low, high, or unclear and entered this information along with the reasons for each decision into the 'Risk of bias' table produced for each study. We used Table 8.5.d in the *Cochrane Handbook for Systematic Reviews of Interventions*, which provides criteria for making judgements regarding risk of bias in each of the seven domains of the tool (Higgins 2011b). We considered the risk of bias of the studies and its contribution to the treatment effect. We then entered the data into Review Manager 5 (Review Manager 2014).

Measures of treatment effect

We performed the data analysis according to Cochrane guidelines. One review author (LM) entered the quantitative data into Review Manager 5 (Review Manager 2014), which was checked by another review author (IN), and analyzed. We presented the results for each outcome with 95% confidence intervals (CIs). We measured treatment effects using the risk ratio (RR) for dichotomous outcomes, mean difference (MD) or standardized mean difference (SMD) (if different methods of measurement were used in the studies) and overall effect size (with 95% CI calculated) for continuous outcomes.

Unit of analysis issues

We considered the number of individual participants as the unit of analysis in this review. As we only identified individually randomized trials, we did not need to analyze for unit of analysis issues as planned in our protocol (Mendes 2018).

Dealing with missing data

When data were missing, we contacted the original researchers to request these data whenever possible. When this was not possible, and we considered that the missing data might introduce serious bias, we performed a sensitivity analysis to explore the impact of including such studies on the overall assessment of results. We assessed and reported dropout rates for each study, and used intention-to-treat (ITT) analyses (analysis of all participant data according to group allocation). We considered the amount of missing data when determining the risk of bias within included studies.

Assessment of heterogeneity

We assessed heterogeneity visually by observing the non-overlapping of CIs in the forest plots. Once identified, we quantified statistical heterogeneity using the I^2 statistic. The I^2 statistic estimates the percentage of total variation across trials due to heterogeneity rather than to chance. We categorized heterogeneity as I^2 values of 40% or less as indicating heterogeneity might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% or above indicating considerable heterogeneity (Higgins 2011c).

Assessment of reporting biases

We intended to perform a funnel plot analysis to assess reporting bias if a sufficient number of studies was identified (i.e. 10 or more). Had asymmetry been present, we would have explored possible causes, including publication bias, poor methodological quality, and true heterogeneity.

Data synthesis

We planned to perform a random-effects meta-analysis and use the fixed-effect method as a sensitivity analysis.

GRADE and 'Summary of findings' table

We assessed the certainty of the evidence by creating a 'Summary of findings' table using the following outcomes: independence in ADL, activities involving limbs, participation,

exercise capacity, balance, and adverse events. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies contributing data to the review for the outcomes (Atkins 2004). We used GRADEpro GDT to prepare the 'Summary of findings' table for the main comparison and to report the certainty of the evidence (GRADEpro GDT).

Subgroup analysis and investigation of heterogeneity

We planned to examine the following subgroup analyses if data were available.

- Type of effect (first subgroup defined as immediate effect or orthotic effect, i.e. the effect seen while using MN; second subgroup defined as relearn effect, i.e. the effect seen after the stimulation is turned off).
- Effect of MN when device was used for varying durations (4 weeks of use, between 5 and 24 weeks of use, 25 weeks of use).
- Effect of MN when used by participants at different phases of disease (< 3 months, 3 months).
- Effect of MN with surface or implantable electrodes.
- Effect of MN when applied on lower limb or upper limb.

We planned to use random-effects methods to produce this subgroup analysis for primary outcomes only.

Sensitivity analysis

We used Cochrane's tool for assessing risk of bias to judge the study methods (Higgins 2011b). We performed sensitivity analyses to assess the robustness of the findings by excluding studies from the analysis that were at high risk of bias in one or more of these three domains: random sequence generation, allocation concealment, and blinding of outcome assessors.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

Our electronic searches and searches of other resources identified a total of 18,579 references. After removal of 4881 duplicates, a total of 13,698 references remained for title and abstract screening. Of these, we excluded 13,616 references as irrelevant. We obtained the full text of 82 reports, and from these identified and included four studies (9 reports) in the review. The results of the search are summarized in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.

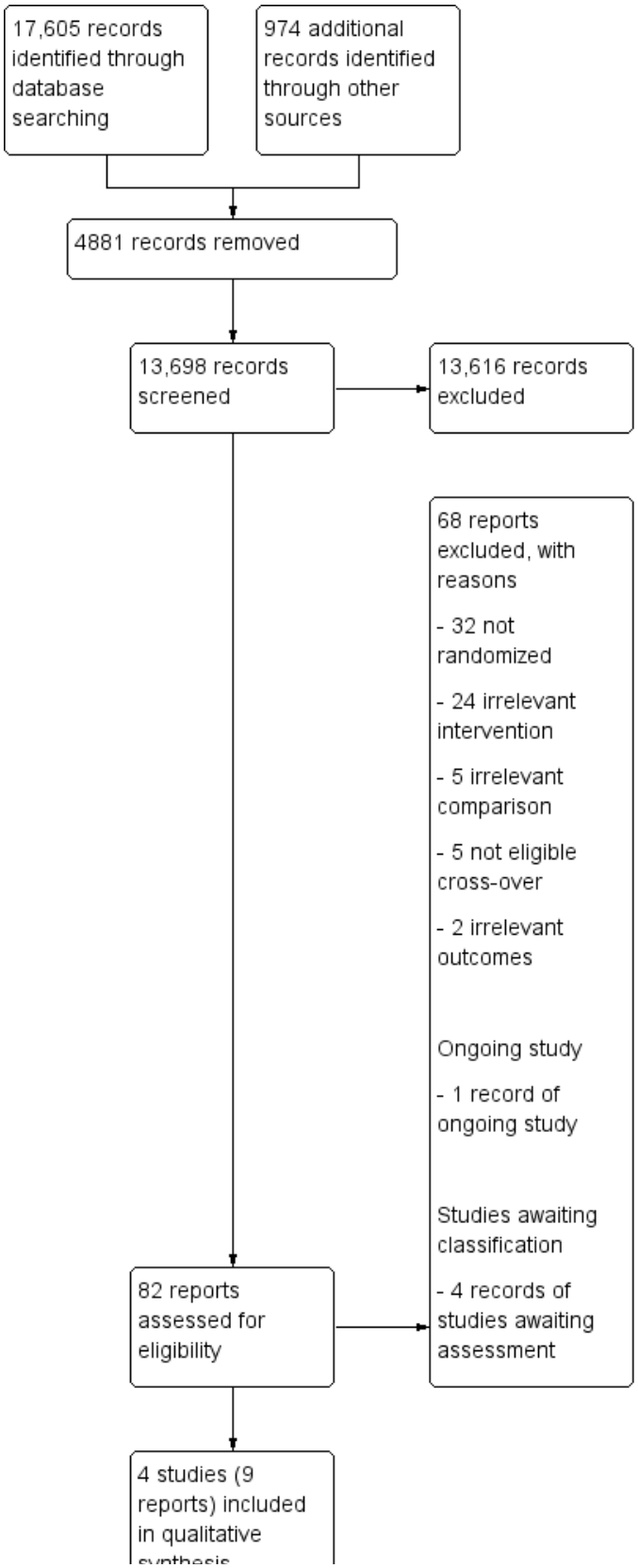
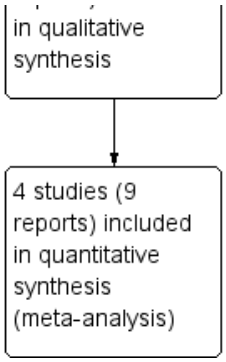


Figure 1. (Continued)



Included studies

See Characteristics of included studies.

Sample size and study location

The four included RCTs involved a total of 831 participants of both sexes, and were published between 2007 and 2015 in the USA, Bethoux 2014; Kluding 2013; Sheffler 2013a, and the Netherlands, Kottink 2007. Sample sizes ranged from 29 (14 and 15 in each group; Kottink 2007) to 497 (242 and 253 in each group; Bethoux 2014).

Participant characteristics

The mean age of participants ranged from 53, in Sheffler 2013a, to 64 years, in Bethoux 2014. Time poststroke varied between studies: Bethoux 2014 and Kottink 2007 recruited participants with a poststroke period of six months or more, whereas Kluding 2013 and Sheffler 2013a included participants with a poststroke period of three months or more. All participants were able to walk: in Sheffler 2013a they were able to walk at least 9.1 meters without an ankle-foot orthosis; in Bethoux 2014 and Kluding 2013 they were able to walk at least 10 meters with or without an assistive device or with a maximum of one person assisting, respectively; and in Kottink 2007 participants needed to walk independently on level and non-level surfaces, stairs, and inclines. The mean walking speed varied among studies, from less than 0.5 m/s, Bethoux 2014; Kluding 2013; Sheffler 2013a, to more than 0.7 and 0.9 m/s, Kottink 2007.

Intervention approaches

The included studies applied MN on a lower limb to facilitate walking in daily activities performed in the home or community context. All studies applied electrical stimuli to the peroneal nerve during the swing phase of gait using commercially available battery-powered devices. Three studies used a single-channel surface peroneal nerve stimulator composed of a stimulator, control unit, sensor, and two surface electrodes (Bethoux 2014; Kluding 2013; Sheffler 2013a), whereas one study used a two-channel implantable device composed of implantable components such as a stimulator, two leads, and two intraneural electrodes, and non-implantable components such as an external transmitter with a built-in antenna and sensor (Kottink 2007). Only one study used a tilt sensor and an accelerometer placed on the participant's leg to trigger the stimulation (Bethoux 2014); the other three studies used a heel switch placed inside the shoe to control the timing of the stimulation. Participants used MN from up to eight hours per day (Sheffler 2013a), to all-day use for ambulation (Bethoux 2014; Kluding 2013; Kottink 2007). During the first weeks of the intervention, all studies used conditioning protocols to adapt participants to MN use; after that, participants used MN for a long time during the day. All conditioning protocols included fitting the device to the participant's leg and giving the participant instructions on the use of MN (Table 1). The duration of the conditioning protocols ranged from two weeks, in Bethoux 2014, to six weeks, in Kluding 2013. These protocols were comprised of different activities, such as a progressive home-wear schedule to gradually increase time of device use, Bethoux 2014; Kluding 2013; Kottink 2007, and physical therapy sessions, which included gait training with the device, performed once or twice a week, Kluding 2013, and additional activities such as passive and active range-of-motion exercises, lower extremity strengthening, standing balance, and weight-shifting activities to the affected limb (Sheffler 2013a). In Kottink 2007, participants underwent a surgical procedure for the implantation of the MN components, and stimulation during walking started in the third week after surgery. The total duration of exposure to interventions varied from 12 weeks, in Sheffler 2013a, to 12 months, in Bethoux 2014. All studies compared the use of MN versus another assistive device (ankle-foot orthosis [AFO]).

Outcomes

Outcome measures for each of the predefined outcome categories are shown in Table 2. No study included primary outcomes related to independence in ADL. As we listed walking speed as a primary outcome related to activities involving limbs, we considered measures that assess speed for a distance of 10 meters (the 10-meter walk test (10MWT)) and kinematic assessment with a motion analysis system (Watson 2002). All studies included comfortable walking speed as a primary outcome measured with the 10MWT, Bethoux 2014; Kluding 2013, or with a motion analysis system, Kottink 2007; Sheffler 2013a. We pooled comfortable walking speed data because both measures assessed speed with the same unit (m/s) and the same distance. Only one study assessed fast walking speed, also using the 10MWT (Kluding 2013). Other outcomes related to activities involving limbs were assessed with TUG, Bethoux 2014; Kluding 2013, and mEFAP, Bethoux 2014; Sheffler 2013a. We included the data for outcomes related to participation in the Stroke-Specific Quality of Life (SSQoL) (Williams 1999), reported in two studies (Bethoux 2014; Sheffler 2013a). It can therefore be said that all studies included outcomes related to participation, but the scale used varied among studies: SF-36 (Kottink 2007), SIS (Bethoux 2014; Kluding 2013), and the SSQoL previously mentioned. The total value of the quality of life scale was only presented in studies that reported SSQoL. One study reported the values of each domain of the scale SF-36

separately as well as the Physical Component Summary (PCS-36) and Mental Component Summary (MCS-36) (Kottink 2007). Kluding 2013 reported the values of some domains of the SIS. Two studies assessed the exercise capacity-related outcome using the 6MWT (Bethoux 2014; Kluding 2013), and the balance-related outcomes using the BBS, Bethoux 2014; Kluding 2013, and FRT, Kluding 2013. Considering that the only study that described FRT also evaluated BBS, and that functional reach is an outcome assessed in the BBS as well, we decided to present only data for BBS in outcomes related to balance.

All studies reported outcomes at baseline and at intervention end (endpoint values), except for Kluding 2013, which presented outcomes as the change from baseline values. However, we were able to extract all outcomes from Kluding 2013 because they were presented in an reference associated with the study (Dunning 2015). Only one study had repeated observations of participants, with an assessment of outcomes in the middle part of the intervention period (Bethoux 2014), and only one study assessed follow-up 12 and 24 weeks post-treatment (Sheffler 2013a).

All of these outcomes except those related to participation/quality of life were assessed either while the participants were using MN or while they were not using MN. Two studies performed final assessments while participants were using MN: one study investigated the training effect of the intervention, so the baseline assessment was performed while the participants used MN (Bethoux 2014), while the other study investigated the total effect of intervention, so the baseline assessment was performed while the participants were not using MN (Kottink 2007). One study assessed the training effect of MN, thus all assessments were performed without the use of MN (Sheffler 2013a). One study evaluated both the training and therapeutic effect, so assessment of each outcome was conducted while participants were using MN and while they were not using MN (Kluding 2013).

All studies reported withdrawal or dropouts for several reasons during the intervention period (Table 3). Only two studies reported data for serious adverse events related to the intervention (Bethoux 2014; Kluding 2013). Although Sheffler 2013a included data for serious adverse events in its trial registry, it was not clear which data were related to the intervention, therefore we did not extract these data. Three studies presented data for falls (Bethoux 2014; Kluding 2013; Sheffler 2013a). Kottink 2007 did not mention any adverse event data in its reports.

Excluded studies

We excluded 68 studies (see Characteristics of excluded studies and Figure 1 for further information).

Studies awaiting assessment

Four studies are still awaiting assessment. We were unable to contact the principal investigator of one study because our email was undelivered (Wright 2004). We contacted the principal investigators of ISRCTN91639560 and NCT03574623 to learn if the electrical stimulation was used as an orthosis in the home or community context, but we have not received a response to date. We also contacted the principal investigator of UMIN000018648, who stated that the electrical stimulation protocol was applied at home. To date, we have received no response clarifying whether the study has already been published. See Characteristics of studies awaiting classification.

Ongoing studies

We identified one ongoing study that appeared to be eligible for inclusion (Ghedira 2014). See Characteristics of ongoing studies.

Risk of bias in included studies

'Risk of bias' assessments are presented for individual studies in Characteristics of included studies. See Figure 2 and Figure 3 for summaries of the results.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

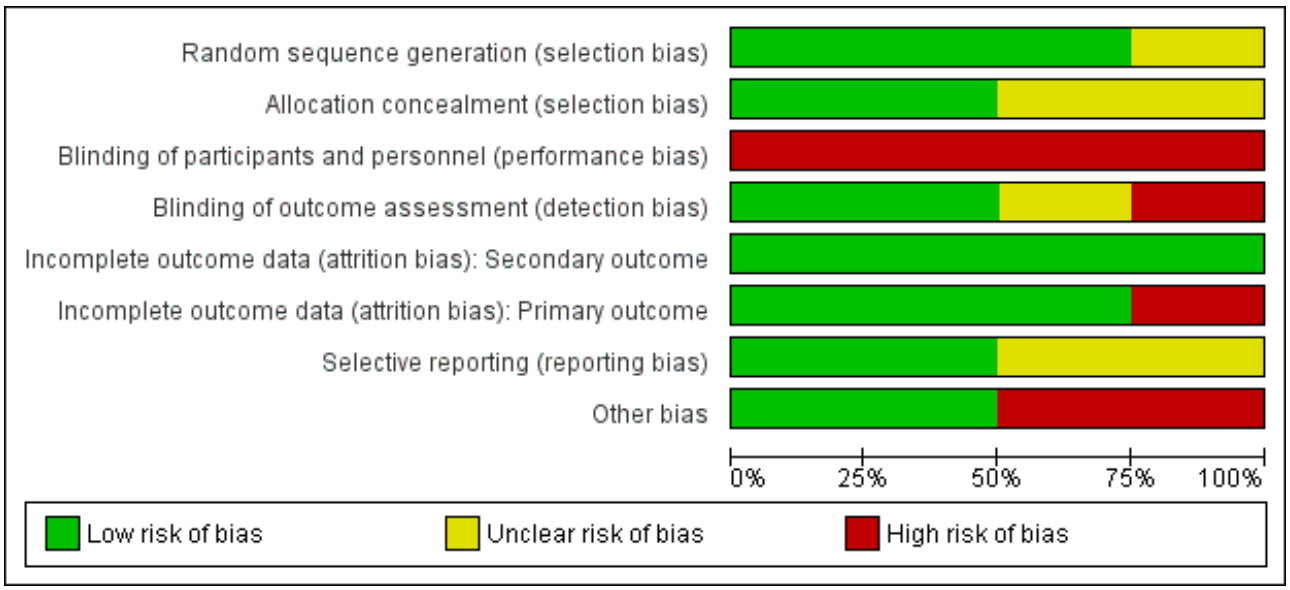
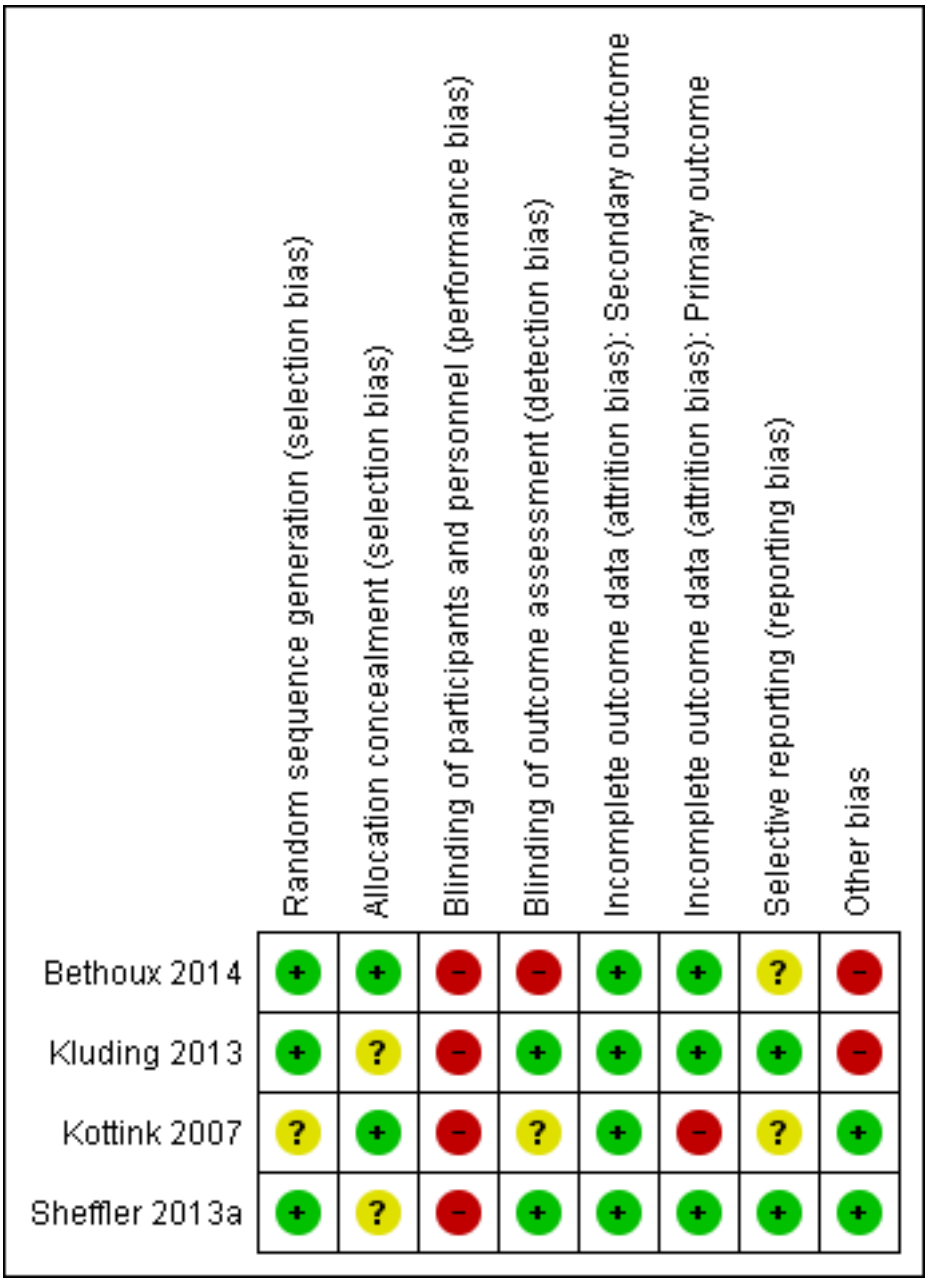


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Generation of randomization sequence was conducted correctly in three studies (Bethoux 2014; Kluding 2013; Sheffler 2013a), which we deemed to be at low risk of bias. One study did not clearly report if the method used for selecting the blocks described a random component in the sequence generation process, therefore we classified it as at unclear risk of bias (Kottink 2007).

Allocation concealment

We judged two trials to be at low risk of bias for allocation concealment (Bethoux 2014; Kottink 2007). We considered the other two included studies to be at unclear risk of bias: Kluding 2013 because the method of concealment was not described in sufficient detail to permit a definitive judgement, and Sheffler 2013a because the investigators did not report whether the envelopes used were sealed or not.

Blinding

Blinding of participants and personnel

None of the studies utilized blinded participants or personnel because of the nature of the intervention. We judged all studies as having a high risk of detection bias.

Blinding of outcome assessment

We assessed two studies where the outcome assessors were blinded to treatment allocation as at low risk of detection bias (Kluding 2013; Sheffler 2013a). One study had a high risk of detection bias because outcome assessments were unblinded (Bethoux 2014), whereas another study provided insufficient information to permit an assessment of level of bias and was therefore classified as at unclear risk of bias (Kottink 2007).

Incomplete outcome data

All studies reported withdrawals or dropouts, but we classified them as having a low risk of bias considering that ITT analyses were performed. Only Kottink 2007 did not perform ITT analysis for the primary outcome, hence we classified it as having a high risk of detection bias.

Selective reporting

We classified two studies as having a low risk of selective reporting because they had protocols available, and all of the prespecified outcomes were reported in the prespecified way (Kluding 2013; Sheffler 2013a). We considered two studies as having an unclear risk of selective reporting: Bethoux 2014 included a secondary variable in the study that was not prespecified in the protocol, and Kottink 2007 provided insufficient information to permit a judgement.

Other potential sources of bias

We assessed two studies that were sponsored by manufacturers of MN as having a high risk of bias (Bethoux 2014; Kluding 2013). No other bias was detected in Kottink 2007 and Sheffler 2013a.

Effects of interventions

See: **Summary of findings for the main comparison** Motor neuroprosthesis compared to another assistive technology device for promoting recovery of function after stroke

See Summary of findings for the main comparison.

We included all four studies in the quantitative analysis (Bethoux 2014; Kluding 2013; Kottink 2007; Sheffler 2013a). All studies compared MN versus another assistive technology device. The outcomes used in these studies were: activities involving limbs (Bethoux 2014; Kluding 2013; Kottink 2007; Sheffler 2013a); participation scales of HRQoL (Bethoux 2014; Kluding 2013; Kottink 2007; Sheffler 2013a); exercise capacity (Bethoux 2014; Kluding 2013); balance (Bethoux 2014; Kluding 2013); number of dropouts (Bethoux 2014; Kluding 2013; Kottink 2007; Sheffler 2013a); serious adverse events related to intervention (Bethoux 2014; Kluding 2013); and falls (Bethoux 2014; Kluding 2013; Sheffler 2013a).

We contacted the principal investigator of Kottink 2007 to request data for outcomes of the 6MWT and walking speed assessed with ITT analysis with and without devices, which were presented in Kottink 2007 and Kottink 2008 only as figures. However, we could not obtain these data, so we excluded the 6MWT results of this study from the quantitative analysis and extracted the walking numerical speed data analyzed without ITT presented in Kottink 2012.

We considered for meta-analysis only Kluding 2013 assessments performed with the participants using a device (MN or another assistive device). The study of Bethoux 2014 had two publications that performed an assessment at different time intervals during the intervention period (repeated observations of the participants). In order to gain a better understanding of the effect of MN on different time periods, we decided to include data from both Bethoux 2014 publications in the meta-analysis.

Kluding 2013 used two measures to assess walking speed: comfortable and fast walking speed. As all studies assessed comfortable walking speed, and no study assessed fast walking speed, we decided to include only the Kluding 2013 data for comfortable walking speed in the meta-analysis.

Comparison: motor neuroprosthesis versus another assistive technology device

Independence in ADL

None of the four included studies reported outcomes related to independence in ADL.

Activities involving limbs

Walking speed until six months of device use

Two studies (605 participants) measured walking speed until six months of device use. One study performed a final assessment with participants using MN; the other study did not perform a final assessment with participants using MN. We found low-certainty evidence that the control intervention (another assistive technology device) had a greater effect than MN on walking speed in six months of device use: the mean difference (MD) (random-effects model) was -0.05 m/s (95% confidence interval (CI) −0.10 to −0.00; P = 0.03; I^2 = 0%; Analysis 1.1). But considering that the minimal important difference for comfortable walking speed in chronic stroke participant is 0.2 m/s, this effect was not enough to be clinically meaningful.

We conducted sensitivity analysis by excluding Bethoux 2014 since this study presented a high risk of bias in the blinding of outcome assessment. The sensitivity analysis showed that there is low certainty that the effect of the control intervention on improving walking speed is no longer present (MD −0.07 m/s, 95% CI −0.16 to 0.02; P = 0.13; I^2 = 0%; 110 participants; Table 4).

Walking speed between six and 12 months of device use

Three studies (713 participants) measured the walking speed of participants between six and 12 months of device use. All three studies performed final assessments while the participants used MN. There is low-certainty evidence that MN is no more beneficial than another assistive device on walking speed between six and 12 months of device use (MD 0.00 m/s, 95% CI −0.05 to 0.05; P = 0.93; I^2 = 17%; Analysis 1.2).

We conducted a sensitivity analysis excluding the study that was at high risk of bias for blinding of outcome assessment, which highlighted that we are very uncertain whether MN is more beneficial than another assistive device on walking speed between six and 12 months of device use (Table 4). Kottink 2007 had a high risk of bias for incomplete outcome data relating to this outcome, but as we did not consider this 'Risk of bias' domain on sensitivity analysis, we decided to maintain these data. However, caution should be used in interpreting these data as their results were visually different from data for other studies.

Walking speed: subgroup analysis for type of MN

We analyzed subgroups considering the type of MN used (823 participants). We compared studies in which the MN used consisted of a superficial device with those in which MN consisted of an implantable device. For this subgroup analysis, we considered the walking speed assessment performed in Bethoux 2014 at 12 months. The test for subgroup differences (between surface MN and implantable MN) revealed no significant difference (P = 0.09; I^2 = 65.1%; Analysis 1.3).

TUG at the end of the intervention phase

Two studies (692 participants) assessed TUG. In both studies, the final assessments of participants were performed while they were using MN. As Bethoux 2014 presented TUG assessment only for six months, these data were included for TUG analysis. There is moderate-certainty evidence that MN is no more beneficial than another assistive device on TUG (MD 0.51 s, 95% CI −4.41 to 5.43; P = 0.84; I^2 = 0%; Analysis 1.4).

The sensitivity analysis performed by excluding Bethoux 2014, which was at high risk of bias for blinding of outcome assessment, highlighted that more information is required to be certain as to whether MN is no more beneficial than another assistive device on TUG (Table 4).

mEFAP at the end of the intervention phase

Two studies (605 participants) assessed mEFAP. One study performed a final assessment of participants while using MN, whereas the other study did not perform a final assessment of the participants while using MN. As Bethoux 2014 presented mEFAP assessment only for six months, these data were included for mEFAP analysis. There is low-certainty evidence that MN is no more beneficial than another assistive device on mEFAP (MD 14.77 s, 95% CI −12.52 to 42.06; P = 0.29; I^2 = 0%; Analysis 1.5).

The sensitivity analysis performed by excluding Bethoux 2014 data highlighted that more information is required to be certain as to whether MN is no more beneficial than another assistive device on mEFAP (Table 4).

Participation scales of HRQoL

All studies assessed at least one participation scale of HRQoL. There was heterogeneity between the selection of scales of HRQoL as well as their presentation (some scales presented the total value of a full version, while others presented the value of some domains separately). In light of this, we decided to include only scales or scale components that represented the whole domain of a scale and to combine data from these different scales using standardised mean difference (SMD) as stated in our protocol. Bethoux 2014 presented two participation scales of HRQoL at six months' assessment; we decided to use the SSQoL for analysis, as the total value was available. We did not include measures that represented only some domains of a scale of HRQoL. We included data from three studies (632 participants) that assessed HRQoL with a participation scale. There is very low-certainty evidence that MN is no more beneficial than another assistive device on participation scale of HRQoL. The random-effects pooled estimate for all trials was SMD 0.26 (95% CI −0.22 to 0.74; P = 0.28; I^2 = 77%; Analysis 1.6).

The sensitivity analysis performed by excluding Bethoux 2014 data highlighted that we are very uncertain as to whether MN is any more beneficial than another assistive device on participation scale of HRQoL, although the magnitude of the effect changed from a small effect (Analysis 1.6) to a moderate effect based on Cohen's rules of thumb (Table 4).

Exercise capacity

Two studies (692 participants) assessed exercise capacity using the 6MWT. Both studies performed final assessments on participants using MN. As Bethoux 2014 presented 6MWT assessment only for six months, these data were included for 6MWT analysis. There is low-certainty evidence that MN is no more beneficial than another assistive device on exercise capacity (MD −9.03 m, 95% CI −26.87 to 8.81; P = 0.32; I^2 = 0%; Analysis 1.7).

The sensitivity analysis performed by excluding Bethoux 2014, which was at high risk of bias for blinding of outcome assessment, highlighted that more information is required to be certain as to whether MN is no more beneficial than another assistive device on exercise capacity (Table 4).

Balance

Two studies (692 participants) assessed balance using the BBS. Both studies performed final assessments on participants using MN. There is moderate-certainty evidence that MN is no more beneficial than another assistive device on balance (MD −0.34, 95% CI −1.96 to 1.28; P = 0.68; I^2 = 0%; Analysis 1.8).

The sensitivity analysis excluding Bethoux 2014 data highlighted that we are very uncertain as to whether MN is more beneficial than another assistive device on balance (Table 4).

Number of dropouts

All studies (829 participants) reported dropouts during the intervention period; the reasons for dropouts are described in detail for each trial in Table 3. For this outcome, we considered the number of dropouts for Bethoux 2014 at 12 months. There is low-certainty evidence that the risk of participants dropping out of the study was increased by 51% with MN when compared with control. The risk ratio (RR) (random-effects model) for dropouts was 1.48 (95% CI 1.11 to 1.97; P = 0.007; I^2 = 0%; Analysis 1.9). The highest dropout rate occurred in Bethoux 2014 (12 months of intervention): 26% in the MN group (62 dropouts out of 242 participants) and 19% in the control group (49 dropouts out of 253 participants). The lowest dropout rate occurred in Kottink 2007: 7% in the MN group (1 dropout out of 14 participants) and 8% in the control group (1 dropout out of 13 participants).

Adverse events

Only one study reported deaths during the intervention period (Bethoux 2014). The death rate was less than 1% for both groups in the six-month intervention report of Bethoux 2014. In the MN group, deaths were due to a nervous system disorder or renal and urinary disorders (2 deaths of 242 participants), whereas deaths in the control group were due to nervous system disorders (2 deaths of 253 participants). In the 12-month intervention report of the Bethoux 2014 study (Bethoux 2015), the death rate was maintained in the MN group (less than 1%; 2 deaths of 242 participants), but was increased by 1% in the control group (3 deaths of 253 participants).

Serious adverse events related to intervention

Two studies (692 participants) provided data on serious adverse events related to the intervention during the treatment period. Bethoux 2014 considered serious adverse events related to device use as serious falls; as this study presented this outcome in both six- and 12-month reports, we decided to include the longer assessment (12 months). Overall, there is low-certainty evidence that the use of MN in people after stroke does not have an effect on risk of adverse events during the treatment period when compared to other assistive devices: RR (random-effects model) of 0.35 (95% CI 0.04 to 3.33; P = 0.36; I^2 = 0%; Analysis 1.10).

Falls

Three studies (802 participants) provided data on falls. There is moderate-certainty evidence that the use of MN in people after stroke does not have an effect on risk of falls during the whole treatment period when compared to other assistive devices: RR (random-effects model) of 1.20 (95% CI 0.92 to 1.55; P = 0.08; I^2 = 33%; Analysis 1.11).

DISCUSSION

Summary of main results

The aim of this review was to assess the effects of MN for improving independence in ADL, activities involving limbs, participation scales of HRQoL, exercise capacity, balance, and adverse events in people after stroke. We included four studies (9 articles) involving a total of 831 participants that compared MN with another assistive technology device. All studies addressed MN application directed to the lower limbs, specifically in the peroneal nerve, to correct foot drop during walking activities in the home or community context, such as an orthosis. In all studies, another assistive technology device (control intervention) used was ankle-foot orthosis (AFO). No studies compared MN with no treatment or with MN without electrical stimulus. Overall, the certainty of the evidence for outcomes ranged from moderate to very low. The main results are presented in the Summary of findings for the main comparison.

No studies reported outcomes related to independence in ADL, so we could not assess the evidence of the effects of MN on ADL. Although we found low-certainty evidence that AFO had an effect on improving walking speed until six months of device use (MD −0.05 m/s, 95% CI −0.10 to −0.00), this effect did not appear to be clinically relevant, given that the minimally significant difference for comfortable walking speed in chronic stroke participants is 0.2 m/s (Hiengkaew 2012). Furthermore, when we excluded one study at high risk of bias related to unblinded outcome assessment from the meta-analysis, this effect was absent, that is both strategies (MN and AFO) proved to have similar effects on walking speed until six months of device use. We found low-certainty evidence that there is no beneficial effect of MN, when compared to another assistive device, for walking speed between six and 12 months of device use. We also observed no difference in effect on walking speed between the surface and implantable MN. We have very little confidence in our estimate of the effect of implantable MN because only one small study with a high risk of bias for incomplete outcome data and unclear risk for random sequence generation, blinding of outcome assessment, and selective reporting investigated its effect. For this reason, the exact effect of implantable MN is likely to be substantially different from the estimate of its effect.

We found moderate-certainty evidence that MN has no effect on balance measured with BBS and activities involving limbs such as TUG. We found low-certainty evidence that MN has no effect on exercise capacity measured with 6MWT and activities involving limbs such as mEFAP. Although there were some limited moderate- or low-certainty evidence, this apparent lack of effect (MN is not any different to AFO) should be interpreted with caution due to the high risk of bias (outcome assessors were unblinded) in the largest study and the broad confidence intervals these outcomes presented. Regarding the secondary outcome measure participation scale of HRQoL, we found very low-certainty evidence that MN does not differ in effect compared to AFO. However, due to the quality of evidence, any potential benefits of the interventions remain uncertain.

We found low-certainty evidence that the use of MN in people after stroke increases the risk of participants dropping out of the study. However, when considering safety, we found that the number of falls (moderate-certainty evidence) and the number of serious adverse events (low-certainty evidence) were not increased related to the use of MN. We considered serious adverse events related to device use as serious falls. Limited data contributed to the results for this outcome, and due to the wide confidence intervals, further information is needed.

Overall completeness and applicability of evidence

Our search results identified a considerable number of studies that applied MN devices in a clinical context for ADL training or even as a home-based program to increase the dose therapy usually done with cyclic stimulation. As this was not the focus of this review, we excluded these studies. We found only four studies (nine articles) that focused on the effects of MN for improving activities and participation in people after stroke, considering its use as an environmental facilitator to enhance the performance of functional abilities in the home or community context. While the number of such studies was small, the number of participants was not (831 participants). We also found trials that used the brain-machine interface (BMI) to control the signals of electrical stimulation devices; however, no study met the inclusion criteria of this review, especially with regard to study design.

The results of this review indicate that little is known about the effect of MN and that further information is needed. There is currently insufficient high-certainty evidence to make conclusions about the benefits or harms of MN. Overall, there is no substantial evidence that MN has an effect on improving activities involving limbs, participation scales of HRQoL, exercise capacity, balance, and adverse events. The only possible effect found was that the use of MN in people after stroke increased the risk of participants dropping out the study for several reasons, which included participant request to discontinue the intervention, lost to follow-up, medical reasons, non-compliance with protocol, and others as mentioned in Table 3.

Considering that we only included studies with MN applied on the lower limb, these results cannot be generalized to include improvement of activities related to the upper limb. Even considering MN directed to the lower limb, the following factors produce uncertainty.

- The majority of interventions were focused on single-channel surface MN for stimulation of the peroneal nerve.

- All interventions consisted of MN applied on the peroneal nerve to facilitate walking activities.
- The activities performed and their duration throughout the conditioning protocols varied between studies. These conditioning protocols prepared participants for MN use for a long period during the day, and all studies included them in the first few weeks of the intervention period.

As all the included studies used non-biological signals such as force/pressure and inertial sensors as an input to trigger the electrical stimulus, the results of this review cannot be generalized for MN triggered with electromyography or electroencephalography signals. Since we considered the use of MN as an orthosis, the only comparison we found was MN versus another assistive technology device. In this way, this review provides incipient data that can help in decision making on the use of MN or AFO, not considering other assistive devices or MN versus no device.

Since none of the studies included participants within three months of stroke, we did not assess if the effects of MN can be generalized for individuals in the early stages of stroke. In addition, the mean walking speed at baseline assessment varied widely between studies that assessed superficial and implantable MN devices.

The most common outcome was walking speed, which was part of activities involving limbs, but no study assessed other important outcomes for people with stroke, such as independence in ADL. Consequently, there is a need to monitor this outcome in future updates to determine the effect of MN on independence in ADL.

Additionally, MN using an environmental facilitator to enhance the performance of functional abilities in the home or community context could possibly create additional costs of rehabilitation after stroke due to the nature of the device and because the structure requires experts to fit, adapt, and train users to use the device; researchers did not quantify the costs of its application. In this context, the results of this review seem to be quite generalizable for industrialized countries that have services and facilities available for the application and adaptation of MN to users.

Quality of the evidence

According to the GRADE criteria, the certainty of evidence ranged from moderate to very low due to the small number of studies included in the review, which led to wide confidence intervals for seven out of the nine included outcomes, and the presence of some judgements of high risk and unclear risk of detection bias in the included studies (see Summary of findings for the main comparison). Three out of four trials showed a high risk of bias for one or two of these 'Risk of bias' domains: blinding of outcome assessment, incomplete outcome data for primary outcome, or other potential sources of bias. The outcome assessors in the largest study were not blinded. The two most significant studies, which represented 83% of included participants, were multicenter and sponsored by manufacturers of MN; because of this, we classified them as being at high risk of other potential sources of bias. However, these studies adopted some precautions that may have minimized the presence of other biases, such as clearly described adverse events related and not related to MN and AFO groups on trial registries, sufficient methodological detail presented with prior protocol publication, or even inclusion of an independent Clinical Events Committee to adjudicate serious adverse events and their connection to the device. All studies had a high risk of bias for blinding participants or personnel because of the nature of the intervention. Poor reporting and lack of clarification from the authors led us to assess studies as being at unclear risk of bias for important criteria such as random sequence generation, allocation concealment, blinding of outcome assessment, and selective reporting. Nevertheless, most of the results were consistent (low heterogeneity).

Potential biases in the review process

Given our extensive searching process, we are confident that our search strategy was comprehensive and detailed; this strategy included searching in databases, electronic registries, websites, and a careful search of grey literature. We thus expect that we have identified all relevant studies; however, there is a small possibility that we failed to identify additional (published or unpublished) papers. Two review authors independently assessed the studies and obtained and extracted data, with a third or fourth review author available to resolve disagreements as needed, thereby minimizing bias; several subjective judgements were required during the review process.

We decided to downgrade our assessment of blinding of participants and personnel, even while knowing that such blinding does not seem feasible for the type of intervention. Another limitation of this review is that some of the studies had methodological shortcomings, such as random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data for the primary outcome, and selective reporting. According to the *Cochrane Handbook for Systematic Reviews of Interventions*, these biases can lead to overestimation of the intervention effect (Higgins 2011b).

Agreements and disagreements with other studies or reviews

We found only one systematic review with meta-analysis of randomized controlled trials on MN for improving activities and participation in people after the stroke that considered MN use as an environmental facilitator to enhance the performance of functional abilities (Prenton 2016). Although that review focused on MN directed to peroneal nerve stimulation as well, it differed from the current review by including studies that used MN in the ward environment, which did not represent a real-life context. The authors referred to the MN device with the use of FES nomenclature. As the comparison included in Prenton 2016 was MN versus AFO on the date of the final assessment of 10-meter walking speed and 6MWT, its results were similar to the results of the current review, which indicated that AFO had positive orthotic effects on walking that are equivalent to FES for foot drop on stroke participants. Similarly, researchers also found little difference in favor of AFO for evaluations performed between 12 and 13 weeks of device use, but they did not perform sensitivity analysis. Prenton 2016 additionally performed a meta-analysis for the mobility domain of the Stroke Impact Scale and found no difference between the two interventions, but did not assess the dropout rate between studies.

As far as we know, no systematic review has evaluated the number of dropouts related of MN use with meta-analysis. There are only separated reports that assess compliance and preference for MN. Among the studies included in this review, only Kluding 2013

evaluated satisfaction related to the use of the devices. The authors of this study used a satisfaction survey that evaluates 12 items with a total range of scores from 0 to 24, with a higher number indicating greater satisfaction with the device. Although there was a higher dropout rate in the MN group (25 of 99 participants) than in the AFO group (10 of 98 participants), the satisfaction was higher in the MN group than in the AFO group. Everaert 2013 recorded the users' preference and asked participants to indicate the reasons for their preference at the end of each arm of a cross-over study. The majority of participants preferred the MN, the reasons most frequently mentioned being function, confidence, comfort, convenience, easy donning and doffing, and safety.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, motor neuroprosthesis (MN) (use of electrical stimulation as an environmental facilitator in the home or community context) does not appear to be more beneficial than other assistive devices for improving activities involving limbs measured by Timed Up and Go, balance (moderate-certainty evidence), activities involving limbs measured by walking speed and modified Emory Functional Ambulation Profile, exercise capacity (low-certainty evidence), and participation scale of health-related quality of life (very low-certainty evidence). As such, MN is not any different to ankle-foot orthosis for the above mentioned outcomes. We could not estimate the effect of MN on independence in activities of daily living because no study assessed this outcome. Although there was moderate certainty that MN did not increase the number of falls and low certainty that MN did not increase serious adverse events related to the intervention during the intervention period, the number of dropouts related to MN use was higher than with the control. Considering the low certainty of the evidence for this outcome (dropouts), our confidence in this effect estimate is limited and needs to be confirmed in future clinical trials.

Because of the specificity found in the included studies that assessed the effects of MN directed to the lower limb in participants more than three months' poststroke, it is not possible to generalize the aforementioned effects to participants less than three months' poststroke and interventions such as upper limb MN or MN triggered by electromyography or electroencephalography signals. Concerning implantable MN, the apparent lack of effect of implantable MN should be interpreted with caution due to the very low certainty of the evidence, which means that the effect of lower limb implantable MN on walking speed could be very different from the estimated effect. Further investigation is needed in this regard.

Implications for research

Further research should improve the certainty of the evidence (GRADE) regarding the effect of MN for improving activities and participation in people after stroke. New well-designed and properly reported randomized controlled clinical trials should be conducted using a larger sample in order to provide high-quality evidence, preferably with blinded outcome assessment.

In order to understand the effects of the whole MN category on activities and participation in people after stroke, it is necessary to design randomized controlled trials with MN directed to the upper limb as well as with implantable devices and devices that use biological signals to trigger the stimulation. These studies should focus on MN use as an environmental facilitator for enhancing the performance of functional abilities in the home or community context, especially involving outcomes related to independence in activities of daily living. As we found a higher dropout rate with MN use, it is important to thoroughly consider the motivations of each participant in relation to compliance or satisfaction in order to understand the cause of higher MN dropouts, as well as to guide future research on the development of these devices.

Considering that there is a variable and prolonged process ranging from the fitting of the MN to the participant's limb to its use as an assistive device for enhancing the performance of functional abilities in the home or community context, it is necessary to assess the outcomes related to activity and participation during all-day use of MN period separately from the conditioning protocols period. In this way it will be possible to precisely assess the use of MN as an orthosis without the contamination of previous conditioning protocols data, as was observed in all studies included in this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bethoux 2014

Methods	Study design: RCT Instruments used: MMSE, BDI, 10MWT, SIS, device-related SAE rate, 6MWT, GaitRite FAP, mEFAP, BBS, TUG, SSQoL Study design as described in the article: Quote: "This study was an unblinded, parallel-group RCT" Study duration: 24 months Year of study: trial ran between April 2010 and April 2012
Participants	Inclusion criteria: ≥ 6 months poststroke; inadequate dorsiflexion with inadequate limb clearance during swing phase of gait; positive response to peroneal nerve stimulation testing; adequate cognitive function (MMSE score > 17); not currently using FES for the treatment of foot drop; ≥ 30 days post-inpatient or outpatient stroke, cardiac, pulmonary, or any other lower extremity physical rehabilitation; able to walk at least 10 meters with or without an assist device; initial gait speed of > 0.0 m/s and < 0.8 m/s; eligible for Medicare or Medicare Choice/Advantage benefits at time of consent; ≥ 90 days post-MI; ≥ 90 days post-stenting procedure (i.e. peripheral, cardiac, carotid, and/or renal); ≥ 90 days post-major orthopedic surgery (i.e. hip, knee, and/or ankle joint replacement); ≥ 6 months post-CABG or cardiac valve procedure; able and willing to give written consent and comply with study procedures, including follow-up visits Exclusion criteria: ankle joint instability other than foot drop; needs AFO for stance control of the foot, ankle, and/or knee; unable to safely clear toes in swing phase on the involved lower extremity, defined as > −5 degrees plantar flexion with the WalkAide device (determined at fitting); diagnosed with peripheral neuropathy, and symptoms obstruct or limit ambulation or participation in study; diagnosed with significant peripheral vascular disease accompanied by lower extremity ulceration and/or disabling claudication; underlying condition(s) that would limit study participation; severe hypertonicity resulting in the need for more involved orthotic strategies; excessive dysesthetic pain secondary to neurological involvement; moderate to very severe chronic obstructive pulmonary disease, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD); New York Heart Association (NYHA) Class

Bethoux 2014 *(Continued)*

	III-IV; malignant skin lesion below the knee on the affected lower extremity; history of seizure disorder and is currently on seizure control medication for this disorder; aphasia, defined as inability to verbalize commands; BDI score of > 29 indicating severe depression; life expectancy less than 12 months; received botulinum toxin injections in the lower extremity within the past 6 months; baclofen pump with unstable dosing in the last 3 months; participating in another clinical trial that, according to the principal investigator, is likely to affect study outcome or confound results; patient has existing electrical stimulation devices (implantable cardioverter defibrillator, pacemaker, spinal stimulation, TENS) Age: MN group mean age (± SD): 63.87 years (± 11.33); control group mean age (± SD): 64.30 years (± 12.01) Country: USA Sample size: 495 participants Sex: MN group: 147 (60.74%) men, 95 (39.26%) women; control group: 157 (62.06%) men, 96 (37.94%) women Time poststroke: ≥ 6 months poststroke. MN group mean time poststroke (± SD): 6.90 years (± 6.43); control group mean time poststroke (± SD): 6.86 years (± 6.64) Type of stroke: not stated
Interventions	Motor neuroprosthesis • Intervention: MN group used WalkAide device for all walking activities on a full-time basis throughout the day. In the first 2 weeks, participants adhered to a progressive wearing schedule, after that they were instructed to wear MN on a full-time basis (i.e. for all walking activities throughout the day). • Number of participants: 242 • Device: a single-channel electrical stimulator composed of a cuff worn around the proximal part of the lower leg, control module, and surface electrodes. This device uses a tilt sensor and accelerometer to trigger ankle dorsiflexion during the swing phase of gait. • Duration of exposure: the length of treatment with MN was 12 months • Place of application of intervention: lower limb Another assistive technology device • Intervention: control group used AFO for all walking activities on a full-time basis throughout the day. In the first 2 weeks, participants adhered to a progressive wearing schedule, after that they were instructed to wear AFO on a full-time basis (i.e. for all walking activities throughout the day). • Number of participants: 253 • Device: AFO could be either articulated or fixed at the ankle based on the professional opinion of the orthotist and clinical needs of the participant • Duration of exposure: the length of treatment with AFO was 12 months • Place of application of intervention: lower limb
Outcomes	Activities involving limbs: walking speed measured with the 10MWT (m/s) • Outcome type: continuous • Assessment time point: baseline, 6 months, and 12 months • Device at assessments: baseline, 6-month, and 12-month assessments performed with MN Activities involving limbs: mEFAP (s) • Outcome type: continuous • Assessment time point: baseline, 6 months, and 12 months • Device at assessments: baseline, 6-month, and 12-month assessments performed with MN Activities involving limbs: TUG (s) • Outcome type: continuous

Bethoux 2014 *(Continued)*

- Assessment time point: baseline and 6 months
- Device at assessments: baseline, 6-month, and 12-month assessments performed with MN

Balance: BBS

- Outcome type: continuous
- Assessment time point: baseline and 6 months
- Device at assessments: baseline, 6-month, and 12-month assessments performed with MN

Exercise capacity: 6MWT (m)

- Outcome type: continuous
- Assessment time point: baseline, 6 months, and 12 months
- Device at assessments: baseline, 6-month, and 12-month assessments performed with MN

Participation scale of HRQoL: SSQoL

- Outcome type: continuous
- Assessment time point: baseline and 6 months

Participation scale of HRQoL: SIS Social participation domain

- Outcome type: continuous
- Assessment time point: baseline and 6 months

Adverse events: dropouts during the intervention period

- Outcome type: binary

Adverse events: serious adverse events related to the intervention

- Outcome type: binary

Adverse events: falls

- Outcome type: binary

Identification	Author's name: Francois Bethoux Institution: The Cleveland Clinic Foundation Email: bethouf@ccf.org Address: The Cleveland Clinic Foundation, Desk U10, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Funding source	Innovative Neurotronics
Notes	This study consisted of 2 articles (Bethoux 2014; Bethoux 2015).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a centralized computer-generated randomization scheme built into the electronic data capture system for this study"
Allocation concealment (selection bias)	Low risk	Quote: "Centralized computer-generated randomization scheme"
Blinding of participants and personnel (performance bias)	High risk	There was no blinding of participants and personnel.

Bethoux 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded outcome assessment
Incomplete outcome data (attrition bias) Secondary outcome	Low risk	Quote: "We conducted an ITT analysis using multiple imputations to account for missing data"
Incomplete outcome data (attrition bias) Primary outcome	Low risk	Quote: "We conducted an ITT analysis using multiple imputations to account for missing data"
Selective reporting (reporting bias)	Unclear risk	Although all of the study's prespecified primary outcomes were reported, a secondary variable was included in the study that was not prespecified in the protocol.
Other bias	High risk	This study was sponsored by Innovative Neurotronics.

Kluding 2013

Methods	Study design: RCT Instruments used: 10MWT, lower extremity Fugl-Meyer, TUG, 6MWT, BBS, FRT, SIS Study design as described in the article: "single-blinded randomized controlled trial" Study duration: 32 months Year of study: trial ran between May 2010 and December 2012
Participants	Inclusion criteria: at least 1 stroke ≥ 3 months before study enrollment, resulting in drop foot; ankle dorsiflexion response with test stimulation in sitting and standing, and adequate ankle and knee stability during gait with test stimulation; medically stable; score ≥ 24 on the MMSE, or have a competent caregiver if < 24; age ≥ 18 year or older; able to walk ≥ 10 meters with a maximum of 1 person assist; self-selected gait speed ≤ 0.80 m/s without orthotic effect Exclusion criteria: fixed ankle contracture at ≥ 5 degrees of plantar flexion in the hemiplegic leg with the knee extended; pain in the affected leg, rated ≥ 4 on a 10-point visual analogue scale; participating in physical therapy, occupational therapy, new exercise program, or any other interventional clinical research studies without the sponsor's approval; botulinum toxin to the hemiplegic leg or arm within the past 6 weeks or planned during the course of the study; expectation of a significant change in oral medications for spasticity; complete lower extremity hemisensory loss; use of any FDS device for foot drop for an accumulative > 3 hours within the last 6 months before study enrollment; any electric or metallic implant; significant swelling/edema in the lower leg; chronic skin problems or cancerous lesion in close proximity to the site of FDS stimulation; pregnant or planning on becoming pregnant; unstable seizure disorder; orthopedic conditions that would affect ambulation; major untreated depression Sample size: 197 participants Country: USA Age: mean age (± SD): 61.14 years (± 11.61) Sex: 79 women and 118 men. MN group: 51 (51.5%) men; control group: 67 (68.4%) men Time poststroke: this study considered 2 subgroups: participants 3 to 6 months after stroke and participants > 6 months after stroke. Mean time poststroke (± SD): 4.55 years (± 4.72)

Kluding 2013 *(Continued)*

	Type of stroke: 145 ischemic, 46 hemorrhagic, 6 data not available
Interventions	Motor neuroprosthesis • Intervention: MN group used NESS L300 device. In the first 6 weeks, participants received 8 physical therapy sessions and also followed the device manufacturer's standard conditioning protocol. The physical therapy sessions focused on education on the MN device use, gait training with MN, and the development of an individualized home exercise program. Treatment time ranged from 30 to 60 minutes. The standard conditioning protocol performed in the first 3 weeks included the gradual increase of walking with MN from 15 minutes each day to all-day use and also involved the use of the device for cyclic stimulation while the participant was not walking. Participants performed cyclic stimulation to gradually strengthen and condition the muscles to avoid fatigue when using the MN. This stimulation was done 2 times daily for 15 minutes in the first week and for 20 minutes over the next 2 weeks. After this initial conditioning phase, participants used MN all day exclusively for ambulation. • Number of participants: 99 • Device: a single-channel electrical stimulator composed of a cuff, control module, surface electrodes, and a pressure sensor to detect gait events and trigger stimulation • Duration of exposure: 30 weeks of MN • Place of application of intervention: lower limb Another assistive technology device • Intervention: control group used AFO. In the first 6 weeks, participants received 8 physical therapy sessions and also received surface sensory stimulation with a TENS device. The physical therapy sessions focused on education on use of the AFO if need, gait training with the AFO, and the development of a home exercise program. Treatment time ranged from 30 to 60 minutes. During the first 3 weeks, participants received surface sensory stimulation on the hemiplegic leg with a TENS device at each physical therapy visit. TENS intensity was set at the lowest stimulation level that yielded a sensory response without motor response, at a frequency of 100 pps and duration of 200 µs. This stimulation was done for 30 minutes in the first week and for 30 to 45 minutes over the next 2 weeks. After this initial conditioning phase, participants used AFO all day exclusively for ambulation. • Number of participants: 98 • Device: AFO (articulated, non-articulated, prefabricated or other) • Duration of exposure: 30 weeks of AFO • Place of application of intervention: lower limb
Outcomes	Activities involving limbs: walking speed measured with the 10MWT (m/s) • Outcome type: continuous • Assessment time point: baseline and 30 weeks • Device at assessments: baseline and 30-week assessments performed with MN and without MN Activities involving limbs: fast walking speed measured with the 10MWT (m/s) • Outcome type: continuous • Assessment time point: baseline and 30 weeks • Device at assessments: baseline and 30-week assessments performed with MN and without MN Activities involving limbs: TUG (s) • Outcome type: continuous • Assessment time point: baseline and 30 weeks • Device at assessments: baseline and 30-week assessments performed with MN and without MN Exercise capacity: 6MWT (m) • Outcome type: continuous • Assessment time point: baseline and 30 weeks • Device at assessments: baseline and 30-week assessments performed with MN and without MN

Kluding 2013 *(Continued)*

	Balance: BBS • Outcome type: continuous • Assessment time point: baseline and 30 weeks • Device at assessments: baseline and 30-week assessments performed with MN and without MN Balance: functional reach (cm) • Outcome type: continuous • Assessment time point: baseline and 30 weeks • Device at assessments: baseline and 30-week assessments performed with MN and without MN Participation scale of HRQoL: SIS - Social participation • Outcome type: continuous • Assessment time point: baseline and 30 weeks Adverse events: dropouts during the intervention period • Outcome type: binary Adverse events: serious adverse events related to intervention • Outcome type: binary Adverse events: falls • Outcome type: binary
Identification	Author's name: Patricia M Kluding Institution: Department of Physical Therapy and Rehabilitation Sciences, University of Kansas Medical Center Email: pkluding@kumc.edu Address: University of Kansas Medical Center, 3901 Rainbow Blvd, Mail Stop 3051, Kansas City, KS 66160, USA
Funding source	Bioness Inc
Notes	Associated reference: Dunning 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Once study eligibility was confirmed, random group assignment was performed by the sponsor using a web-based application prepared by the study statistician."
Allocation concealment (selection bias)	Unclear risk	Although the study protocol mentioned that the process is concealed by the site, the method of concealment is not described in sufficient detail to permit a definitive judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "To maintain blinding, a nonblinded research team member coordinates outcome testing and all subjects wear loose pants, a lower leg and shoe

Kluding 2013 *(Continued)*

All outcomes		cover ('gaiter') on the involved lower extremity (to conceal the AFO or FDS cuff and pressure sensor), and an FDS control unit"
Incomplete outcome data (attrition bias) Secondary outcome	Low risk	ITT analysis was performed.
Incomplete outcome data (attrition bias) Primary outcome	Low risk	ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	High risk	This trial was funded by Bioness Inc.

Kottink 2007

Methods	Study design: RCT Instruments used: 6MWT, Vicon system, activPAL Professional, surface electromyographic (sEMG) activity, SF-36, DIP, EQ-5D Study design as described in the article: "Randomized controlled trial" Study duration: not stated Year of study: not stated
Participants	Inclusion criteria: drop foot identified by an inability to achieve a normal heel strike during walking; first hemiplegia of at least 6 months in duration as a result of a cerebrovascular accident with a stable neurology; individual is an outdoor walker; able to give an informed consent Exclusion criteria: under age 18 years; passive dorsiflexion of the ankle 5 degrees with knee in extension; medical conditions other than cerebrovascular accident, i.e. neurologic, rheumatic, cardiovascular, or systemic disorders (including diabetes mellitus) limiting the function of walking; injury to deep and superficial peroneal nerve and sciatic nerve; any medical condition that would exclude the use of a surgical procedure or anesthetic; not able to don and doff the equipment; pregnancy Age: MN group mean age (± SD): 55.2 years (± 11.36); control group mean age (± SD): 52.87 years (± 9.87) Country: the Netherlands Sample size: 29 Sex: MN group: 10 men and 4 women; control group: 10 men and 5 women Time poststroke: ≥ 6 months poststroke. MN group mean time poststroke (± SD): 9.07 years (± 9.29); control group mean time poststroke (± SD): 5.67 years (± 4.64) Type of stroke: not stated
Interventions	Motor neuroprosthesis • Intervention: MN group used STIMuSTEP device. The intervention began with the surgical procedure for the implantation of STIMuSTEP device. After 2 weeks of the surgery the wound was checked and first test stimulation took place. At week 3 the stimulation during walking was tested, and the stimulator was taken home by the participant. In weeks 4 and 5 the use of the stimulator was gradually increased. In weeks 6 to 26 the participants were allowed to use the system all day.

Kottink 2007 *(Continued)*

- Number of participants: 14
- Device: a 2-channel electrical stimulator composed of an external transmitter with a built-in antenna, a foot switch, and implantable components consisting of the stimulator, the 2 leads, and the bipolar intraneural electrode. The on-and-off switch of the stimulation was determined by a foot switch sensor. Electrodes are placed under the epineurium of the peroneal nerve.
- Duration of exposure: 26 weeks of MN
- Place of application of intervention: lower limb

Another assistive technology device

- Intervention: the control group continued using their conventional walking device all day for correction of their foot drop (i.e. AFO, orthopedic shoes, or no walking device)
- Number of participants: 15
- Device: polypropylene non-articulated AFO (with 2 crossed posterior steels and an open heel, with a large posterior steel, with a small posterior steel, or with a large posterior steel)
- Duration of exposure: 26 weeks of AFO
- Place of application of intervention: lower limb

Outcomes	Activities involving limbs: walking speed (m/s) • Outcome type: continuous • Assessment time point: baseline and 26 weeks • Device at assessments: baseline assessment performed without MN, 26-week assessment performed with MN Participation scale of HRQoL: SF-36 - Social functioning • Outcome type: continuous • Assessment time point: baseline and 26 weeks Adverse events: dropouts during the intervention period • Outcome type: binary
Identification	Author's name: Anke I Kottink Institution: Roessingh Research and Development Email: a.kottink@rrd.nl Address: Roessingh Research and Development, PO Box 310, 7500 AH, Enschede, the Netherlands
Funding source	Not reported
Notes	This study consisted of 4 articles that were part of a PhD thesis (Kottink 2007; Kottink 2008; Kottink 2010; Kottink 2012). We did not include outcomes of 6MWT and walking speed assessed with and without devices because these data were presented only as figures (Kottink 2007; Kottink 2008). We contacted the principal investigator, but the author did not respond to our request for data. References associated with this study: Kottink 2008; Kottink 2010; Kottink 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors stated that blocked randomization was used, but it is not clear if the method used for selecting the blocks describes a random component in the sequence generation process.

Kottink 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	Random procedure was carried out by an independent person.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) Secondary outcome	Low risk	ITT analysis was performed.
Incomplete outcome data (attrition bias) Primary outcome	High risk	The study had withdrawals, and no ITT was performed for the primary outcome of 10MWT (Kottink 2012).
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other bias detected.

Sheffler 2013a

Methods	Study design: RCT Instruments used: lower limb portion of the Fugl-Meyer Assessment, mEFAP, SSQoL, gait analysis with Vicon system Study design as described in the article: "Single-blinded randomized controlled trial" Study duration: not stated Year of study: not stated
Participants	Inclusion criteria: age ≥ 18 years, ≥ 12 weeks poststroke with unilateral hemiparesis and ankle dorsiflexion strength of ≤ 4/5 on the Medical Research Council (MRC) scale. Participants were required to ambulate ≥ 30 feet without an AFO, score ≥ 24 on the BBS, and demonstrate correction of foot drop using a PNS without evidence of knee hyperextension during stance. Exclusion criteria: lower extremity edema, skin breakdown, or absent sensation; serious cardiac arrhythmias, pacemakers or other implanted electronic systems; pregnancy; uncontrolled seizure disorder; concomitant lower motor neuron dysfunction and non-stroke upper motor neuron dysfunction; uncompensated hemineglect; sensory or motor peripheral neuropathy; fixed ankle plantarflex or contracture; or lower extremity botulinum toxin injection within the 3 months prior to study enrollment Age: MN group mean age (± SD): 52.8 years (± 12.2); control group mean age (± SD): 53.2 years (± 10.1) Country: USA Sample size: 110 participants Sex: MN group: 30 men and 24 women; control group: 37 men and 19 women Time poststroke: > 12 weeks poststroke. MN group mean time poststroke (± SD): 44.7 months (± 97.5); control group mean time poststroke (± SD): 44.9 months (± 79.2)

Sheffler 2013a *(Continued)*

	Type of stroke: MN group: 13 embolic, 17 thrombotic, 9 lacunar, and 15 hemorrhagic; control group: 12 embolic, 23 thrombotic, 6 lacunar, and 15 hemorrhagic
Interventions	Motor neuroprosthesis • Intervention: MN group used Odstock Dropped-Foot Stimulator (ODFS) device up to 8 hours per day once device safety was demonstrated. In the first 5 weeks the Functional Training phase (2 x 1-hour sessions per week) took place, in which participants were trained to use the MN device for home and community mobility with an assistive device, such as a straight cane, quad cane, or walker, if needed. Activities included passive and active range-of-motion exercises, lower extremity strengthening, standing balance and weight-shifting activities to the affected limb with transition to least-restrictive assistive device, and refinement of a reciprocal gait pattern. Exercises were done with multiple repetitions with an increase in difficulty and decrease in cues, with and without the MN, as appropriate. In the last 7 weeks the Post-Functional Training phase (3 x 1-hour sessions) took place, in which device function, application, and usage guidelines were reviewed with each participant to maximize MN compliance. • Number of participants: 54 • Device: a single-channel surface stimulator with surface electrodes. The stimulation was triggered by an insole pressure sensor. • Duration of exposure: 12 weeks of independent use of MN • Follow-up: 12 and 24 weeks' post-treatment • Place of application of intervention: lower limb Another assistive technology device • Intervention: control group consisted of treatment with AFO or no device up to 8 hours per day. In the first 5 weeks the Functional Training phase (2 x 1-hour sessions per week) took place, in which participants were trained to use the AFO device for home and community mobility with an assistive device, such as a straight cane, quad cane, or walker, if needed. Activities included passive and active range-of-motion exercises, lower extremity strengthening, standing balance and weight-shifting activities to the affected limb with transition to less restrictive assistive device, and refinement of a reciprocal gait pattern. Exercises were done with multiple repetitions with an increase in difficulty and decrease in cues, with and without the AFO, as appropriate. In the last 7 weeks the Post-Functional Training phase (3 x 1-hour sessions) took place, in which device function, application, and usage guidelines were reviewed with each participant to maximize AFO compliance. • Number of participants: 56 (48 participants used AFO as usual care, and 6 participants used no device) • Device: a custom-molded hinged AFO with plantarflexion block that was fabricated using conventional techniques • Duration of exposure: 12 weeks of independent use of AFO • Place of application of intervention: lower limb
Outcomes	Activities involving limbs: mEFAP (s) • Outcome type: continuous • Assessment time point: baseline, 12 weeks, 12 weeks post-treatment, and 24 weeks post-treatment • Device at assessments: baseline, 12 weeks, 12 weeks post-treatment, and 24 weeks post-treatment assessments performed without MN Activities involving limbs: walking speed (m/s) • Outcome type: continuous • Assessment time point: baseline, 12 weeks, 12 weeks post-treatment, and 24 weeks post-treatment • Device at assessments: baseline, 12 weeks, 12 weeks post-treatment, and 24 weeks post-treatment assessments performed without MN Participation scale of HRQoL: SSQoL • Outcome type: continuous • Assessment time point: baseline, 12 weeks, 12 weeks post-treatment, and 24 weeks post-treatment

Sheffler 2013a *(Continued)*

	Adverse events: dropouts during the intervention period • Outcome type: binary Adverse events: falls • Outcome type: binary
Identification	Author's name: Lynne R Sheffler Institution: Department of Physical Medicine and Rehabilitation, Case Western Reserve University, Cleveland, OH; Cleveland FES Center; Dept of PM&R, MetroHealth Rehabilitation Institute of Ohio, USA Email: lsheffler@metrohealth.org Address: MetroHealth Medical Center, 4229 Pearl Road, N5-524, Cleveland, OH 44109, USA
Funding source	MetroHealth Medical Center
Notes	This study consisted of 2 articles (Sheffler 2013a; Sheffler 2015).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators described that envelopes were used as a random component in the sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Although the investigators stated that the randomization sequence was concealed, there is no mention as to whether the envelopes were sealed or not.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinded outcomes assessor".
Incomplete outcome data (attrition bias) Secondary outcome	Low risk	ITT analysis was performed.
Incomplete outcome data (attrition bias) Primary outcome	Low risk	ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	No other bias detected.

6MWT: 6-minute walk test
10MWT: 10-meter walk test
AFO: ankle-foot orthosis
BDI: Beck Depression Inventory
BBS: Berg Balance Scale

CABG: coronary artery bypass grafting
DIP: Disability Impact Profile
FAP: Functional Ambulation Profile
FDS: foot drop stimulator
FES: functional electrical stimulation
FRT: Functional Reach Test
HRQoL: health-related quality of life
ITT: intention-to-treat
MMSE: Mini Mental State Exam
mEFAP: modified Emory Functional Ambulation Profile
MI: myocardial infarction
MN: motor neuroprosthesis
PNS: peroneal nerve stimulation
pps: pulses per second
RCT: randomized controlled trial
SAE: serious adverse event
SD: standard deviation
SF-36: 36-item Short Form Health Survey
SIS: Stroke Impact Scale
SSQoL: Stroke-Specific Quality of Life
TENS: transcutaneous electrical nerve stimulation
TUG: Timed Up and Go

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alon 2002	Not randomized
Alon 2003a	Not randomized
Alon 2007	Irrelevant intervention
Alon 2008	Irrelevant intervention
Baker 2004	Irrelevant comparison
Barrett 2010	Not randomized
Berner 2004	Not randomized
Bundy 2017	Not randomized
Burridge 1997a	Irrelevant intervention
Burridge 1997b	Irrelevant outcomes
Burridge 1997c	Not randomized
Burridge 2007a	Not randomized
Burridge 2007b	Not randomized
Burridge 2011	Not randomized
Chae 2009	Irrelevant intervention
Chan 2009	Irrelevant intervention

Study	Reason for exclusion
ChiCTR-IOR-17013339	Irrelevant comparison
Daly 2011	Irrelevant intervention
Dujović 2017	Irrelevant intervention
Embrey 2010	Not eligible cross-over trial
Ernst 2013	Not randomized
Everaert 2010	Not randomized
Everaert 2013	Not eligible cross-over trial
Fujiwara 2009	Not randomized
Gabr 2005	Not eligible cross-over trial
Ghédira 2017	Irrelevant comparison
Granat 1996	Not randomized
Hara 2008	Irrelevant intervention
Hausdorff 2008	Not randomized
Jonsdottir 2017	Irrelevant intervention
Karniel 2019	Not randomized (quasi-randomized controlled trial)
Kim 2016	Irrelevant comparison
Kimberley 2004	Irrelevant intervention
Knutson 2012	Irrelevant intervention
Kojovic 2009	Irrelevant intervention
Laufer 2009	Not randomized
Mann 2011	Not randomized
Martin 2016	Not randomized
Marvulli 2016	Irrelevant intervention
McCabe 2015	Irrelevant intervention
Morone 2012	Irrelevant intervention
NCT03946488	Not eligible cross-over trial
NCT04014270	Irrelevant intervention (electrical stimulation performed in clinical setting)
Ochi 2018	Irrelevant intervention (electrical stimulation performed in clinical setting)

Study	Reason for exclusion
Page 2012	Irrelevant intervention
Popovic 2004a	Not eligible cross-over trial
Popovic 2004b	Not randomized
Popovic 2005	Irrelevant intervention
Qian 2017	Irrelevant intervention
Ring 2005	Not randomized
Ring 2009	Not randomized
Sabut 2010	Not randomized
Salisbury 2013	Irrelevant intervention
Sheffler 2006	Not randomized
Sheffler 2013b	Not randomized
Shindo 2017	Irrelevant intervention
Singer 2013	Irrelevant comparison
Taylor 1999	Not randomized
Taylor 2013	Not randomized
Thorsen 2013	Irrelevant intervention
Turk 2008	Not randomized
UMIN000026624	Irrelevant outcomes
Van Swigchem 2012	Not randomized
Varkuti 2013	Not randomized
Veltink 2003	Not randomized
Von Lewinski 2009	Not randomized
Wilkinson 2015	Irrelevant intervention
Yao 2017	Not randomized

Characteristics of studies awaiting assessment *[ordered by study ID]*

ISRCTN91639560

Methods	Study design: the study author only stated at trial registry that this is a randomized controlled pilot study

ISRCTN91639560 *(Continued)*

	Instruments used: walking speed; Physiological Cost Index; visual gait analysis from video using Rivermead Visual Gait Assessment; 6MWT; Canadian Occupational Performance Measure; Hospital Anxiety and Depression Scale; Rivermead Mobility Index Study duration: not stated Year of study: registered in 2007
Participants	Inclusion criteria: participants will be over 18 years; participants will be medically fit enough to undertake physiotherapy (consultant and GP approval will be sought prior to starting the trial); current inpatient stay will be for rehabilitation following first stroke; during the inpatient period participants will have demonstrated they have sufficient motivation, memory, and cognitive ability to participate in treatment within physiotherapy and practice outside of treatment sessions; participants will be able to understand spoken instructions; participants' goals must include improving gait; suitable participants will be returning home after hospital discharge with a Rivermead Mobility Index of between 6 and 10; participants will be able to attend the hospital for twice-weekly physiotherapy, i.e. will have suitable transport and live within 25 miles of the hospital Exclusion criteria: unable to tolerate sensation of stimulation (assessed prior to acceptance into the trial); poor skin condition making stimulation unsuitable; previous neurological conditions likely to influence response to treatment; orthopedic/other health problems limiting ability to participate or use stimulation/physiotherapy; score of 25 or under on Mini Mental Test; pacemaker and other active implant users; poorly controlled epileptics; pregnancy Age: stated only that participants were adults Sample size: 30 participants Sex: men and women Time poststroke: less than 6 months of stroke Type of stroke: not stated
Interventions	Motor neuroprosthesis • Intervention: the experimental group received physiotherapy with the addition of electrical stimulation • Device: principal investigator only reported that all participants will receive 2 physiotherapy sessions a week for 6 weeks and will also be instructed in exercises to perform at home which include electrical stimulation • Duration of exposure: 6 weeks • Place of application of intervention: lower limb Another assistive technology device • Intervention: the control group received physiotherapy • Device: there is no device, only physiotherapy • Duration of exposure: 6 weeks • Place of application of intervention: lower limb
Outcomes	• Activities involving limbs: walking speed (m/s) • Activities involving limbs: Rivermead Mobility Index • Exercise capacity: 6MWT
Notes	We contacted the principal investigator to request more detailed information about the intervention to determine if the intervention was used as an orthosis in the home or community context, but as of yet have not received a response.

NCT03574623

Methods	Study design: the study author only stated at trial registry that this is a randomized parallel-assignment trial Instruments used: Stroke Upper Limb Capacity Scale (SULCS); Box & Blocks Test Study duration: not stated Year of study: registered in 2018
Participants	Inclusion criteria: 6 to 24 months since a first clinical cortical or subcortical, hemorrhagic or non-hemorrhagic stroke; unilateral upper limb hemiparesis with finger extensor strength of grade no more than 4 out of 5 on the Medical Research Council (MRC) scale; score of at least 1 and no more than 11 out of 14 on the hand section of the upper extremity Fugl-Meyer Assessment; adequate active movement of the shoulder and elbow to position the hand in the workspace for table-top task practice (necessary for the lab task practice sessions); able to follow 3-stage commands; able to recall at least 2 of a list of 3 items after 30 minutes; skin intact on the hemiparetic arm; surface stimulation of the paretic finger and thumb extensors produces functional hand opening without pain (this will exclude those who have too much flexor spasticity); able to hear and respond to cues from stimulator; not receiving occupational therapy (no concomitant occupational therapy); full voluntary opening/closing of the contralateral (less affected) hand; demonstrates ability to follow instructions for operating the stimulator or have a caregiver who will assist them Exclusion criteria: co-existing neurologic diagnosis of peripheral nerve injury, Parkinson's disease, spinal cord injury, traumatic brain injury, or multiple sclerosis; uncontrolled seizure disorder; brainstem stroke; uncompensated hemineglect; severe shoulder or hand pain; insensate forearm or hand; history of potentially fatal cardiac arrhythmias with hemodynamic instability; implanted electronic systems (e.g. pacemaker); botulinum toxin injections to any upper extremity muscle within 3 months of enrolling; pregnant women due to unknown risks of surface NMES during pregnancy; lack of functional passive range of motion of the wrist or fingers of affected side; diagnosis (apart from stroke) that substantially affects paretic arm and hand function; deficits in communication that interfere with reasonable study participation; lacking sufficient visual acuity to see the stimulator's display; concurrent enrollment in another investigational study Age: 21 to 90 years Sample size: 129 participants Sex: men and women Time poststroke: not stated Type of stroke: not stated
Interventions	Motor neuroprosthesis • Intervention: the experimental group used a contralaterally controlled FES • Device: electrical stimulator directed to paretic finger and thumb extensor muscles with the use of surface electrodes. The stimulator will be programmed to deliver stimulation with an intensity that corresponds to the opening of a glove instrumented with sensors and plugged into the stimulator. • Duration of exposure: 12 weeks • Place of application of intervention: upper limb Another assistive technology device • Intervention: the control group used Cyclic NMES • Device: electrical stimulator directed to paretic finger and thumb extensor muscles with the use of surface electrodes. The stimulator will be programmed to turn on and off in a repetitive cyclic fashion. • Duration of exposure: 12 weeks

NCT03574623 *(Continued)*

	• Place of application of intervention: upper limb
Outcomes	• Activities involving limbs: Box & Blocks Test
Notes	We contacted the principal investigator to request more detailed information about the intervention to determine if the intervention was used as an orthosis in the home or community context, but as of yet have not received a response.

UMIN000018648

Methods	Study design: the study author only stated at trial registry that this is a randomized cross-over trial Instruments used: Fugl-Meyer Assessment, Mortor Activity Log, Box & Blocks Test, Motor Assessment Scale Study duration: not stated Year of study: not stated
Participants	Inclusion criteria: time from stroke onset > 5 months; no cognitive deficit; no severe proprioceptive deficit; no severe contracture in paretic hand; independent for locomotion Exclusion criteria: severe heart failure; severe pulmonary dysfunction; severe hypertension; uncontrolled seizure; pacemaker and other implants; other serious medical condition Age: 15 to 80 years old Sample size: 40 participants Sex: men and women Time poststroke: not stated Type of stroke: not stated
Interventions	Motor neuroprosthesis • Intervention: the experimental group used HANDS therapy • Device: HANDS therapy that combines a closed-loop EMG-controlled NMES with a wrist splint • Duration of exposure: 4 weeks, 8 hours a day • Place of application of intervention: upper limb Another assistive technology device • Intervention: the control group used subthreshold electrical stimulation with HANDS system • Device: HANDS therapy that combines a closed-loop EMG-controlled NMES with a wrist splint • Duration of exposure: 4 weeks, 8 hours a day • Place of application of intervention: upper limb
Outcomes	• Activities involving limbs: Motor Activity Log • Activities involving limbs: Box & Blocks Test
Notes	The principal investigator stated that the HANDS protocol was applied at home. We wrote to the principal investigator to ask if this study is already published but as of yet have not received a response.

Wright 2004

Methods	Study design: not stated. The study author reported that participants were randomly assigned to groups. Instruments used: 10MWT, Physiological Cost Index, endurance (3-minute test), modified Ashworth Scale, Rivermead Mobility Index Study duration: not stated Year of study: not stated
Participants	Inclusion criteria: single stroke of vascular origin with hemiplegia (< 6 months); assessed by a clinical specialist physiotherapist to confirm that both a stimulator and an AFO would be suitable for the participant; affected by a drop-foot, identified by failure to achieve a heel strike, and corrected by FES; inability to achieve an effective push-off at terminal stance, identified by clinical observation Exclusion criteria: use of a dropped-foot stimulator or AFO in the 4 weeks prior to start of the intervention; required an AFO other than that selected for the trial Age: not stated Sample size: 22 participants Sex: not stated Time poststroke: not stated Type of stroke: not stated
Interventions	Motor neuroprosthesis • Intervention: experimental group used Odstock Dropped-Foot Stimulator • Device: a 2-channel surface stimulator with surface electrodes. The stimulation was triggered by an insole pressure sensor. • Duration of exposure: 24 weeks • Place of application of intervention: lower limb Another assistive technology device • Intervention: the control group used AFO • Device: Orthomerica Supra-Lite AFO • Duration of exposure: 24 weeks • Place of application of intervention: lower limb
Outcomes	• Activities involving limbs: walking speed (s) • Activities involving limbs: Rivermead Mobility Index • Exercise capacity: the total distance in 3 minutes
Notes	We were unable to contact the principal investigator (email returned undeliverable).

6MWT: 6-minute walk test
10MWT: 10-meter walk test
AFO: ankle-foot orthosis
FES: functional electrical stimulation
GP: general practitioner
HANDS: Hybrid Assistive Neuromuscular Dynamic Stimulation
EMG-controlled NMES: electromyography-controlled neuromuscular electrical stimulation

Characteristics of ongoing studies *[ordered by study ID]*

Ghedira 2014

Trial name or title	Randomized controlled trial comparing implanted peroneal nerve stimulation and ankle foot orthosis in spastic paresis
Methods	Not stated Random allocation
Participants	24 participants with chronic paresis
Interventions	Motor neuroprosthesis • Intervention: implantable motor neuroprosthesis applied to the peroneal nerve during gait and used at home • Number of participants: 12 Another assistive technology device • Intervention: ankle-foot orthosis used at home • Number of participants: 12
Outcomes	Activities involving limbs: walking speed (m/s)
Starting date	Not stated
Contact information	Mouna Ghédira, PhD Laboratoire ARM - Analyse et Restauration du Mouvement Service de Rééducation Neurolocomotrice CHU Henri Mondor email: mouna.ghedira@aphp.fr
Notes	This study was published only as an abstract. We contacted the principal investigator, who reported that the full text has not yet been published.

DATA AND ANALYSES

Comparison 1. Motor neuroprosthesis versus another assistive technology device

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Activities involving limbs: walking speed until 6 months of device use	2	605	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.10, -0.00]
2 Activities involving limbs: walking speed between 6 and 12 months of device use	3	713	Mean Difference (IV, Random, 95% CI)	0.00 [-0.05, 0.05]
3 Activities involving limbs: walking speed	4	823	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.06, 0.04]

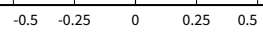
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Surface MN	3	802	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.06, 0.02]
3.2 Implantable MN	1	21	Mean Difference (IV, Random, 95% CI)	0.12 [-0.04, 0.28]
4 Activities involving limbs: TUG	2	692	Mean Difference (IV, Random, 95% CI)	0.51 [-4.41, 5.43]
5 Activities involving limbs: mEFAP	2	605	Mean Difference (IV, Random, 95% CI)	14.77 [-12.52, 42.06]
6 Participation scale of HRQoL	3	632	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.22, 0.74]
7 Exercise capacity: 6MWT	2	692	Mean Difference (IV, Random, 95% CI)	-9.03 [-26.87, 8.81]
8 Balance: BBS	2	692	Mean Difference (IV, Random, 95% CI)	-0.34 [-1.96, 1.28]
9 Adverse events: number of dropouts during the intervention period	4	829	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.11, 1.97]
10 Adverse events: serious adverse events related to intervention/during the intervention period	2	692	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.33]
11 Adverse events: falls	3	802	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.92, 1.55]

Analysis 1.1. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 1 Activities involving limbs: walking speed until 6 months of device use.

Study or subgroup	Motor neuroprosthesis N	Motor neuroprosthesis Mean(SD)	another assistive technology device N	another assistive technology device Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bethoux 2014	242	0.6 (0.3)	253	0.7 (0.3)		71.21%	-0.05[-0.11,0.01]
Sheffler 2013a	54	0.4 (0.3)	56	0.5 (0.2)		28.79%	-0.07[-0.16,0.02]
Total ***	**296**		**309**			**100%**	**-0.05[-0.1,-0]**

Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%

Test for overall effect: Z=2.14(P=0.03)



Another assistive device — Motor neuroprosthesis

Analysis 1.2. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 2 Activities involving limbs: walking speed between 6 and 12 months of device use.

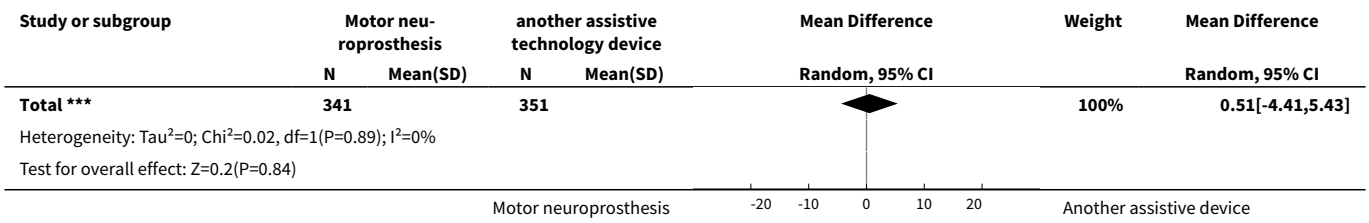
Study or subgroup	Motor neuroprosthesis N	Motor neuroprosthesis Mean(SD)	another assistive technology device N	another assistive technology device Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bethoux 2014	242	0.6 (0.3)	253	0.7 (0.3)		55.68%	-0.01[-0.07,0.04]
Kluding 2013	99	0.6 (0.3)	98	0.6 (0.3)		35.11%	-0.01[-0.09,0.07]
Kottink 2007	9	1 (0.1)	12	0.8 (0.2)		9.2%	0.12[-0.04,0.28]
Total ***	**350**		**363**			**100%**	**0[-0.05,0.05]**
Heterogeneity: Tau^2=0; Chi^2=2.4, df=2(P=0.3); I^2=16.56%							
Test for overall effect: Z=0.03(P=0.97)							

Analysis 1.3. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 3 Activities involving limbs: walking speed.

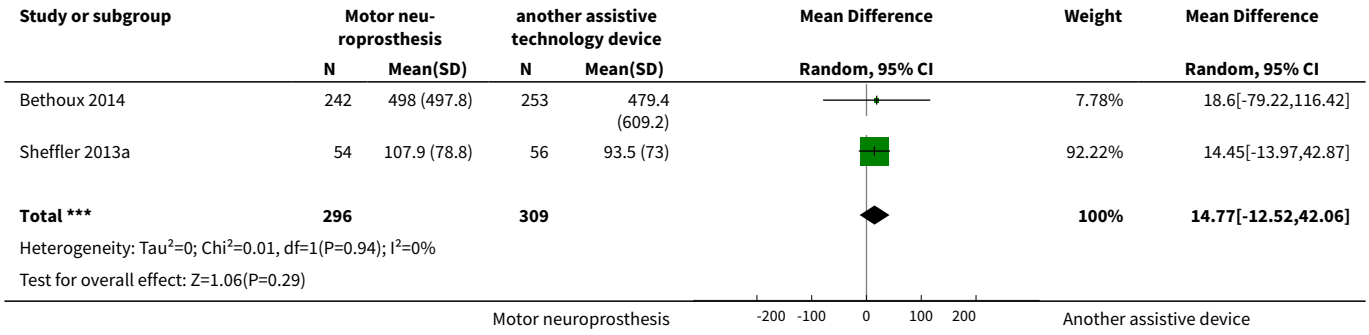
Study or subgroup	Motor neuroprosthesis N	Motor neuroprosthesis Mean(SD)	another assistive technology device N	another assistive technology device Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 Surface MN							
Bethoux 2014	242	0.6 (0.3)	253	0.7 (0.3)		41.54%	-0.01[-0.07,0.04]
Kluding 2013	99	0.6 (0.3)	98	0.6 (0.3)		28.51%	-0.01[-0.09,0.07]
Sheffler 2013a	54	0.4 (0.3)	56	0.5 (0.2)		21.54%	-0.07[-0.16,0.02]
Subtotal ***	**395**		**407**			**91.59%**	**-0.02[-0.06,0.02]**
Heterogeneity: Tau^2=0; Chi^2=1.28, df=2(P=0.53); I^2=0%							
Test for overall effect: Z=1.1(P=0.27)							
1.3.2 Implantable MN							
Kottink 2007	9	1 (0.1)	12	0.8 (0.2)		8.41%	0.12[-0.04,0.28]
Subtotal ***	**9**		**12**			**8.41%**	**0.12[-0.04,0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.47(P=0.14)							
Total ***	**404**		**419**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Tau^2=0; Chi^2=4.14, df=3(P=0.25); I^2=27.52%							
Test for overall effect: Z=0.51(P=0.61)							
Test for subgroup differences: Chi^2=2.86, df=1 (P=0.09), I^2=65.08%							

Analysis 1.4. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 4 Activities involving limbs: TUG.

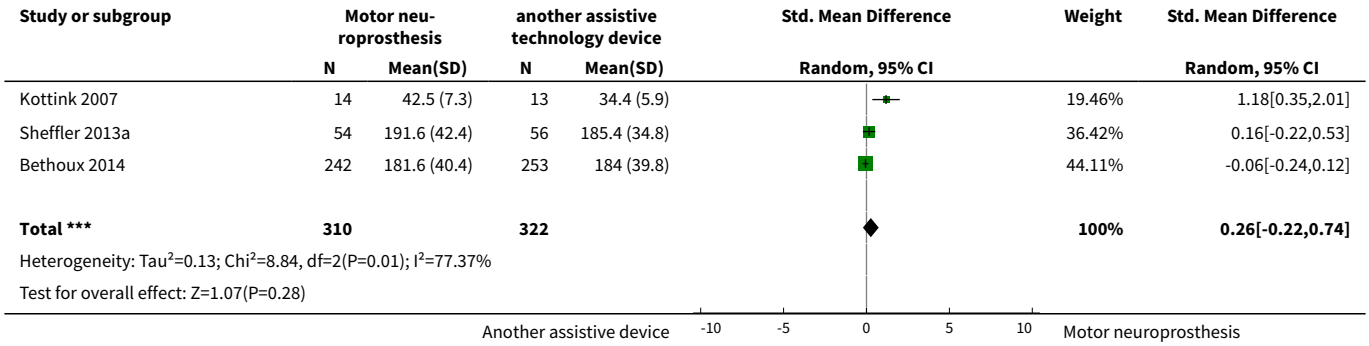
Study or subgroup	Motor neuroprosthesis N	Motor neuroprosthesis Mean(SD)	another assistive technology device N	another assistive technology device Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kluding 2013	99	29 (24)	98	28.1 (27.8)		46.14%	0.88[-6.36,8.12]
Bethoux 2014	242	27.2 (42)	253	27 (33.4)		53.86%	0.2[-6.5,6.9]



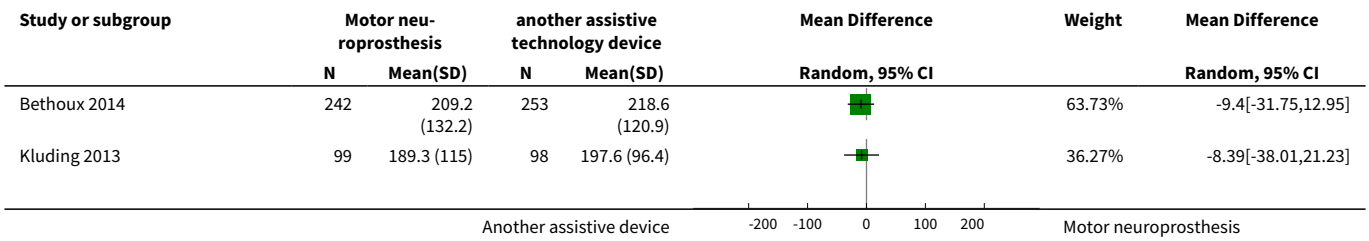
Analysis 1.5. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 5 Activities involving limbs: mEFAP.

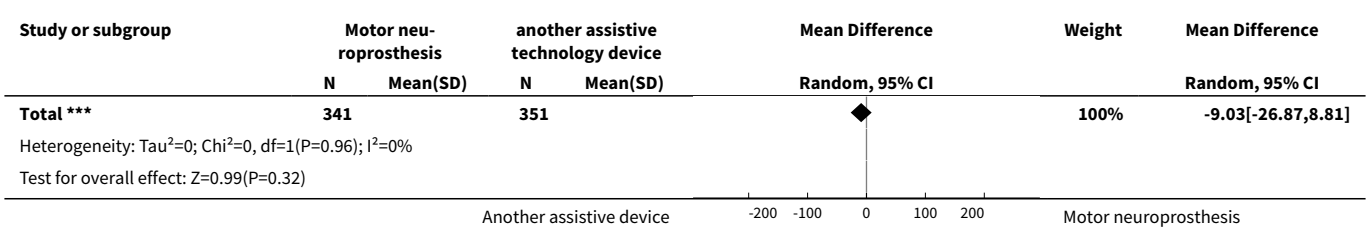


Analysis 1.6. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 6 Participation scale of HRQoL.

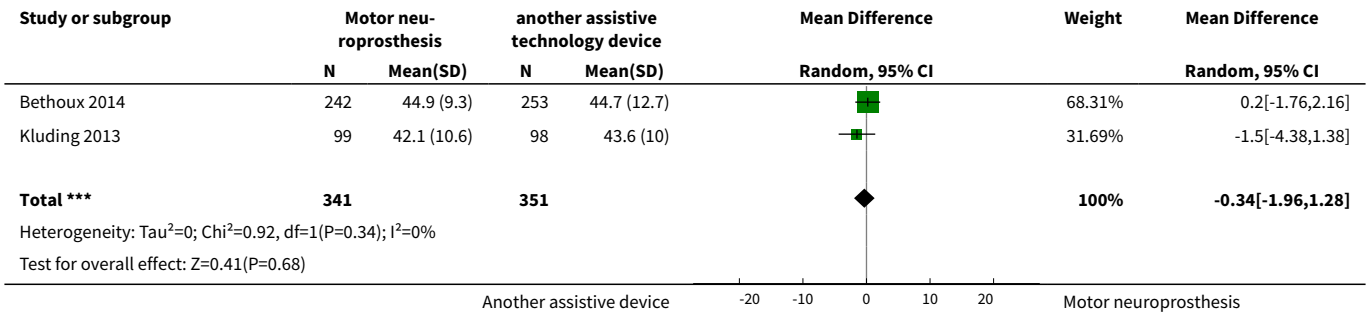


Analysis 1.7. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 7 Exercise capacity: 6MWT.

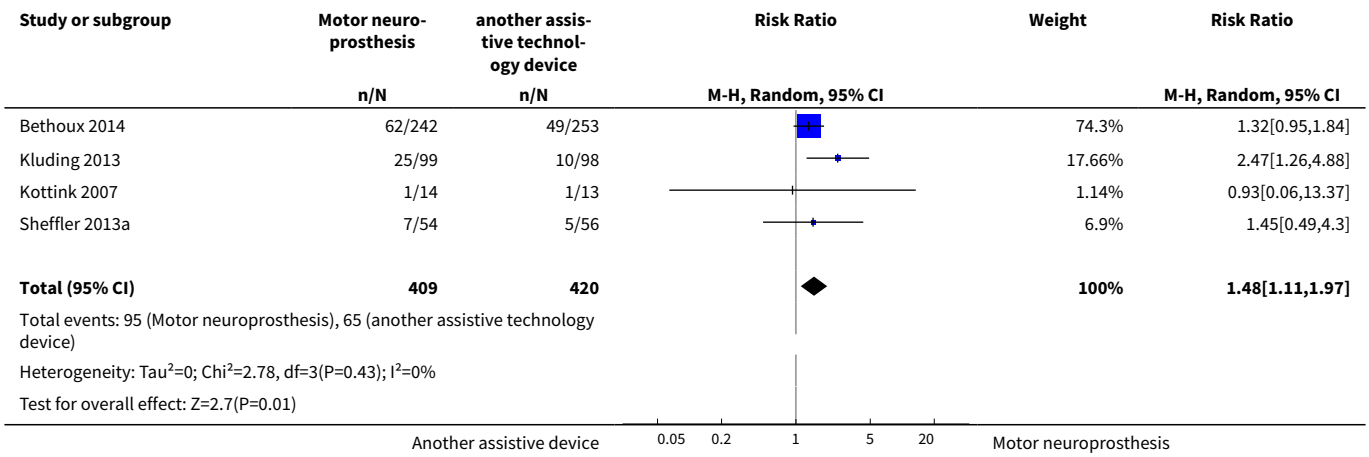




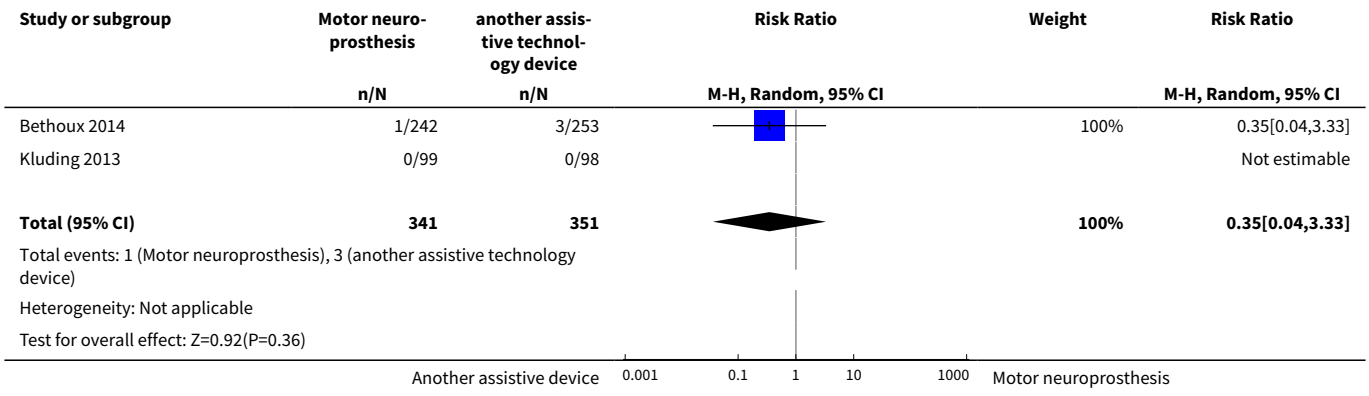
Analysis 1.8. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 8 Balance: BBS.



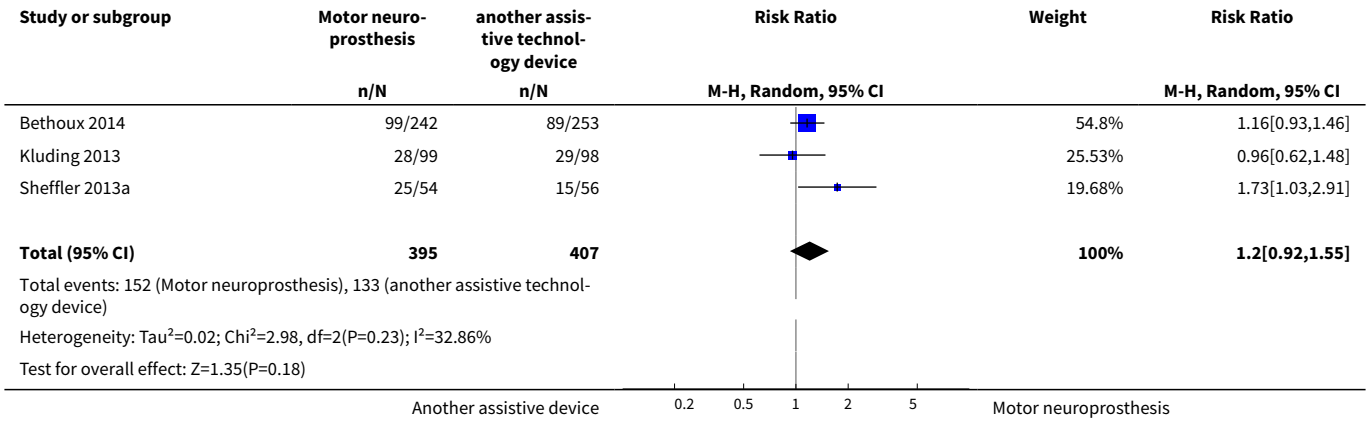
Analysis 1.9. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 9 Adverse events: number of dropouts during the intervention period.



Analysis 1.10. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 10 Adverse events: serious adverse events related to intervention/during the intervention period.



Analysis 1.11. Comparison 1 Motor neuroprosthesis versus another assistive technology device, Outcome 11 Adverse events: falls.



ADDITIONAL TABLES

Table 1. Intervention characteristics of the MN used in the included trials

Study ID (report)	MN device	Duration of exposure to MN intervention	Conditioning protocol used to adapt participants to MN use	MN use/daily use for increasing the activities and participation in the home or community context
Bethoux 2014	The MN used was the WalkAide device (Innovative Neurotronics, Austin, TX, USA). It is a commercially available, battery-operated, single-channel surface peroneal nerve stimulator that consists of a cuff worn around the	The duration of MN intervention was 12 months. The conditioning protocol occurred in the first 2 weeks, after	The first part consisted of fitting and programming the MN device as well as patient education performed by WalkAide-certified orthotist or licensed physical therapist. The conditioning protocol in-	Participants were instructed to wear MN device on a full-time basis (quote: "ie, for all walking activities

Table 1. Intervention characteristics of the MN used in the included trials *(Continued)*

	proximal part of the lower leg, which holds the control module and surface electrodes. This device uses a tilt sensor and an accelerometer to trigger ankle dorsiflexion and control the timing and duration of peroneal nerve stimulation during the swing phase of gait to alleviate foot drop.	which participants started daily use of MN device.	cluded a 2-week progressive wearing schedule of MN device.	throughout the day").
Kluding 2013	The MN used was the NESS L300 device (Bioness Inc, Valencia, CA, USA). It is a commercially available, battery-operated, single-channel surface peroneal nerve stimulator that consists of a cuff with integrated stimulation unit and electrodes, a control unit, and an in-shoe pressure sensor. The pressure sensor detects heel off and initial contact events during gait. It transmits wireless signals to the stimulation cuff, which initiates or pauses the stimulation of deep and superficial branches of the peroneal nerve via 2 surface electrodes that activate dorsiflexors and evertors muscles to ensure foot clearance during the swing phase of gait and prevent excessive ankle inversion during early stance.	The duration of MN intervention was 30 weeks. The conditioning protocol occurred in the first 6 weeks. Participants used the MN device all day between week 4 and week 30.	The first part consisted of initial fitting of the device, gait training, wearing schedule, home exercise program, and participant education based on manufacturer standardized protocols. For the first 3 weeks, participants followed the standard conditioning protocol (gradually increasing walking with the MN from 15 minutes each day to all-day use). During the same period, participants also used the MN for cyclic stimulation while not walking in order to gradually strengthen and condition the muscles to avoid fatigue when using the device (Dunning 2013).* During the first 6 weeks of the study, participants also received 8 dose-matched sessions of physical therapy. The first 2 to 4 therapy visits focused on education on device use, initial gait training, and an individualized home exercise program. The remaining physical therapy sessions focused on gait training (Kluding 2013).	Participants used the MN all day for ambulation (Dunning 2013).*
Kottink 2007	The MN used was the STIMuSTEP device (FineTech Medical Ltd, Hertfordshire, UK). It is a commercially available, battery-operated, 2-channel implantable device composed of implantable components such as a stimulator, 2 leads, and bipolar intraneural electrodes, and non-implantable components such as an external transmitter with a built-in antenna and a pressure sensor. 1 electrode is surgically positioned under the epineurium of the superficial peroneal nerve and the other under the epineurium of the deep peroneal nerve. This device promotes the ankle dorsiflexion/eversion during gait to correct foot drop, and a pressure sensor placed inside	The duration of MN intervention was 26 weeks. The intervention began with the surgical procedure for placement of the implant. After 2 weeks of the surgery, the wound was checked and first test stimulation took place. The conditioning protocol began at the third week, and all-day MN use be-	Quote: "Two weeks after the surgery the wound was checked and a first test stimulation took place. In the third week, stimulation during walking was tested and the stimulator was taken home by the patient. The use of the stimulator was gradually increased over 2 weeks to prevent severe muscle pain and fatigue. After this period patients were allowed to use the system all day."	Participants were allowed to use the system all day between week 6 and week 26.

Table 1. Intervention characteristics of the MN used in the included trials *(Continued)*

	the shoe determines the on and off switching of the stimulation.	gan at the sixth week.		
Sheffler 2013a	The MN used to correct foot drop was the Odstock Dropped-Foot Stimulator (ODFS) device (Odstock Medical Ltd, Salisbury Wiltshire, UK). The ODFS is a commercially available, battery-operated, single-channel surface peroneal nerve stimulator consisting of an electrical stimulator, a control module, pressure sensors, and surface electrodes. The stimulation is triggered by an insole pressure-sensing foot switch that detects heel rise at pre-swing.	The duration of MN intervention was 12 weeks. The conditioning protocol occurred over the 12 weeks. Daily MN use began once device safety was demonstrated by participants.	In the first 5 weeks the Functional Training phase (2 x 1-hour sessions per week) took place, in which participants were trained to use MN device for home and community mobility with an assistive device, if needed. Activities included passive and active range-of-motion exercises, lower extremity strengthening, standing balance and weight-shifting activities to the affected limb with transition to least-restrictive assistive device, and refinement of a reciprocal gait pattern. Exercises were done with multiple repetitions with an increase in difficulty and a decrease in cues, with and without the MN device, as appropriate. In the last 7 weeks the Post-Functional Training Phase (3 x 1-hour sessions) took place, in which device function, application, and usage guidelines were reviewed with each participant to maximize MN compliance.	The article did not explicitly mention when participants started all-day MN use, but reported that as soon as participants demonstrated safe use of the device, it was used up to 8 hours per day.

MN: motor neuroprosthesis
*Dunning 2013 corresponds to the published protocol of the study Kluding 2013.

Table 2. Outcome measures used from the included trials

Study ID (report)	Independence in ADL	Activities involving limbs	Participation scales of HRQoL	Exercise capacity	Balance
Bethoux 2014 (Bethoux 2014; 6-month assessment)	-	Comfortable walking speed measured by 10MWT, TUG, mEFAP	SSQoL (total value); SIS (all domains)	6MWT	BBS
Bethoux 2014 (Bethoux 2015; 12-month assessment)	-	Comfortable walking speed measured by 10MWT, mEFAP	-	6MWT	-
Kluding 2013 (Kluding 2013)	-	Comfortable and fast walking speed measured by 10MWT, TUG	SIS (ADL/iADL, Mobility, Participation domains)	6MWT	BBS; FRT
Kottink 2007 (Kottink 2007; Kottink 2008; Kottink 2010; Kottink 2012)	-	Comfortable walking speed motion analysis system	SF-36 (all domains)	-	-

Table 2. Outcome measures used from the included trials *(Continued)*

Sheffler 2013a (Sheffler 2013a; Sheffler 2015)	-	Comfortable walking speed measured by motion analysis system, mEFAP	SSQoL (total value)	-	-

6MWT: 6-minute walk test
10MWT: 10-meter walk test
ADL: activities of daily living
BBS: Berg Balance Scale
FRT: Functional Reach Test
HRQoL: health-related quality of life
iADL: instrumental activities of daily living
mEFAP: modified Emory Functional Ambulation Profile
SF-36: 36-item Short Form Health Survey
SIS: Stroke Impact Scale
SSQoL: Stroke-Specific Quality of Life
TUG: Timed Up and Go test

Table 3. Dropouts

Study ID (report)	Motor neuroprosthesis	Another assistive technology device
Bethoux 2014 (Bethoux 2014; 6-month assessment)*	2 deceased; 25 non-compliance with protocol; 15 participant request; 7 medical reasons; 4 lost to follow-up; 2 investigator withdrew	2 deceased; 13 non-compliance with protocol; 18 participant request; 4 medical reasons; 3 lost to follow-up; 1 investigator withdrew
Bethoux 2014 (Bethoux 2015; 12-month assessment)**	2 deceased; 25 non-compliance with protocol; 16 participant request; 7 medical reasons; 6 lost to follow-up; 6 investigator withdrew	3 deceased; 15 non-compliance with protocol; 19 participant request; 4 medical reasons; 6 lost to follow-up; 2 investigators withdrew
Kluding 2013 (Kluding 2013)	2 lost to follow-up; 23 discontinued intervention	1 lost to follow-up; 9 discontinued intervention
Kottink 2007 (Kottink 2007; Kottink 2008; Kottink 2010; Kottink 2012)	1 technical defect in the epineural electrode	1 psychological issues not related to the study
Sheffler 2013a (Sheffler 2013a)	6 non-medical reasons; 1 medical reason • 12-week follow-up: 2 non-medical reasons • 24-week follow-up: 4 non-medical reasons, 1 medical reason	2 non-medical reasons; 3 medical reasons • 12-week follow-up: 1 non-medical reason • 24-week follow-up: 3 non-medical reasons, 1 medical reason

*Bethoux 2014 (six-month assessment) corresponds to the first report of Bethoux 2014 study whose assessment was made after six months of motor neuroprosthesis use.
**Bethoux 2014 (12-month assessment) corresponds to the second report of Bethoux 2014 study whose assessment was made after 12 months of motor neuroprosthesis use.

Table 4. Sensitivity analysis excluding studies from the analysis that were at high risk of bias for blinding of outcome assessors

Outcome	Study ID (report)	Analysis results
Activities involving limbs: walking speed until 6 months of device use	Sheffler 2013a	MD −0.07, 95% CI −0.16 to 0.02; P = 0.13; participants = 110; I^2 = 0%

Table 4. Sensitivity analysis excluding studies from the analysis that were at high risk of bias for blinding of outcome assessors *(Continued)*

Activities involving limbs: walking speed between 6 and 12 months of device use	Kluding 2013; Kottink 2007	MD 0.04, 95% CI −0.09 to 0.16; P = 0.57; participants = 218; I^2 = 52%
Activities involving limbs: TUG	Kluding 2013	MD 0.88, 95% CI −6.36 to 8.12; P = 0.81; participants = 197; I^2 = 0%
Activities involving limbs: mEFAP	Sheffler 2013a	MD 14.45, 95% CI −13.97 to 42.87; P = 0.32; participants = 110; I^2 = 0%
Participation scale of HRQoL	Kottink 2007; Sheffler 2013a	SMD 0.60, 95% CI −0.39 to 1.59; P = 0.24; participants = 137; I^2 = 79%
Exercise capacity: 6MWT	Kluding 2013	MD −8.39, 95% CI −38.01 to 21.23; P = 0.58; participants = 197; I^2 = 0%
Balance: BBS	Kluding 2013	MD −1.50, 95% CI −4.38 to 1.38; P = 0.31; participants = 197; I^2 = 0%

6MWT: 6-minute walk test
BBS: Berg Balance Scale
CI: confidence interval
HRQoL: health-related quality of life
MD: mean difference
mEFAP: modified Emory Functional Ambulation Profile
SMD: standardized mean difference
TUG: Timed Up and Go test

APPENDICES

Appendix 1. The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1	MeSH descriptor: [Cerebrovascular Disorders] explode all trees
#2	MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] explode all trees
#3	MeSH descriptor: [Brain Ischemia] explode all trees
#4	MeSH descriptor: [Carotid Artery Diseases] explode all trees
#5	MeSH descriptor: [Cerebral Small Vessel Diseases] explode all trees
#6	MeSH descriptor: [Intracranial Arterial Diseases] explode all trees
#7	MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees
#8	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#9	MeSH descriptor: [Stroke] this term only
#10	MeSH descriptor: [Brain Infarction] explode all trees
#11	MeSH descriptor: [Stroke, Lacunar] this term only

(Continued)

#12	MeSH descriptor: [Vasospasm, Intracranial] this term only
#13	MeSH descriptor: [Vertebral Artery Dissection] this term only
#14	(stroke* or poststroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva* or SAH):ti,ab,kw (Word variations have been searched)
#15	((brain* or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) near/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw (Word variations have been searched)
#16	((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid) near/5 (h?emorrhag* or h?ematoma* or bleed*)) .tw.:ti,ab,kw (Word variations have been searched)
#17	MeSH descriptor: [Hemiplegia] this term only
#18	MeSH descriptor: [Paresis] explode all trees
#19	MeSH descriptor: [Gait Disorders, Neurologic] explode all trees
#20	(hemipleg* or hemipar* or paresis or paraparesis or paretic):ti,ab,kw (Word variations have been searched)
#21	{or #1-#20}
#22	MeSH descriptor: [Electric Stimulation] explode all trees
#23	MeSH descriptor: [Electric Stimulation Therapy] this term only
#24	MeSH descriptor: [Electrodes] this term only
#25	MeSH descriptor: [Electrodes, Implanted] this term only
#26	MeSH descriptor: [Implantable Neurostimulators] explode all trees
#27	MeSH descriptor: [Ion-Selective Electrodes] this term only
#28	MeSH descriptor: [Microelectrodes] this term only
#29	MeSH descriptor: [Signal Processing, Computer-Assisted] this term only
#30	MeSH descriptor: [Man-Machine Systems] this term only
#31	MeSH descriptor: [User-Computer Interface] this term only
#32	MeSH descriptor: [Electromyography] this term only
#33	(neuroprosthes* or neuroprosthetic*):ti,ab,kw (Word variations have been searched)
#34	((neuro* or neural* or nervous or sensor* or electrod*) near/3 (prosthes* or prosthetic* or devic* or technolog* or implant* or interface)):ti,ab,kw (Word variations have been searched)
#35	(neurostim* or electroneurostim* or electrostim*):ti,ab,kw (Word variations have been searched)

(Continued)

#36	((electric* or nerv* or neuro*) near/3 stimul*):ti,ab,kw (Word variations have been searched)
#37	((electromyography or emg) near/3 trigger*):ti,ab,kw (Word variations have been searched)
#38	(foot drop near/3 stimulat*):ti,ab,kw (Word variations have been searched)
#39	{or #22-#38}
#40	#21 and #39

Search results: 2554

Appendix 2. MEDLINE search strategy

MEDLINE (Ovid) search strategy (from 1946)

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebral small vessel diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/

2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.

3. ((brain$ or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch? emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h? ematoma$ or bleed$)).tw.

5. hemiplegia/ or exp paresis/ or exp Gait Disorders, Neurologic/

6. (hemipleg$ or hemipar$ or paresis or paraparesis or paretic).tw.

7. or/1-6

8. exp Electric Stimulation/

9. Electric Stimulation Therapy/

10. electrodes/ or electrodes, implanted/ or exp implantable neurostimulators/ or ion-selective electrodes/ or microelectrodes/

11. Signal Processing, Computer-Assisted/

12. man-machine systems/ or user-computer interface/

13. electromyography/

14. (neuroprosthes$ or neuroprosthetic$).tw.

15. ((neuro$ or neural$ or nervous or sensor$ or electrod$) adj3 (prosthes$ or prosthetic$ or devic$ or technolog$ or implant$ or interface)).tw.

16. (neurostim$ or electroneurostim$ or electrostim$).tw.

17. ((electric$ or nerv$ or neuro$) adj3 stimul$).tw.

18. ((electromyography or emg) adj3 trigger$).tw.

19. (foot drop adj3 stimulat$).tw.

20. or/8-19

21. randomized controlled trial.pt.

22. controlled clinical trial.pt.

23. randomized.ab.

24. placebo.ab.

25. randomly.ab.

26. trial.ab.

27. groups.ab.

28. or/21-27

29. 7 and 20 and 28

Search results: 2512

Appendix 3. Embase Ovid search strategy

1. cerebrovascular disease/ or brain disease/ or exp basal ganglion hemorrhage/ or exp brain hemangioma/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or exp cerebral artery disease/ or exp cerebrovascular accident/ or exp cerebrovascular malformation/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or exp vertebrobasilar insufficiency/

2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.

3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch? emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h? ematoma$ or bleed$)).tw.

5. exp hemiplegia/ or exp paresis/ or neurologic gait disorder/

6. (hemipleg$ or hemipar$ or paresis or paraparesis or paretic).tw.

7. or/1-6

8. electrotherapy/ or exp high frequency electrotherapy/ or exp low frequency electrotherapy/

9. electrostimulation/

10. electrode/ or cortical electrode/ or electromyograph electrode/ or microelectrode/ or ion selective electrode/

11. implantable neurostimulator/ or neurological implant/

12. motor neuroprosthesis/ or neuroprosthesis/ or "neurological prosthesis and implant"/

13. electromyograph electrode/ or electromyograph/ or electromyography/

14. (neuroprosthes$ or neuroprosthetic$).tw.

15. ((neuro$ or neural$ or nervous or sensor$ or electrod$) adj3 (prosthes$ or prosthetic$ or devic$ or technolog$ or implant$ or interface)).tw.

16. (neurostim$ or electroneurostim$ or electrostim$).tw.

17. ((electric$ or nerv$ or neuro$) adj3 stimul$).tw.

18. ((electromyography or emg) adj3 trigger$).tw.

19. (foot drop adj3 stimulat$).tw.

20. or/8-19

21. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/

22. Randomization/

23. Controlled clinical trial/ or "controlled clinical trial (topic)"/

24. control group/ or controlled study/

25. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/

26. Crossover Procedure/

27. Double Blind Procedure/

28. Single Blind Procedure/ or triple blind procedure/

29. placebo/ or placebo effect/

30. (random$ or RCT or RCTs).tw.

31. (controlled adj5 (trial$ or stud$)).tw.

32. (clinical$ adj5 trial$).tw.

33. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

34. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

35. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

36. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

37. (cross-over or cross over or crossover).tw.

38. (placebo$ or sham).tw.

39. trial.ti.

40. (assign$ or allocat$).tw.

41. controls.tw.

42. or/21-41

43. 7 and 20 and 42

Search results: 6460

Appendix 4. CINAHL EBSCO search strategy

S1 (MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Carotid Artery Diseases+") OR (MH "Cerebral Ischemia+") OR (MH "Cerebral Vasospasm") OR (MH "Intracranial Arterial Diseases+") OR ((MH "Intracranial Embolism and Thrombosis")) OR (MH "Intracranial Hemorrhage+") OR (MH "Stroke") OR (MH "Vertebral Artery Dissections") OR (MH "Stroke Patients") OR (MH "Stroke Units")
S2 TI (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH)
S3 TI ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) N5 (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*)) OR AB ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) N5 (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*))
S4 TI ((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid) N5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)) OR AB ((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal

or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid) N5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*))
S5 (MH "Hemiplegia") or (MH "Gait Disorders, Neurologic+")
S6 TI (hemipleg* or hemipar* or paresis or paretic) OR AB (hemipleg* or hemipar* or paresis or paretic)
S7 (MH "Brain Injuries") OR (MH "Brain Damage, Chronic") OR (MH "Brain Concussion+") OR (MH "Head Injuries") OR (MH "Brain Abscess+")
S8 TI (((brain or head or intracran* or cerebr* or cerebell* or orbit* or brainstem or vertebrobasil*) N5 (abscess* or injur* or contusion* or hypoxi* or damage* or inflamm* or concussion or trauma* or fractur* or infection* or lesion*))) OR AB (((brain or head or intracran* or cerebr* or cerebell* or orbit* or brainstem or vertebrobasil*) N5 (abscess* or injur* or contusion* or hypoxi* or damage* or inflamm* or concussion or trauma* or fractur* or infection* or lesion*)))
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (MH "Lower Extremity+")
S11 (MH "Tarsal Joint+") OR (MH "Toe Joint+") OR (MH "Ankle Joint") OR (MH "Knee Joint+")
S12 TI ((lower extremit* or leg or legs or ankle* or foot or feet or heel* or toe* or hip or knee or knees or thigh*)) OR AB ((lower extremit* or leg or legs or ankle* or foot or feet or heel* or toe* or hip or knee or knees or thigh*))
S13 TI ((walk* or gait* or ambulat* or mobil* or locomot* or balanc* or stride or foot-drop)) OR AB ((walk* or gait* or ambulat* or mobil* or locomot* or balanc* or stride or foot-drop))
S14 (MH "Locomotion+")
S15 S10 OR S11 OR S12 OR S13 OR S14
S16 (MH "Guided Imagery") OR (MH "Imagination") OR (MH "Mirror Therapy") OR (MH "Reflection")
S17 (MH "Mental Processes") OR (MH "Perception+")
S18 (MH "Imitative Behavior")
S19 (MH "Psychomotor Performance+")
S20 TI (((motor or locomot*) N3 (imag* or visual* or ideation))) OR AB (((motor or locomot*) N3 (imag* or visual* or ideation)))
S21 TI ((action N3 (immitat* or observ* or visuali* or ideation))) OR AB ((action N3 (immitat* or observ* or visuali* or ideation)))
S22 TI (((cognitive or covert* or mental) N3 (practic* or rehears* or represent* or visual* or image*))) OR AB (((cognitive or covert* or mental) N3 (practic* or rehears* or represent* or visual* or image*)))
S23 TI (((visual or mirror*) N3 (reflection or illusion or feedback or therapy)).) OR AB (((visual or mirror*) N3 (reflection or illusion or feedback or therapy)).)
S24 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S25 MH Random Assignment or MH Single-blind Studies or MH Double-blind Studies or MH Triple-blind Studies or MH Crossover design or MH Factorial Design
S26 TI ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or AB ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or SU ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study")
S27 TI random* or AB random*
S28 AB "latin square" or TI "latin square"
S29 TI (crossover or cross-over) or AB (crossover or cross-over) or SU (crossover or cross-over)
S30 MH Placebos
S31 AB (singl* or doubl* or trebl* or tripl*) or TI (singl* or doubl* or trebl* or tripl*)
S32 TI blind* or AB mask* or AB blind* or TI mask*
S33 S31 and S32
S34 TI Placebo* or AB Placebo* or SU Placebo*
S35 MH Clinical Trials
S36 TI (Clinical AND Trial) or AB (Clinical AND Trial) or SU (Clinical AND Trial)
S37 S25 or S26 or S27 or S28 or S29 or S30 or S33 or S34 or S35 or S36
S38 S9 AND S15 AND S24 AND S37

Search results: 782

Appendix 5. AMED Ovid search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or cerebral infarction/ or cerebral ischemia/ or cerebrovascular accident/

2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.

3. ((brain$ or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch? emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h? ematoma$ or bleed$)).tw.

5. hemiplegia/

6. gait disorders/

7. (hemipleg$ or hemipar$ or paresis or paraparesis or paretic).tw.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. electric stimulation/

10. electrotherapy/ or functional electric stimulation/

11. electrodes/ or prosthesis/ or prosthesis design/

12. electromyography/

13. (neuroprosthes$ or neuroprosthetic$).tw.

14. ((neuro$ or neural$ or nervous or sensor$ or electrod$) adj3 (prosthes$ or prosthetic$ or devic$ or technolog$ or implant$ or interface)).tw.

15. (neurostim$ or electroneurostim$ or electrostim$).tw.

16. ((electric$ or nerv$ or neuro$) adj3 stimul$).tw.

17. ((electromyography or emg) adj3 trigger$).tw.

18. (foot drop adj3 stimulat$).tw.

19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. clinical trials/

21. randomized controlled trials/

22. comparative study/

23. double blind method/

24. random allocation/

25. placebos/

26. random$.tw.

27. (controlled adj5 (trial$ or stud$)).tw.

28. (clinical$ adj5 trial$).tw.

29. placebo$.tw.

30. controls.tw.

31. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32. 8 and 19 and 31

Search results: 267

Appendix 6. PEDro (Physiotherapy Evidence Database) search strategy

"Therapy": electrotherapies, heat, cold

"Problem": motor incoordination

"Subdiscipline": neurology

"Method": clinial trial

Search results: 667

Appendix 7. REHABDATA search strategy

1. '"neur* AND orthos*"'

2. '"neur* AND prosthes*"'

3. '"neuroprosthes*"'

Search results: 29

Appendix 8. IEEE search strategy

"Document Title": stroke OR cerebrovascular or cerebral OR intracerebral OR intracranial

(("Document Title":neuroprosthesis OR neurostimulation OR neurostim* OR electroneurostim* OR electrostim*) AND "Document Title":stroke OR cerebrovascular)

Search results: 585

Appendix 9. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov search strategy

(neuroprosthesis OR neuroprosthetic OR "functional electrical stimulation") AND (Brain Infarction OR Intracranial Hemorrhages OR Carotid Artery Diseases OR Brain Ischemia OR Cerebral Hemorrhage OR Cerebrovascular Disorders OR Stroke) [DISEASE]

Search results: 88

Appendix 10. World Health Organization (WHO) International Clinical Trials Registry Platform search strategy

stroke AND neuroprosthesis OR stroke AND neuroprosthetic OR stroke AND functional electrical stimulation OR stroke AND electroneurostimulation OR stroke AND electrostimulation

cerebrovascular AND neuroprosthesis OR cerebrovascular AND neuroprosthetic OR cerebrovascular AND functional electrical stimulation OR cerebrovascular AND electroneurostimulation OR cerebrovascular AND electrostimulation

Search results: 113

Appendix 11. Stroke Trials Registry search strategy

"Interventions":

Neuroprosthesis

Functional Electrical Stimulation

Functional electrical stimulation (FES)

Functional Electrical Stimulation (FES) through the Ness H200

Functional Electrical Stimulation (FES) treatment

Functional Electric Stimulation

Functional electrical stimulator

Functional Neuromotor Stimulation

Neuromuscular electrical stimulator

Neuromuscular electrical stimulation (NMES)

Surface Functional Electrical Stimulation

Surface functional electrical stimulation (FES) assisted moviment training

Surface Functional Neuromuscular Stimulation

Self-designed surface functional electrical stimulator

Electrical stimulation

Electrical stimulation with exercises

Electrical Stimulation; Rehabilitation Robot

Electrical stimulator

Electrically Assisted Movement Therapy

Intramuscular Electrical Stimulator

electrodes

Walking with ankle electrical stimulation

Contralaterally Controlled Neuromuscular Electrical Stimulation

Electrical Stimulation with Intramuscular Electrodes

Functional Neuromuscular stimulation with intramuscular electrodes

Smart glove system with functional electrical stimulation

Electrical stimulation-dynamic hand orthosis

Myoelectric-Elbow-Wrist-Hand orthosis

Electrical stimulation-dynamic hand orthosis

DC-stimulation (Neuroconn, Germany)

Neuromodulation electroencephalographic signals and functional electrical stimulation

Cortical Electrical Stimulation

Implantation of NeuroPort Arrays in motor cortex

BCI-controlled neurorehabilitation device

Robot-assisted neurocognitive therapy of hand function

Search results: 54

Appendix 12. ISRCTN registry search strategy

"Condition": Stroke

Search results: 377

Appendix 13. Australian New Zealand Clinical Trials Registry search strategy

"Registry": ANZCTR

"Intervention code": Treatment: Devices OR Treatment: Other OR Rehabilitation OR Other interventions

"Study type": Interventional

"Allocation to intervention": Randomised

"Health Condition(s) or problem(s) studied": Stroke

"Condition category": Neurological

"Age group": Adult (18yrs and over)

Search results: 31

Appendix 14. Health Technology Assessment (HTA) database - Centre for Reviews and Dissemination, University of York search strategy

1. MeSH DESCRIPTOR Cerebrovascular Disorders EXPLODE ALL TREES IN HTA

Search results: 55

Appendix 15. OAIster search strategy

neuroprosthes*
neuro prosthes*

Search results: 98

Appendix 16. The Directory of Open Access Repositories – OpenDOAR search strategy

Searched using CORE

title:((neuroprosthes*)) abstract:((neuroprosthes*))

Search results: 37

Appendix 17. British Library Ethos search strategy

Stroke and “electrical stimulation”

Search results: 30

Appendix 18. ProQuest Dissertations & Theses Global search strategy

(AB,TI(stroke* or poststroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva* or SAH) OR AB,TI((brain* or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or "anterior circulation" or "posterior circulation" or basilar artery or vertebral artery or space-occupying) AND (ischaemi* or ischemi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)) OR AB,TI((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or "posterior fossa" or hemispher* or subarachnoid) AND (haemorrhag* or hemorrhag* or haematoma* or hematoma or bleed*))) AND (AB,TI(neuroprosthes* or neuroprosthetic*) OR AB,TI((neuro* or neural* or nervous or sensor* or electrod*) AND (orthos* or orthotic* or prosthes* or prosthetic* or devic* or technolog* or implant* or implant* or interface)) OR AB,TI(neurostim* or electroneurostim* or electrostim*) OR AB,TI((electric* or nerv* or neuro*) AND stimul*) OR AB,TI(foot drop AND stimulat*))

Search results: 1292

Appendix 19. Email sent to equipment manufacturers

My name is Luciana Mendes. I am currently undertaking a Cochrane Review that focuses on motor neuroprosthesis directed to upper or lower limb for improving activities and participation in people after stroke ('Motor neuroprosthesis for recovery of function after stroke' available at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012991/full).
This way, I contact this company to know if you developed or sponsored randomised controlled trial (published or unpublished) that uses motor neuroprosthesis devices as an orthosis in home or community context. If so, let me know that I will assess the study and examine the possibility of inclusion of it in the review.

If you have any questions let me know. I am available for any clarification regarding the review.

Appendix 20. The Canadian Agency for Drugs and Technologies in Health – CADTH search strategy

Health Technology Assessment (HTA) Agencies:

1. Alberta Health and Wellness

Keyword: Stroke

2. Canadian Agency for Drugs and Technologies in Health (CADTH)

Keyword: Stroke

3. Drug Safety and Effectiveness Network (DSEN)

Filter items: electrical

4. Health Quality Council of Alberta (HQCA)

Keyword: "electrical"

5. Health Quality Ontario (HQO)

Search: "electrical stimulation"

6. Institut national d'excellence en santé et en services sociaux (INESSS)

Keyword: accident vasculaire cerebral

7. Institute of Health Economics (IHE)

Keyword: stroke

8. McGill University Health Centre (MUHC). Technology Assessment Unit Reports

Search: "electrical stimulation"

9. NLCAHR : Newfoundland and Labrador Centre for Applied Health Research. Contextualized Health Research Synthesis Program (CHRSP) Completed CHRSP projects

Ongoing projects at "Current CHRSP Projects" link

10. Ottawa Hospital Research Institute (OHRI) Knowledge Synthesis Group

11. Programs for assessment of Technology in Health (Canada) Reports (PATH)

12. Therapeutics Initiative. Therapeutics Letter

13. INAHTA Secretariat. International Network of Agencies for Health Technology Assessment (INAHTA)

Keywords: electrical stimulation

14. World Health Organization Regional Office for Europe. Health Evidence Network (WHO HEN)

Keyword: electrical stimulation

15. Australian Government. Department of Health and Ageing. Australia and New Zeland Horizon Scanning Network (ANZHSN)

Keyword: electrical stimulation

16. Australian Government Department of Health and Ageing. Medical Services Advisory Committee (MSAC). MSAC Applications

Search: "electrical stimulation"

17. Joanna Briggs Institute (JBI) JBI EBP Database

Search: "electrical stimulation" (Title, Abstract or Keywords) AND stroke (Title, Abstract or Keywords)

18. Queensland Government (Australia). Health Technology Reference Group. Health Technologies Evaluated-Reports and Briefs (COAG Health Council)

Search: "electrical stimulation"

19. Kenniscentrum voor de Gezondheidszorg / Le Centre d'expertise des soins de santé. Belgian Health Care Knowledge Centre (KCE)

Topic: Neurology and brain disease

20. Haute Autorité de santé/ French National Authority for Health (HAS). Haute Autorité de santé

Topic: Prostheses and implants

21. Health Information and Quality Authority. Health Technology Assessments

Keywords: electrical

22. Health Service Executive. Irish Health Repository (Lenus)

Search: "electrical stimulation"

23. Zorginstituut Nederland. National Health Care Institute Netherlands

Keywords: stimulation

24. Nasjonalt kunnskapssenter for helsetjenesten. Norwegian Knowledge Centre for the Health Services.Publications

Keywords: stimulation

25. Swedish Council on Health Technology Assessment (SBU).

Search: stimulation

26. Healthcare Improvement Scotland. Published Resources

Search: electrical

27. National Institute for Health and Care Excellence (NICE). NHS National Institute for Health and Care Excellence

Search: electrical

28. National Institute for Health Research. (NIHR).Innovation Observatory

Search: neuroprosthesis

29. NHS Purchasing and Supply Agency. Centre for Evidence-based Purchasing (CEP)

Search: electrical [All Report Types]

30. NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC). Research Project

Keywords: "electrical stimulation"

31. National Health Service UK (NHS). NHS England

Keywords: "electrical stimulation"

32. Washington State Health Care Authority (HCA). Health Technology Review

Search: neuroprosthesis

Databases (FREE)

1. LILACS

Search: stroke AND stimulation

2. McMaster University, McMaster Health Forum. Health Systems Evidence

Search: stroke AND stimulation

3. TRIP Database (TRIP). Trip Database - Clinical Search Engine

Search: neuroprosthesis

CONTRIBUTIONS OF AUTHORS

Luciana Mendes: conceived the review question; developed, completed, and edited the first draft of the protocol; drafted the final protocol; and made an intellectual contribution to the protocol. She searched some electronic databases with the help of the Information Specialist, screened titles and abstracts of publications identified by the search, selected and assessed trials, extracted trial and outcome data, contacted trialists about unpublished data, assessed the methodological quality of selected trials, carried out statistical analysis and interpretation of the data, drafted the review, and approved the final manuscript of the review.

Íllia Lima: developed and completed part of the first draft of the protocol and made an intellectual contribution to the protocol. Together with Luciana Mendes she screened titles and abstracts of publications identified by the search and selected and assessed trials; she also checked the outcome data extracted by Luciana Mendes.

Túlio Souza: contributed with clinical expertise, advised on and developed the protocol, and made an intellectual contribution to the protocol. He advised in case of disagreement on the selection of studies, data extraction, and assessment of risk of bias; contributed to the interpretation of the data; and approved the final manuscript of the review.

George Nascimento: contributed with clinical expertise on devices, advised on and developed the protocol, made an intellectual contribution to the protocol, and approved the final version prior to submission. He contributed to the interpretation of the data and approved the final manuscript of the review.

Vanessa Resqueti: advised on and developed the protocol, participated as an arbiter, and made an intellectual contribution to the protocol. She advised in case of disagreement on the selection of studies, data extraction, and assessment of risk of bias; contributed to the interpretation of the data; and approved the final manuscript of the review.

Guilherme Fregonezi: developed and co-ordinated the protocol, secured funding, advised on and made an intellectual contribution to the protocol, and approved the final version prior to submission. He interpreted the data and the analysis, and corrected and approved the final manuscript of the review.

DECLARATIONS OF INTEREST

Luciana Mendes: none known

Íllia Lima: none known

Túlio Souza: none known

George Nascimento: none known

Vanessa Resqueti: none known

Guilherme Fregonezi: none known

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Internal sources

- Federal University of Rio Grande do Norte, Brazil.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used Covidence software for the selection of studies, data extraction, and assessment of risk of bias (Covidence). We included another review author (TS) to help the third review author (VR) in the evaluation of discrepancies and providing advice in case of disagreement on the selection of studies, data extraction, and assessment of risk of bias.

We conducted an extensive search, and are therefore confident that we have identified all relevant studies in the field. However, we did not use Science Citation Index Cited Reference Search for forward tracking of important articles. Due to technical problems with OpenDOAR repository, we used CORE for this repository content search.

We only identified individually randomized trials for this review, so we did not need to analyze for unit of analysis issues as planned in our protocol (Mendes 2018).

Our protocol prespecified a number of subgroup analyses including type of effect and duration of use of device. However, as we analyzed the outcome data only as endpoint values (and not changes from baseline), we decided not to perform a subgroup analysis for type of effect. Regarding the subgroup analysis duration of use of device, we decided to define some primary outcomes based on different periods (such as walking speed up to six months of device use, walking speed between six and 12 months of device use) instead of carrying out the proposed subgroup analysis. This change was based on the fact that we could gain a better understanding of the effect of MN on different periods of use without unit of analysis error (Higgins 2011c), considering that studies could have repeated observations on participants for the same study. We did not perform subgroup analysis for the effect of MN when applied to lower limb or upper limb or for the effect of MN when used by participants in different phases of stroke because there were no data available for MN applied to upper limb, and there were no data for participants less than three months since stroke onset.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Electric Stimulation Therapy [*methods]; Motor Activity [physiology]; Quality of Life; Randomized Controlled Trials as Topic; Recovery of Function; Stroke [therapy]; Stroke Rehabilitation [*methods]

MeSH check words

Humans