Prenton, Sarah, Hollands, Kristen L. and Kenney, Laurence P.

Functional electrical stimulation versus ankle foot orthoses for foot-drop: a meta-analysis of orthotic effects

Original Citation


This version is available at http://eprints.hud.ac.uk/29032/

The University Repository is a digital collection of the research output of the University, available on Open Access. Copyright and Moral Rights for the items on this site are retained by the individual author and/or other copyright owners. Users may access full items free of charge; copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational or not-for-profit purposes without prior permission or charge, provided:

- The authors, title and full bibliographic details is credited in any copy;
- A hyperlink and/or URL is included for the original metadata page; and
- The content is not changed in any way.

For more information, including our policy and submission procedure, please contact the Repository Team at: E.mailbox@hud.ac.uk.

http://eprints.hud.ac.uk/
TITLE PAGE

Running Head: FES versus AFO for foot-drop

Title: Functional electrical stimulation versus ankle foot orthoses for foot-drop: a meta-analysis of orthotic effects

Authors:

1. Mrs Sarah Prenton. BSc (Hons) Physiotherapy, PGCert Higher Education Research and Practice. [1] s.prenton@hud.ac.uk
2. Dr. Kristen L. Hollands. PhD. [2] k.hollands@salford.ac.uk

Institutions:

1. University of Huddersfield, School of Human and Health Sciences, Department of Health Sciences, Health and Rehabilitation division, England.
2. University of Salford, School of Health Sciences, England.

Acknowledgement: Some of this material was presented as a poster on 8th & 9th May 2015 at iFESSUKI at the University of Sheffield

Acknowledgements to be presented at the end of the manuscript: We would like to thank the corresponding authors from Bethoux et al (Francois Bethoux/ Helen Rogers), Kluding et
al (Kari Dunning) and Salisbury et al (Lisa Salisbury) for generously providing their unpublished results. We would also like to thank John Stephenson, from the University of Huddersfield, for his support with the meta-analyses.

Conflicts of interest: The authors have no perceived or actual conflicts to disclose.

Corresponding author: Mrs Sarah Prenton, Room RG/23, Ramsden Building University of Huddersfield, Queensgate, Huddersfield, West Yorkshire, HD1 3DH. S.Prenton@hud.ac.uk
+44 (0)1487473861

Reprints are not available.
ABSTRACT

Objective: To compare the effects on walking of Functional Electrical Stimulation (FES) and Ankle Foot Orthoses (AFO) for foot-drop of central neurological origin, assessed in terms of unassisted walking behaviours compared with assisted walking following a period of use (combined-orthotic effects).

Data Sources: MEDLINE, AMED, CINAHL, Cochrane Central Register of Controlled Trials, Scopus, REHABDATA, PEDro, NIHR Centre for Reviews and Dissemination and clinicaltrials.gov. plus reference list, journal, author and citation searches.

Study Selection: English language comparative Randomised Controlled Trials (RCTs).

Data Synthesis: Seven RCTs were eligible for inclusion. Two of these reported different results from the same trial and another two reported results from different follow up periods so were combined; resulting in five synthesised trials with 815 stroke participants. Meta-analyses of data from the final assessment in each study and three overlapping time-points showed comparable improvements in walking speed over ten metres (p=0.04-0.95), functional exercise capacity (p=0.10-0.31), timed up-and-go (p=0.812 and p=0.539) and perceived mobility (p=0.80) for both interventions.

Conclusion: Data suggest that, in contrast to assumptions that predict FES superiority, AFOs have equally positive combined-orthotic effects as FES on key walking measures for foot-drop caused by stroke. However, further long-term, high-quality RCTs are required. These should focus on measuring the mechanisms-of-action; whether there is translation of improvements in impairment to function, plus detailed reporting of the devices used across diagnoses. Only then can robust clinical recommendations be made.

Key words: electrical stimulation therapy, nervous system diseases, stroke, walking, foot drop, systematic review, meta-analysis.
INTRODUCTION

Conditions such as stroke, brain injury (BI), multiple sclerosis (MS), spinal cord injury (SCI) and cerebral palsy (CP) affect upper motor neuronal pathways (1) and are collectively referred to as pathologies of central neurological origin (CNO) (2). In the United Kingdom (UK) there are approximately 1.2 million people living with stroke (3), 100,000 MS and 40,000 SCI (4), there are 160,000 BI admissions per year (5), and 1 in 400 people have CP (6). Foot-drop is a common impairment seen across these conditions (7) and although prevalence data in some of the CNO conditions is very limited, a commonly cited figure suggests that it is seen in 20-30% of people with stroke (7, 8).

Foot-drop is categorized as an inability to dorsiflex the foot, with or without excessive inversion and is most commonly caused by weakness in the dorsiflexor (and evertor) and/or overactivity in the plantarflexor (and invertor) muscle groups. Foot-drop results in walking being slower, less efficient and potentially unsafe (7); as foot clearance during swing and initial foot contact at the start of the stance phase are compromised. These factors have been associated with an increased risk of falls (7), reduced quality of life (7, 9) and increased levels of mortality (10).

Current practice in the treatment of foot-drop normally involves a form of ankle foot orthosis (AFO)(11). Functional electrical stimulation (FES) is also used but less frequently (9).
AFOs stabilise the foot and ankle and lift the toes when stepping (12). Meta-analyses have shown them to have positive effects on some aspects of walking (12, 13) but these analyses are primarily based on non-randomised control trial (RCT) evidence. AFOs have been criticised for detrimental effects on the adaptability of walking, propulsion, aesthetics and comfort (14-16) which can impact compliance and satisfaction.

Foot-drop FES uses electrical pulse trains to stimulate the common peroneal nerve over key phases of the gait cycle to correct the foot-drop impairment (17). This phasic stimulation can be delivered via surface or implanted electrodes. Foot-drop FES has been shown to have positive effects on walking speed (18, 19) but meta-analyses have also, in part, been based on non-RCT evidence. For surface systems, limitations have been cited in relation to issues with effort of setup, skin irritation and pain (20), which again affects compliance and satisfaction. Implanted systems address some of these limitations but are more costly (21).

Despite their limitations both are endorsed in the management of foot-drop with clinical guidelines existing for AFO as a result of stroke (22, 23) MS (24), CP (25) and BI (26) and FES guidelines promoting use across all CNO diagnoses (2). However, these guidelines have had to rely on some non-RCT sources of evidence and as intervention specific guidelines, comparing to no treatment or physiotherapy, do not consider evidence from direct comparisons between these interventions. As a result current guidelines do not provide clinicians with a clear patient pathway. Recently a number of RCTs providing direct comparisons have been published. Furthermore, these studies have advanced our understanding of the effects these interventions may produce:

a) Immediate-orthotic effects where same-day comparisons are made between AFO/FES unassisted and assisted walking behaviours (16, 27).
b) Therapeutic effects (19, 28) where unassisted walking behaviours are compared with unassisted walking on a day some period later (16, 27).

c) Training effects (16) where assisted walking behaviours are compared with assisted walking on a day some period later.

d) Combined-orthotic effects (15) where unassisted walking behaviours on one day are compared with assisted walking on a day some period later (16, 27).

The suggested mechanism-of-action for AFO is that the device remedies the loss of dorsiflexion/eversion by holding the foot in a neutral position but this can result in negative effects on neuromuscular control and muscle biomechanics with long-term use (29-31). Therefore, it has been assumed that they only provide immediate-orthotic effects (a) (12), a notion supported by the only known long-term AFO specific RCT in the field (32).

In contrast, there are many reports of long-term neuromuscular control improvements with FES (19, 33) which are attributed to changes in neural plasticity, muscular strength and cardiovascular efficiency (31, 34, 35). The mechanism for these improvements has been hypothesised as being due to the coinciding of antidromic electrical stimulation-generated action potentials with volitional activity leading to strengthening of modifiable Hebb-synapses at a segmental level (34, 36, 37).

Given these proposed mechanisms-of-action it could be assumed that FES will provide a distinct advantage over AFO with long-term use.

Two recent reviews (9, 38) have explored the long-term effects evidence for AFOs versus FES in stroke survivors; both concluding that there was a preference for FES but insufficient evidence to recommend one over the other. However, the first was not systematic (39) and included non-RCT studies (9) and the other did not meta-analyse; possibly due to the breadth
of question posed (38). This review (38) reported that FES was superior at conserving energy but included a paper where FES was combined with botulinum toxin (40) and another that compared FES to therapy as opposed to AFO (41).

In order to provide improved clinical guidelines which will help clinicians determine which of these interventions to prescribe and what the directly comparable effects are over a period of use gold standard meta-analysis of RCT level evidence is required (42). Given that both interventions are most commonly prescribed as long-term orthotics (9, 30) and the assumption that studying long-term use will highlight any differences in walking behaviours resulting from the different mechanisms-of-action we sought to perform a systematic examination of the evidence base to address the question:

Are the combined-orthotic effects on walking for foot-drop of CNO greater for FES than AFO?

**METHODS**

This review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (43). The full review protocol can be found at: http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=9892&UserID=6114

Nine electronic databases were searched. These were MEDLINE (Ovid), AMED (Ovid), CINAHL (EBSCO), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, REHABDATA, PEDro, NIHR Centre for Reviews and Dissemination and clinicaltrials.gov.
A search strategy including controlled vocabularies related to “electric stimulation”, “walking” and “nervous system diseases” and terms such as “foot drop” and “electric* stimulat*” were used with no date limits (full search strategy available on request from the corresponding author). Reference list, citation, key author and journal searches were also completed and all searches were limited to the English language.

Once duplicates were removed one reviewer (SP) screened titles and abstracts categorising each as ‘possibly’ or ‘clearly not’ relevant against the inclusion criteria (Table I). Full length articles were retrieved for ‘possibly relevant’ studies and two unmasked reviewers (SP and KH) independently assessed their eligibility (Table I) classing them as ‘relevant’, ‘definitely irrelevant’ or ‘unsure’. Different outcome measurements from the same trial reported in separate publications were treated as a single publication; as were separate publications that reported different data collection time-points within the same trial. Any disagreements or ‘unsure’ publications were discussed (between SP and KH). A third reviewer was available to resolve any disagreements (LK).

Table I. Inclusion Criteria.

SP extracted data using a predesigned proforma; trial details extracted related to the characteristics of the included studies, participant and intervention details. Missing data and/or aspects that required clarification were requested from trial authors (14, 16, 44, 45), by SP (Appendix I). KH reviewed the extracted data for accuracy.

As an RCT-based review, and to avoid the limitations of scaled quality assessment tools (42, 46), the Cochrane risk of bias assessment tool (42) was used independently by two reviewers (SP and KH) with a third reviewer (LK) available if necessary. To ensure impartiality, risk of
bias was based on published work only. Performance bias was not considered as the interventions precluded blinding of participants and measures were primarily objective (46). Outcomes across the World Health Organisation’s (WHO) International Classification of Functioning, Disability and Health (ICF) (47) were extracted. This helped to identify if there was any comparative evidence to support the assumed mechanisms-of-action and whether they translated into function. Therefore, all measurements were categorised as either being within the body functions and structures (BFS), activity or participation domain (47) by SP, using supporting literature (47-50). All post-intervention data collection point assisted-walking means and standard deviations (SD) were extracted with final-assessment data pooled for data analysis. Given the hypothesised mechanisms-of-action suggesting that FES would have greater benefits than AFO with longer-term use; broadly overlapping time-point data was also grouped for meta-analysis where possible. Standard errors were converted to SDs (14, 42, 51) and functional exercise capacity (an activity domain measurement (52)) was considered as metres walked so was converted as necessary (15).

Meta-analyses were performed using RevMan 5.3® software. Where the same measurement was used across more than two trials, outcomes were combined using mean difference (MD) with 95% confidence intervals (CIs). Where an outcome was measured using different approaches, such as functional exercise capacity (distance walked in metres measured over two, three or six minutes), standardised mean difference (SMD) with 95% CIs was used. For crossover trials only pre-crossover data was extracted (15). Where there was more than one arm looking at the same intervention the similarity at baseline to the other intervention and size were used to decide which to use and the data from the most comparable group extracted (15).
Heterogeneity was examined using visual inspection of forest plot, chi² test and I² statistic. If the chi² test showed heterogeneity which the I² statistic identified as being moderate to low, (<50% (42)) a fixed-effects model was used. A random-effects model was used for heterogeneity of >50%.

RESULTS

1836 citations were found of which seven were eligible for inclusion. Two of these reported outcomes from the same participants (44, 53) so were grouped, and subsequently referred to by the first publication date (44). One trial published results up to six months (14) and had another publication reporting results at 12 months (51); so were also grouped. For meta-analysis the relevant publication was used with the source identified by the date of the publication on the corresponding forest plot. Thus a total of five RCTs, published between 2007 and 2015 with 815 participants, were available for meta-analysis (Fig. 1).

Fig. 1. Flowchart of trial selection.

Table II. Characteristics of included trials, participant and intervention details.

Characteristics of included trials
One trial used a multiple-site crossover design (15) with two AFO arms. Data from arm 2 (AFO-FES) was used as it was larger and similar to the FES group at baseline. The remaining four trials used two arm parallel RCT design, two single-site (44, 45) and two multiple-site (14, 16) (Table II).

**Participant details**

All the participants were over the age of 18 years and had suffered a stroke. Average time since diagnosis ranged from 51.7 days (45) up to 6.9 years (14, 51). Of those trials that reported hemiplegic side (16, 44, 45) there was a relatively even distribution (116:47.9% right, 126: 52.1% left). Two of the trials recruited current AFO users (16, 44) whereas the remaining four introduced the interventions to both groups for the first time (Table II).

**Intervention details**

Three of the trials (14-16, 51) reported providing “customized” AFOs prescribed by an orthotist; plus a physiotherapist for Kluding et al (16). One used off-the-shelf AFOs (45) which is appropriate practice with their, sub-acute, population (54) and one used a combination (44). No trial reported any further details of the AFOs or how prescription decisions were made; none were hinged. All-but-one study used surface FES systems (44), one trial highlighted that “clinicians” setup FES for measurement (45) but no trial reported details of setup parameters such as electrode placement, ramping, amplitude or frequency. The setting where interventions were used varied with participants from three of the studies
using the devices within their own environment (14, 15, 44, 51). One trial used them in both the participants own environment and under supervision (16) and one used them only under supervision (45). All-day-use was encouraged in all-but-one of the trials (45), some with a gradual introduction, although whether this was adhered to was not reported. Three trials provided concurrent therapy for both groups (16, 44, 45) (Table II).

Methodological Quality

Table III. Risk of Bias

Table III summarises the quality assessment, Kluding et al (16) alone had no identified areas of high risk of bias.

Table IV. Outcome measurements and intervention effects

Outcome Measurements

All trials utilised ICF activity domain measurements; most commonly the 10-metre walk test (Table IV). However, one did not collect any BFS domain measurements (14, 51) and another lacked participation domain measurements (15). The intervention period studied ranged from six weeks (15) – 12 months (51).
To allow direct comparison of the assumed mechanisms-of-action and functional translation the following results are presented according to ICF domains. The narrative comparison found in Table IV is summarised below. Final-assessment meta-analyses are presented first. There were three overlapping data time-points found at 4-6 weeks, 12-13 weeks and 26-30 weeks for activity domain measurements. These are categorised as short, medium and longer-term respectively (Table IV); meta-analyses at these time-points are then presented.

**BFS**

Physiological cost index (PCI) (15), cadence (45), spatiotemporal/kinematics (44) and lower limb Fugl-Meyer (16) were reported by single trials; therefore pooled-analysis was not possible. All the trials found within-group improvements but no significant statistical differences were reported for any of these measures by the primary authors except Kottink et al (44) who found some spatiotemporal and kinematic differences in favour of FES (p<0.05) (Table IV).

**Activity**

Final-assessment outcomes of 10-metre walking speed (all five trials, n=789) and functional exercise capacity (three trials, n=761) were pooled. Meta-analysis showed between-group comparable improvement (MD= 0.01, [-0.04, 0.05]; I²=0%; p=0.79, Fig. 2a); and SMD -0.07 [0.22, 0.07], I²=0%; p=0.31, Fig. 3a) respectively.
The timed up-and-go test was used in two trials (16, 51), both reported between-group comparable improvement (p=0.812 and p=0.539), therefore meta-analysis was not required (Table IV).

All other final-assessment activity measures were used in single trials with between-group comparable improvement in all cases (Table IV).

Meta-analysis was possible for the 10-metre walk test using data at short (four trials, n=771), medium (three trials, n=699) and longer-term (three trials, n=713) time-points (Fig. 2b-d). It revealed comparable improvement in the short-term (MD= 0.02 [-0.05, 0.10]; I²=66%; p=0.54, Fig. 2b) and longer-term (MD= -0.00 [-0.04, 0.04]; I²=14%; p=0.95, Fig. 2d)). In the medium-term there was a marginal, but significant, difference in favour of AFO (MD= -0.04 [-0.09,-0.00]; I²=0%; p=0.04, Fig. 2c)).

Functional exercise capacity meta-analyses were performed for short (three trials, n=761) and medium-term (two trials, n=692) time-points (Fig. 3b and c). Meta-analyses revealed between-group comparable improvement (SMD= -0.12 [-0.26-0.02]; I²=0%; p=0.10, Figure 3b) and SMD= -0.10 [-0.25, 0.05]; I²=0%; p=0.19, Fig. 3c)).

**Participation**
The mobility domain of the Stroke Impact Scale (SIS) was collected by three trials (n=701) (14, 16, 45). Meta-analysis showed between-group comparable improvement (MD 0.31 [-2.06, 2.68]; \(I^2=41\%\); \(p=0.80\), Fig. 4).

Fig. 4. Participation domain measurement: Stroke Impact Scale (mobility sub-scale).

Activity monitoring was used by two trials (16, 44) (Table IV) but their data collection methods varied too significantly (steps taken compared to time spent in different positions) to pool results. Kluding et al (16) found no significant differences in the number of steps taken and Kottink et al (44) found the FES group spent significantly more time in sitting/lying than the AFO group (\(p=0.04\)).

All other final-assessment participation measurements were used by a single trial (14) with between-group comparable improvements found (Table IV).

DISCUSSION

This is the first systematic review, including meta-analysis, of studies comparing AFO to FES as interventions for people with CNO foot-drop which focusses on the clinically relevant combined-orthotic effects on walking. As a RCT-based review with meta-analysis guided by the PRISMA statement (55) the results provide the highest level of evidence currently available to support clinical decision making (42).
The RCTs were deemed to be of medium-methodological quality, which provides some confidence in our results that both interventions demonstrate equal combined-orthotic improvements in 10-metre walking speed, functional exercise capacity, timed-up-and-go and the mobility sub-scale of the SIS; regardless of the length of time used.

Given the different hypothesized mechanisms-of-action detailed in the introduction it is somewhat surprising that there was no differentiation between the two interventions for any of the pooled measurements. To explore this result we examined outcome measurements within the BFS domain (which directly reflect mechanisms-of-action (48)) and whether or not these changes in BFS coincide with changes in activity and participation differentially between the interventions and over different time-points of use.

**BFS**

The majority of measurements used in the reviewed trials suggest that there are no differences between the two interventions. However, given the suggestions of a negative influence of AFO and a positive influence of FES on volitional muscle activation it was surprising that none of the included trials reported electromyography (EMG) or strength data. Throughout our systematic search of the literature we found only one RCT (which explored therapeutic as opposed to combined-orthotic effects) which compared EMG activity between FES and AFO treatments. This trial reported that EMG activity was greater following a period of FES than AFO use (56).

Kottink et al (53) was the only reviewed trial to measure gait features and found differences between a FES group and an AFO group. Despite these findings, that are supported by results of non-RCT studies (57-61), no further inferences can be drawn at this time. Future trials
should capture such measurements to determine whether restorative as opposed to compensatory changes are made (62) in order to more accurately understand the mechanisms-of-action.

Activity & Participation

Meta-analysis of three validated measures of the activity domain (49, 52) and one mobility specific participation domain measurement (49, 52) indicate that AFOs and FES produce equivalent functional improvements to walking for people with foot-drop as a result of stroke; regardless of length of use. The equivalency of effects between these interventions is supported by non-RCT studies which have found no significant changes in activity domain measurements when FES is provided to AFO users (59, 60, 63).

Given the difference in hypothesized mechanisms-of-action between FES and AFO and the lack of BFS measurements, the question remains as to how these comparable effects on activity/participation are achieved. One explanation is that both simply correct the mechanical problem of foot-drop; as is suggested for AFO. However, this does not fully explain the differences between immediate-orthotic effect and orthotic effect after a period of use. The activity monitoring results from one trial highlight another potential explanation. Kluding et al (16) found that the number of steps taken per day increased with use of either intervention (1891-2069, AFO and 2092-2369, FES at six and 30 weeks). This increase in repetition of walking in both FES and AFO intervention groups (facilitated by the correction of foot-drop) could explain the observed comparable improvements. Indeed intensity of task-specific repetition is widely accepted as critical for effective improvements of motor-impairments (64-66). This hypothesis is consistent with Kluding et al’s suggestion that both
interventions achieve combined-orthotic effects through immediate-orthotic and training effects (16).

A final hypothesis is that RCTs to date have not been long enough to detect differences given the predominantly chronic populations investigated (67). Bethoux et al (51) did not find differences at 12 months which may suggest even longer-term follow up is required (68). To facilitate comparisons all future trials should ensure that data collection time-points are justified against physiological processes underlying treatment effects.

This review had some limitations. Firstly, it has revealed that until 2007 research has been limited to examinations of a single intervention for a single diagnosis precluding comparisons between interventions which might usefully inform clinicians which intervention may be most suitable. Since 2007 comparative RCTs have been undertaken, making this review timely. Whilst future FES (9, 69) and AFO specific studies (13, 70, 71) are necessary for intervention development, where possible, research should be impairment focused in order to facilitate more discerning prescription.

Secondly, despite the literature search encompassing all CNO diagnoses, the reviewed trials only included participants who had experienced a stroke and who were over the age of 18 so our results can only be applied to this population. Trials using different CNO populations are necessary given that current clinical guidelines encompass them. Similarly, in order to form clinical guidelines indicating which subgroups of patients with any given CNO diagnosis (e.g. time points post-stroke, severity of foot-drop impairment) might benefit most from either intervention future studies with carefully defined inclusion/exclusion criteria are needed. This approach is of critical importance in subsequent trials so that potentially important clinical effects are not diluted in heterogeneous study groups. Until such a time as sufficient high-quality RCTs in specific groups of patients become available any meta-analyses will also suffer similar limitations.
Thirdly, risk of bias was present in the reviewed studies with detection bias (assessor blinding) the most common area. While this might impact our results this area of bias is common within rehabilitation research. Indeed, previous FES (28) and AFO (12) reviews have chosen to discount it, suggesting it is impractical to address in studies of medical devices. It can also be argued that objective measures minimize the risk of this source of bias. However, two trials (15, 16) attempted to control for this, suggesting that it is feasible to blind assessors and should at least be considered in future trials (72). We based the quality assessment on published material alone; so as not to advantage trial authors who respond to requests for additional data. Therefore a lack of reported methodological detail might account for some of the other unclear and high areas of bias found.

Finally, the reader should note that a range of different AFO and FES devices were used in the included trials and our analysis combined these. While combining data from different types of AFO/FES does not allow a detailed look at the possible different effects of each individual sub-type, assuming the prescription of devices within each trial was provided on the basis of clinical judgement and complies with current guidelines, this allows for a clinically relevant comparison. Furthermore, limited reports of the details of AFO and FES interventions preclude reliable sub-group analyses. The traditional description of AFOs on the basis of the material used (carbon fibre, plastic, metal) or mode of manufacture (customized versus off-the-shelf (54) as with our included trials) should be discontinued. The mechanical properties (stiffness, mass) of an AFO determine its behaviour (73) so it is these that should be measured and reported (73-75). Similarly, differences in outcome between therapist and patient FES setup have been found (76, 77) so this should also be reported. None of the included trials reported details of FES setup parameters and it remains unclear which set of parameters would be most useful when comparing across trials; further work is required in this area.
In conclusion, despite very different hypothesised mechanisms-of-action for AFO and FES this RCT, state-of-the-art review, with meta-analysis (39) conservatively indicates that AFOs have positive combined-orthotic effects on walking that are equivalent to FES for foot-drop caused by stroke. Methodological and reporting limitations within the current RCT pool preclude clinical recommendations regarding which type of AFO or FES set-up to use for particular patient groups from being made; as they do in guiding clinicians which intervention to prescribe for a specific patient. However crucially, and for the first time, barriers to achieving such clinical recommendations within research design and reporting have been identified to progress future research. Furthermore long-term, high-quality RCTs are required across CNO diagnoses. These should focus on measuring the mechanisms-of-action, whether there is translation of improved impairment to function and reporting the correct device details; only then will discerning prescription be possible.

REFERENCES


69. Miller L, Rafferty D, Paul L, Mattison P. A comparison of the orthotic effect of the Odstock Dropped Foot Stimulator and the Walkaide functional electrical stimulation systems
on energy cost and speed of walking in Multiple Sclerosis. Disabil Rehabil Assist Tech 2014; 10: 482-485.


Table I. Inclusion Criteria.

<table>
<thead>
<tr>
<th>Design</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Randomised Controlled Trials (RCT)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Participants with foot-drop of a central neurological origin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Common peroneal nerve FES to address the specific impairment of foot-drop, with or without other areas of stimulation</td>
</tr>
<tr>
<td></td>
<td>Stimulation eliciting a muscular contraction</td>
</tr>
<tr>
<td></td>
<td>Trials where common peroneal stimulation is used during walking (overground or treadmill) as part of the intervention</td>
</tr>
<tr>
<td></td>
<td>Trials studying combined-orthotic effects of foot-drop FES</td>
</tr>
<tr>
<td></td>
<td>Trials where foot-drop FES and another intervention are used in combination but foot-drop FES is measured independently</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparator</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Trials comparing foot-drop FES with AFO (the term therapy was allowed as might involve AFO)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Measures of walking</td>
</tr>
</tbody>
</table>
Table II. Characteristics of included trials, participant and intervention details.

<table>
<thead>
<tr>
<th>Trial design</th>
<th>N Diagnosis (R):(L)</th>
<th>Men: Women</th>
<th>Age (years)</th>
<th>Time since diagnosis</th>
<th>Current or new AFO users</th>
<th>AFO Mechanical properties reported</th>
<th>FES Setup for measurement done by</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux (2014 &amp; 2015)+</td>
<td>2 arm parallel Multiple sites</td>
<td>495 (242 FES: 253 AFO) CVA Not specified</td>
<td>FES=147:95 (11.33) AFO=157:96 (12.01)</td>
<td>FES=63.87 (6.43) AFO=64.3 (6.64)</td>
<td>New Customized</td>
<td>No</td>
<td>Surface Walkaide</td>
<td>Home 2wk progressive wearing schedule then AD</td>
</tr>
<tr>
<td>Everaert (2013)*</td>
<td>3 arm crossover Multiple sites</td>
<td>78 (43 FES: 35 AFO) CVA Not specified</td>
<td>FES=32:6** AFO=19:12**</td>
<td>FES=57.1 (12.9)** AFO=55.6 (11.9)**</td>
<td>New Customized</td>
<td>No</td>
<td>Surface Walkaide</td>
<td>Home AD</td>
</tr>
<tr>
<td>Kluding (2013)+</td>
<td>2 arm parallel Multiple sites</td>
<td>197 (99 FES: 98 AFO) CVA 93:104</td>
<td>FES=51:48 AFO=67:31 (12.24) AFO=61.58 (10.98)</td>
<td>FES=60.71 (5.29) AFO=4.34yrs (4.1)</td>
<td>Current Customized*** PLUS TENS for 2wks</td>
<td>No</td>
<td>Surface NESS L300</td>
<td>Not specified Both</td>
</tr>
<tr>
<td>Kottink (2007)*~</td>
<td>2 arm parallel Single site</td>
<td>29 (14 FES: 15 AFO) CVA 13:16</td>
<td>FES=10:04 AFO=10:05 (11.36) AFO=10:05 (9.87)</td>
<td>FES=55.2 (9.29) AFO=52.87 (4.67)</td>
<td>Current Combination***</td>
<td>No</td>
<td>Implanted 2-channel implant</td>
<td>Not specified Home Gradual increase over 2wks, then AD</td>
</tr>
<tr>
<td>Salisbury (2013)†</td>
<td>2 arm parallel Single site</td>
<td>16 (9 FES: 7 AFO) CVA 10:6</td>
<td>FES=03:06 AFO=03:04 (11.3) AFO=52.6 (17.2)</td>
<td>FES=58.8 (34.6) AFO=51.7 days (34.6)</td>
<td>New Off the shelf ***</td>
<td>No</td>
<td>Surface ODFS</td>
<td>Clinician for FES Supervised Part of physiotherapy 20mins, 5 x wk with supervised/ independent walking as appropriate.</td>
</tr>
</tbody>
</table>

Abbreviations: FES= functional electrical stimulation; AFO=ankle-foot orthosis; *=post intervention/dropout characteristics; +=ITT completed; —=based on 2007 not 2012 data; †= Pre intervention/drop out characteristics; CVA=Cerebrovascular accident/Stroke; ** post intervention/drop characteristics at later time point than is included in this review (12 weeks); yrs=years; mos=months; Customized= custom made/modified AFO; Combination= Different AFOs used by different participants; off the shelf= prefabricated/unmodified AFO; ***= both groups continued with physical therapy alongside intervention; TENS= transcutaneous electrical nerve stimulation with no motor response; wk=week; NESS L300=Bioness model; ODFS= Odstock foot-drop system; AD=all day.
Table III. Risk of Bias.

<table>
<thead>
<tr>
<th></th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux 2014/2015</td>
<td>U</td>
<td>H</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Everaert 2013</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>H</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Kluding 2013</td>
<td>L</td>
<td>L</td>
<td>U</td>
<td>L</td>
<td>U</td>
<td>L</td>
</tr>
<tr>
<td>Kottink 2007</td>
<td>H</td>
<td>U</td>
<td>H</td>
<td>U</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Salisbury 2013</td>
<td>H</td>
<td>L</td>
<td>H</td>
<td>U</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

Abbreviations: L= Low; U=Unclear; H=High.
### Table IV. Outcome measurements and intervention effects.

<table>
<thead>
<tr>
<th>Walking outcome measures used &amp; ICF level</th>
<th>Outcome collection points</th>
<th>Combined-orthotic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 10MWT†</td>
<td>0</td>
<td>FES↑=AFO↑</td>
</tr>
<tr>
<td>• 6min walk test (distance)</td>
<td>Short: 1mos (not published)</td>
<td></td>
</tr>
<tr>
<td>• Gaitrite Functional Ambulation Profile+</td>
<td>Medium: 3mos (not published)</td>
<td></td>
</tr>
<tr>
<td>• mEFAP (including TUG)</td>
<td>Long: 6mos</td>
<td></td>
</tr>
<tr>
<td>Participation+::</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SIS (Mobility, ADL/IADL &amp; social participation domains combined)†</td>
<td>12 mos+</td>
<td></td>
</tr>
<tr>
<td>• SIS mobility sub-scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Perry ambulation categories based on 10MWT results</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Everaert et al (2013)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFS:</td>
<td>0, 3wks</td>
<td>Modified RMI: between-</td>
</tr>
<tr>
<td>Activity:</td>
<td>Short: 6wks</td>
<td>group, post-intervention</td>
</tr>
<tr>
<td>• PCI over 4min test†</td>
<td></td>
<td>differences not reported</td>
</tr>
<tr>
<td>• 4min walking test (speed)†</td>
<td></td>
<td>FES↑=AFO↑; for other</td>
</tr>
<tr>
<td>• 10MWT</td>
<td></td>
<td>measures</td>
</tr>
<tr>
<td>• Modified RMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kluding et al (2013)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFS:</td>
<td>0</td>
<td>FES↑=AFO↑</td>
</tr>
<tr>
<td>Activity:</td>
<td>Short: 6 weeks</td>
<td></td>
</tr>
<tr>
<td>• LL Fugl Meyer</td>
<td>Medium: 12 weeks</td>
<td></td>
</tr>
<tr>
<td>• 10MWT (self and fast)†</td>
<td>Long: 30wks (only change</td>
<td></td>
</tr>
<tr>
<td>• TUG</td>
<td>data published)</td>
<td></td>
</tr>
<tr>
<td>• 6min walk test (distance)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SIS mobility sub-scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Activity monitoring (Stepwatch ®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kottink et al (2007)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFS:</td>
<td>0</td>
<td>FES&gt;AFO: Longer 1st</td>
</tr>
<tr>
<td>Activity:</td>
<td>Long: 26wks</td>
<td>single support phase %*;</td>
</tr>
<tr>
<td>• stride time*</td>
<td></td>
<td>shorter Stance phase; 1st</td>
</tr>
<tr>
<td>• stride length*</td>
<td></td>
<td>double support phase</td>
</tr>
<tr>
<td>• stride width*</td>
<td></td>
<td>%<em>; Speed</em>; 10MWT;</td>
</tr>
<tr>
<td>• step length*</td>
<td></td>
<td>6min walk (speed) at 26</td>
</tr>
<tr>
<td>• stance phase %*</td>
<td></td>
<td>wks</td>
</tr>
<tr>
<td>• 1st double support phase %*</td>
<td></td>
<td>AFO spent less time less</td>
</tr>
<tr>
<td>• 1st single support phase %*</td>
<td></td>
<td>in sitting/lying than FES</td>
</tr>
<tr>
<td>• kinematics=hip, knee &amp; ankle*</td>
<td></td>
<td>FES↑=AFO↑; all other</td>
</tr>
<tr>
<td>Participation:</td>
<td></td>
<td>measures</td>
</tr>
</tbody>
</table>
- Activity monitoring (ActivPAL®)

| Abbreviations: wks=weeks; mos=months; min(s)=minute(s); mEFAP=modified Emory Functional Ambulation Profile; TUG=Timed Up and Go; QoL=Quality of Life; SIS=Stroke Impact Scale; ADL/IADL=Activities of Daily Living/Instrumental Activities of Daily Living; 10MWT=10-metre walk test; PCI=Physiological Cost Index; RMI=Rivermead Mobility Index; BBS=Berg Balance Scale; *=from Kottink et al (2012); FAC=Functional Ambulation categories; |=identified as primary outcome measure by authors; += not reported in Bethoux 2015 12 month follow up publication; ↑=increase; ≥=greater than; = =equal to; < =less than. |
Fig. 1. Flowchart of trial selection.

Records identified through database searching (n = 1593)
- MEDLINE 690
- PEDro 76
- Naric 189
- CINAHL 176
- CENTRAL 161
- AMED 162
- PEDro 76
- CENTRAL 161
- AMED 162
- clinicaltrials.gov 36
- Scopus 103

Additional records identified through other sources (n = 243)

Records after duplicates/obviously irrelevant removed (n = 703)

Records screened by titles and abstract (n = 703)

Records excluded (n = 635)
Reasons include: non-RCT design, not peroneal stimulation, not FES, participants were healthy, not exploring walking, non-human, technical or surgical exploration

Full-text articles assessed for eligibility (n = 68)

Full-text articles excluded (n = 62)
Many had multiple reasons:-
- Not combined-orthotic effects: 43
- Not RCT: 17
- Not foot-drop: 13
- Not peroneal nerve: 10
- Not functional during walking: 9
- Walking not measured: 6
- Sensory stimulation: 5
- Only FES setups or healthy comparisons: 2
- Potentially relevant: 1

Studies included in narrative & quantitative synthesis (Meta-analysis) (n = 7, 2x2 combined so n=5)
Fig. 2. Activity measure: 10-metre (m) walk test metres per second (m/s).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FES Mean</th>
<th>SD</th>
<th>Total</th>
<th>AFO Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux 2015</td>
<td>0.647</td>
<td>0.312</td>
<td>242</td>
<td>0.318</td>
<td>263</td>
<td>64.2%</td>
<td>-0.01</td>
<td>[0.07, 0.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eversen 2013</td>
<td>0.625</td>
<td>0.309</td>
<td>38</td>
<td>0.291</td>
<td>31</td>
<td>9.2%</td>
<td>0.06</td>
<td>[0.06, 0.19]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kluding 2013</td>
<td>0.58</td>
<td>0.28</td>
<td>98</td>
<td>0.56</td>
<td>68</td>
<td>29.3%</td>
<td>0.00</td>
<td>[0.06, 0.08]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holmberg 2007</td>
<td>0.95</td>
<td>0.13</td>
<td>9</td>
<td>0.93</td>
<td>12</td>
<td>6.5%</td>
<td>0.12</td>
<td>[0.04, 0.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salisbury 2013</td>
<td>0.35</td>
<td>0.16</td>
<td>3</td>
<td>0.46</td>
<td>4</td>
<td>0.7%</td>
<td>-0.16</td>
<td>[-0.92, 0.62]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 391

Heterogeneity: $\chi^2 = 3.84$, df = 4 ($P = 0.60$); $I^2 = 0$
Test for overall effect: $Z = 0.26$ ($P = 0.79$)

2a) Final-assessment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FES Mean</th>
<th>SD</th>
<th>Total</th>
<th>AFO Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux 2014</td>
<td>0.601</td>
<td>0.265</td>
<td>242</td>
<td>0.619</td>
<td>263</td>
<td>35.1%</td>
<td>-0.04</td>
<td>[0.03, 0.11]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eversen 2013</td>
<td>0.625</td>
<td>0.309</td>
<td>38</td>
<td>0.261</td>
<td>31</td>
<td>18.2%</td>
<td>0.66</td>
<td>[0.03, 0.19]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kluding 2013</td>
<td>0.53</td>
<td>0.25</td>
<td>98</td>
<td>0.54</td>
<td>89</td>
<td>36.7%</td>
<td>-0.01</td>
<td>[0.08, 0.08]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salisbury 2013</td>
<td>0.31</td>
<td>0.1</td>
<td>5</td>
<td>0.12</td>
<td>14</td>
<td>16.0%</td>
<td>0.19</td>
<td>[0.04, 0.34]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 384

Heterogeneity: $\chi^2 = 0.00$, df = 3 ($P = 0.99$); $I^2 = 0$
Test for overall effect: $Z = 0.62$ ($P = 0.54$)


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FES Mean</th>
<th>SD</th>
<th>Total</th>
<th>AFO Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux 2014</td>
<td>0.617</td>
<td>0.236</td>
<td>242</td>
<td>0.667</td>
<td>253</td>
<td>65.9%</td>
<td>-0.05</td>
<td>[0.11, 0.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kluding 2013</td>
<td>0.54</td>
<td>0.27</td>
<td>98</td>
<td>0.57</td>
<td>96</td>
<td>33.4%</td>
<td>-0.03</td>
<td>[0.15, 0.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salisbury 2013</td>
<td>0.35</td>
<td>0.15</td>
<td>5</td>
<td>0.45</td>
<td>4</td>
<td>0.0%</td>
<td>-0.15</td>
<td>[0.62, 0.32]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 344

Heterogeneity: $\chi^2 = 0.36$, df = 2 ($P = 0.83$); $I^2 = 0$
Test for overall effect: $Z = 2.02$ ($P = 0.04$)


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FES Mean</th>
<th>SD</th>
<th>Total</th>
<th>AFO Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux 2015</td>
<td>0.647</td>
<td>0.312</td>
<td>242</td>
<td>0.596</td>
<td>263</td>
<td>60.2%</td>
<td>-0.01</td>
<td>[0.07, 0.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eversen 2013</td>
<td>0.625</td>
<td>0.309</td>
<td>38</td>
<td>0.586</td>
<td>31</td>
<td>9.0%</td>
<td>0.00</td>
<td>[0.06, 0.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kluding 2013</td>
<td>0.58</td>
<td>0.28</td>
<td>98</td>
<td>0.56</td>
<td>68</td>
<td>32.9%</td>
<td>0.06</td>
<td>[0.06, 0.08]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holmberg 2007</td>
<td>0.95</td>
<td>0.13</td>
<td>9</td>
<td>0.94</td>
<td>12</td>
<td>7.2%</td>
<td>0.12</td>
<td>[0.04, 0.28]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salisbury 2013</td>
<td>0.35</td>
<td>0.16</td>
<td>3</td>
<td>0.46</td>
<td>4</td>
<td>0.0%</td>
<td>-0.16</td>
<td>[-0.92, 0.62]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 358

Heterogeneity: $\chi^2 = 2.33$, df = 2 ($P = 0.31$); $I^2 = 14$
Test for overall effect: $Z = 0.07$ ($P = 0.94$)

**Fig. 3.** Activity measure: Functional exercise capacity metres (m).


```
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FES</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux 2014</td>
<td>192.4</td>
<td>98.29</td>
<td>242</td>
<td>207.0</td>
<td>132.55</td>
<td>253</td>
<td>65.1%</td>
<td>-0.15 [-0.33, 0.03]</td>
</tr>
<tr>
<td>Everest 2013</td>
<td>199.44</td>
<td>49.2</td>
<td>36</td>
<td>102.72</td>
<td>42.96</td>
<td>31</td>
<td>9.0%</td>
<td>0.14 [0.03, 0.25]</td>
</tr>
<tr>
<td>Kluding 2013</td>
<td>176.38</td>
<td>95.67</td>
<td>98</td>
<td>180.38</td>
<td>91.81</td>
<td>98</td>
<td>25.6%</td>
<td>-0.13 [-0.41, 0.15]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>379</td>
<td>382</td>
<td>100.0%</td>
<td>-0.12 [-0.26, 0.02]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```

Heterogeneity: $\chi^2 = 1.29, df = 2 (P = 0.52); I^2 = 0%$
Test for overall effect: $Z = 1.62 (P = 0.10)$


```
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FES</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethoux 2014</td>
<td>297</td>
<td>115.44</td>
<td>242</td>
<td>210.3</td>
<td>114.3</td>
<td>253</td>
<td>71.6%</td>
<td>-0.09 [-0.39, 0.05]</td>
</tr>
<tr>
<td>Kluding 2013</td>
<td>181.38</td>
<td>100.66</td>
<td>90</td>
<td>195.78</td>
<td>95.09</td>
<td>98</td>
<td>28.4%</td>
<td>-0.15 [-0.43, 0.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>341</td>
<td>351</td>
<td>100.0%</td>
<td>-0.10 [-0.25, 0.05]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```

Heterogeneity: $\chi^2 = 0.15, df = 1 (P = 0.70); I^2 = 0%$
Test for overall effect: $Z = 1.32 (P = 0.19)$

3c) Medium-term. Data obtained via correspondence with authors

---

33
**Fig. 4.** Participation measure: Stroke Impact Scale (mobility sub-scale).
APPENDIX I

Unpublished data

- Salisbury et al (45) published results were a combination of assisted and unassisted walking data. On request assisted data was provided.
- Kluding et al (16) published change as opposed to post-intervention data, this was provided on request.
- Kottink et al (44) only displayed results from their 2007 study in graphical form and did not respond to request for raw data.
- Bethoux et al (14) published standard error, these were converted to SD (42).
- Both Bethoux et al (14) and Kluding et al (16) provided unpublished time-point data on request.
- Functional exercise capacity was converted from the speed (metres per second) for Everaert et al (15).