

The clinical- and cost-effectiveness of functional electrical stimulation and ankle-foot orthoses for foot drop in Multiple Sclerosis: a multicentre randomized trial

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1 **The clinical and cost effectiveness of functional electrical stimulation and**
2 **ankle-foot orthoses for foot drop in Multiple Sclerosis: a multicentre**
3 **randomised trial**

4 **Introduction**

5 Impairment of walking ability is a significant concern for 85% of people with Multiple
6 Sclerosis.¹ Foot drop, a frequently occurring problem in Multiple Sclerosis presents
7 as a reduction in dorsiflexion during heel strike and the swing phase of walking,
8 resulting in poor foot clearance, increasing the risks of trips and falls and impacting
9 on health-related quality of life.¹

10 Two assistive devices, ankle-foot orthoses and functional electrical stimulation are
11 commonly used in the treatment of foot drop. Ankle-foot orthosis, a polypropylene
12 device worn on the lower leg and foot, limits the range of motion at the ankle and
13 aids foot clearance.² Functional electrical stimulation, delivers electrical stimulation
14 applied to the common peroneal nerve by means of surface or implanted electrodes,
15 contracting the anterior tibialis muscle during the swing phase of gait.³

16 The effects of both devices on walking can be described as orthotic (the difference
17 walking with the device compared to without), or therapeutic (the difference walking
18 without the device over time). There is growing evidence of positive initial and
19 ongoing orthotic effects of functional electrical stimulation.⁴ Despite ankle-foot
20 orthoses being considered as usual care in the United Kingdom, few studies have
21 investigated their impact on gait in Multiple Sclerosis^{5,6} and only three small studies
22 have compared the effects of both devices.⁷⁻⁹ The cost benefit of functional electrical
23 stimulation has been investigated in Multiple Sclerosis^{10,11}, however no comparison
24 between these devices has been undertaken.

25 The primary aim of our study was to compare the clinical and cost effectiveness of
26 ankle-foot orthoses and functional electrical stimulation over 12 months in people
27 with Multiple Sclerosis presenting with foot drop.

28 **Methods**

29 This study was prospectively registered with the UK Clinical Trials Gateway
30 (Identifier: 15884) [https://www.ukctg.nihr.ac.uk/clinical-trials/search-for-a-clinical-](https://www.ukctg.nihr.ac.uk/clinical-trials/search-for-a-clinical-trial/)
31 [trial/](https://www.ukctg.nihr.ac.uk/clinical-trials/search-for-a-clinical-trial/). The study was funded by the Multiple Sclerosis Society UK (grant reference:
32 001). It commenced on 1st April 2014 and was completed on 31st March 2018.
33 Ethical approval was granted by the West of Scotland Research Ethics Committee
34 (14/WS/0014) and the study was sponsored by NHS Ayrshire and Arran Research
35 and Development department. A fully powered, multicentre, non-blinded, randomised
36 trial design was employed.

37
38 Potential participants known to Multiple Sclerosis healthcare practitioners working
39 across seven out-patient centres in Scotland; Ayrshire & Arran, Greater Glasgow &
40 Clyde, Dumfries and Galloway, Lanarkshire, Lothian, Fife and Tayside, were
41 informed of the study and issued with a participant information sheet. Potential
42 participants contacted the researchers if they were interested in participating.
43 Participants required to have; a clinical diagnosis of Multiple Sclerosis, persistent
44 foot drop (lasting a minimum of 3 months) observed during a 5-minute walk test,
45 stable disease (no change in the Extended Disability Status Score¹² or relapse in
46 previous 3 months), 5° of passive dorsiflexion, and tolerance of functional electrical
47 stimulation. Participants were excluded if they had; previously used functional
48 electrical stimulation or an ankle-foot orthosis for foot drop, moderate to severe
49 cognitive impairment (scored < 26, Montreal Cognitive Assessment¹³), foot drop due

50 to other disorders, other conditions significantly affecting gait, contraindications to
51 functional electrical stimulation, marked proximal weakness, plantar flexor spasticity,
52 stance phase instability or severe lower limb/ trunk ataxia affecting gait.

53

54 Potential participants were screened for eligibility, and written informed consent was
55 gained prior to randomisation. Participants were randomly assigned (1:1) to receive
56 an ankle-foot orthosis or functional electrical stimulation device, by selecting the next
57 envelope from eighty-five randomly ordered prefilled sealed opaque envelopes.

58 Demographics were collected; age, gender, Multiple Sclerosis subtype and time
59 since diagnosis. Disability was determined by the Extended Disability Status Score
60 by an unblinded assessor trained in the Neurostatus Scoring System.¹⁴

61

62 Outcome measures were administered by two unblinded assessors (RH and AL) at
63 baseline (0), 3, 6 and 12 months, except for the Psychological Impact of Assistive
64 Devices Score¹⁵ which was administered at twelve months only. The primary
65 outcome was walking speed as measured by the 5-minute self-selected walk test.
66 Participants walked twice, once with their device and once without, resting for 20
67 minutes between. The order of testing was randomised between participants but was
68 kept consistent for each participant throughout the trial. Participants walked at their
69 preferred walking speed around a 9.5m elliptical course for 5 minutes, resulting in a
70 10-meter shuttle length. The total distance walked was recorded and the mean
71 walking speed (m/s) calculated. This protocol has been used previously by our
72 group.¹⁶⁻¹⁸

73

74 Two further secondary walking outcomes; the oxygen cost of walking and Timed 25
75 Foot Walk¹⁹ were included. The oxygen cost of walking was measured during the 5-
76 minute self-selected walk test. Participants wore the COSMED K4b2 (COSMED,
77 Rome, Italy) portable gas analysis system, a facemask (Hans Rudolph Inc., Kansas
78 City, MO, USA) and Polar heart-rate monitor (Polar, Finland). Calibration was
79 undertaken prior to each assessment and participants sat for 5 minutes prior to the
80 test to ensure resting metabolism was established. The oxygen uptake per kilogram
81 body weight ($\text{mL min}^{-1}\text{kg}^{-1}$) recorded between minutes three and four of the walk test
82 was used to determine the oxygen cost per unit distance walked ($\text{mL min}^{-1}\text{kg}^{-1}\text{m}^{-1}$),
83 The COSMED system is a valid system for measuring oxygen uptake in healthy
84 adults.²⁰ For the Timed 25 Foot Walk participants walked along a 25 foot course “as
85 quickly as possible, but safely”. The test was repeated four times, twice with and
86 twice without the device. The time taken to complete the walks was recorded using a
87 stop watch and the mean time for each pair of walks was used to calculate gait
88 speed (m/s).

89

90 Other secondary patient reported outcome measures included; the Multiple Sclerosis
91 Impact Scale-29²¹, Multiple Sclerosis Walking scale-12²², Modified Fatigue Impact
92 Scale²³, Activities-specific Balance and Confidence Scale²⁴, Euroqol five-dimension
93 five-level questionnaire (EQ-5D-5L)²⁴ and Psychological Impact of Assistive Devices
94 Scale.¹⁵ The Multiple Sclerosis Impact scale-29 has two sub scales; physical and
95 psychological, with higher scores indicating a greater physical and psychological
96 impact of Multiple Sclerosis on an individual’s life. The Psychological Impact of
97 Assistive Devices scale consists of three subscales; Competence (C), Adaptability
98 (A), and Self-Esteem (SE) which measure the impact of assistive devices on

99 functional independence, well-being, and quality of life.²⁶ The EQ-5D-5L consists of a
100 visual analogue scale of perceived health from zero to one hundred and a
101 questionnaire, the results from which were converted to a utility index, which was
102 used to calculate a health outcome measure, quality-adjusted life years.

103

104 Participants randomised to the usual care group were fitted with a custom-made,
105 solid, ankle-foot orthosis by an orthotist, within four weeks of their initial assessment.
106 The recommendations made by the Best Practice Statement for ankle-foot orthoses
107 following stroke were applied.²⁷ The orthoses were made with 5mm homopolymer
108 polypropylene, trim lines were anterior to the malleoli and reinforcements added to
109 the ankle section as required. The angle of the tibia was inclined forward,
110 approximately 10° to vertical and each orthosis was 'tuned' by the addition or
111 removal of small heel wedges.

112

113 Participants randomised to the functional electrical stimulation group were assessed
114 and fitted with an Odstock Dropped Foot Stimulator Pace (OML, Salisbury) device by
115 a physiotherapist experienced in functional electrical stimulation (AL). Wired heel
116 switches and a stimulation frequency of 40Hz were applied. Electrode position, pulse
117 width, waveform and ramping parameters were adjusted for each participant in order
118 to achieve a comfortable and efficient muscle contraction. The current amplitude
119 ranged from 7 to 72mA (mean=40mA). Participants in both groups were instructed to
120 gradually increase the wear of their devices over the first few 6 weeks.

121

122 *Data analysis*

123 Data from the 5-minute self-selected walk test collected from our initial study⁵ was
124 applied to determine the sample size. A minimum of thirty-seven participants were
125 required to detect a change of at least 75% of 1 standard deviation value (0.16 m/s)
126 to achieve a power of 90% at a 5% level of significance. Eighty-five participants were
127 recruited allowing for an approximate 15% attrition rate.

128

129 Descriptive statistics for demographic data are presented as means and standard
130 deviations unless otherwise indicated. A repeated measures ANOVA model was
131 employed to analyse the outcome variables where the main factors, Group (ankle-
132 foot orthoses/functional electrical stimulation), Time (Baseline (0), 3, 6, 12 months)
133 and for the speed and oxygen cost of walking measures, the Condition (with/without
134 device) and their interactions. The estimated means, standard errors and estimated
135 differences were calculated to inform the ongoing and total orthotic effects and the
136 therapeutic effect on the objective walking outcomes. A Restricted Maximum
137 Likelihood approach to fitting mixed models was employed to allow intention to treat
138 assumptions to cope with missing data. All analysis was performed on IBM SPSS
139 v24, using a 5% level of significance.

140

141 A cost-utility analysis was performed to compare the value for money of functional
142 electrical stimulation with ankle-foot orthoses (usual care). A National Health Service
143 and Personal Social Services perspective analyses was adopted and a discount rate
144 of 3.5% to future costs and health benefits was applied as recommended by the
145 National Institute for Clinical Excellence.²⁸ Equipment costs for both devices were
146 derived from purchase costs at the time of the study. National Health Service staff
147 costs were based on time spent delivering the interventions during the clinical trial,

148 following interviews with the clinicians involved. The staff time was then multiplied by
149 the relevant Information Services Division unit cost. The EQ-5D-5L data was
150 converted to a utility index using a published algorithm²⁹ and analysis applied the
151 area under the curve method to determine quality-adjusted life years. Missing values
152 were accounted for by carrying forward the last data point and drop outs were
153 assumed to revert to an average of the baseline values to capture expected disease
154 progression. The analysis adopted a time horizon of two years to determine cost-
155 effectiveness for a further year beyond the trial. The analysis assumes that quality-
156 adjusted life years estimates derived over the first year are maintained for the
157 additional 12 months. Uncertainty was evaluated by undertaking a sensitivity
158 analysis, by varying a number of parameters by up to 10%. Several scenarios were
159 analysed to test the sensitivity of the model to changes in structural assumptions.
160 The base case results are presented as an incremental cost-effectiveness ratio. An
161 incremental cost-effectiveness ratio below the standard threshold of £20,000
162 (€22962.00) -£30,000(€34443) per quality-adjusted life year is indicative that an
163 intervention is cost-effective.³⁰ The incremental cost-effectiveness ratio for functional
164 electrical stimulation was calculated using the following standard formula:

$$\frac{\text{Total cost of treatment FES} - \text{Total cost of treatment AFO}}{\text{Total QALYs of treatment FES} - \text{Total QALYs of treatment AFO}}$$

165 Abbreviations- FES: functional electrical stimulation; AFO: ankle-foot orthoses;
166 QALYs: quality-adjusted life years

167 **Results**

168 Eighty-five participants met the criteria for inclusion and consented to participate in
169 the study between September 2014 and January 2017 (Figure 1). Five participants
170 withdrew between the screening and assessment visit. Seventy-nine participants

171 completed the baseline assessment and were included in subsequent analysis. The
172 recruitment and flow of patients through the study is shown in Figure 1, and the
173 baseline demographic data are detailed in Table 1. Thirty-seven participants dropped
174 out over the course of the study and although there was no statistically significant
175 difference in drop-out rates between the groups, the proportion was higher in the
176 ankle-foot orthoses group.

177

178 *Insert Figure 1 near here*

179

180 *Insert Table 1 near here*

181

182 Table 2 presents the data for all outcomes, for both groups, at all assessment points
183 (0, 3, 6, 12 months) and the results for the repeated measures ANOVA model
184 employed for all outcomes.

185

186 *Impact of devices on measures of walking performance*

187 For the primary outcome measure, walking speed as measured by the 5-minute self-
188 selected walk test, a significant difference was observed between the groups
189 ($p=0.005$) with the functional electrical stimulation group consistently walking faster
190 at all assessment points. Over the 12 months a significant improvement occurred in
191 both groups ($p<0.001$), although the groups changed differently over this time
192 ($p=0.028$). The functional electrical stimulation group improved steadily for the first 6
193 months then declined, whereas changes in the ankle-foot orthoses group fluctuated
194 over 12 months. There was no significant difference between the groups with
195 regards to the effects of the devices.

196

197 For the Timed 25 Foot Walk the functional electrical stimulation group walked faster
198 overall compared to the ankle-foot orthoses group ($p=0.043$). There was no
199 significant difference between the groups, nor did the groups react differently over
200 the 12 months. There was a significant change in oxygen cost of walking at 12
201 months ($p=0.002$) for both groups, however there was no difference between the
202 groups.

203

204 *Insert Table 2 here*

205

206 *Impact of devices on Patient Reported Outcome Measures*

207 Significant improvements in the physical sub-scale of the Multiple Sclerosis Impact
208 Scale ($p=0.040$) and the Multiple Sclerosis Walking scale-12 ($p=0.002$) were
209 observed and this was most notable at 3 months in both groups respectively
210 ($p=0.045$; $p<0.001$). There were no differences between the groups for Patient
211 Reported Outcome Measures, except for all sub scales of the Psychological Impact
212 of Assistive Devices Scale, where the functional electrical stimulation group
213 demonstrated significantly higher scores for Competence ($p=0.016$), Adaptability
214 ($p=0.001$) and Self-Esteem ($p =0.006$) at 12 months.

215

216 *Orthotic and therapeutic effects on the speed and oxygen cost of walking*

217 Clinically significant effects were determined by an observed increase in walking
218 speed of $\geq 0.05\text{m/s}$, which has been previously identified by Perera et al.³¹ A
219 clinically significant ongoing orthotic effect for both walk tests was demonstrated in

220 the functional electrical stimulation, but not the ankle-foot orthoses group (Table 3).

221 A clinically significant total orthotic effect on the primary walking outcome measure

222 was noted in the ankle-foot orthoses, but not the functional electrical stimulation

223 group at 12 months.

224 There was a negative total orthotic and therapeutic effect on oxygen cost of walking

225 with both devices, except for the ankle-foot orthoses at 12 months where a positive

226 total orthotic effect was observed.

227

228 *Insert Table 3 here*

229

230 *Cost effectiveness*

231 The total quality-adjusted life years were higher for functional electrical stimulation

232 than ankle-foot orthoses (Table 4). Further deterministic sensitivity and scenario

233 analysis indicated that the base case incremental cost-effectiveness ratio in the two-

234 year model was relatively robust to changes in parameter values or structural

235 assumptions.

236

237 *Insert Table 4 here*

238

239 **Discussion**

240 Both devices demonstrated improvements in walking speed at 12 months, although

241 there were no significant differences in their effects. There were many drop outs over

242 the course of the study and the proportion was higher for ankle-foot orthoses,

243 although there was no statistically significant difference between the groups. The

244 non-significant positive ongoing orthotic effects observed with functional electrical
245 stimulation were of a similar magnitude to the results previously published in a meta-
246 analysis from our group with respect to the combined long walk (i.e. 0.04m/s), but
247 not the short walking tests (i.e. 0.08m/s).⁴ Two small studies previously investigating
248 the ongoing orthotic effect of ankle-foot orthoses on walking speed reported
249 inconclusive results.^{5,6} Only three small non randomised studies have previously
250 compared the impact of these two devices on walking outcomes in Multiple
251 Sclerosis.⁷⁻⁹ Sheffler et al.⁷ reported mixed results on gait speed (n=4), and a more
252 recent study (n=20)⁹ found no difference between the devices on the speed or
253 energy cost of walking. Street et al.⁸ reported a significant difference in walking
254 speed (n=40, p=0.03) in favour of functional electrical stimulation, however
255 participants issued with functional electrical stimulation had already rejected ankle-
256 foot orthoses, potentially biasing results. Such results suggest that devices may offer
257 similar efficacy, or that the walking performance measures selected may not be
258 sensitive enough to detect differences that exist.

259

260 No clinically significant therapeutic effects on walking speed were observed in either
261 group, although the pattern of effect was different. Results from a recent meta-
262 analysis comparing the therapeutic effect of both devices in a stroke and cerebral
263 palsy population also reported comparable positive effects.³² No previous studies
264 have evaluated therapeutic effects of ankle-foot orthoses in Multiple Sclerosis,
265 however several functional electrical stimulation studies have investigated these
266 effects over shorter time frames³³⁻³⁷ with inconclusive results. Our previous meta-
267 analysis reported a deterioration in unstimulated walking speed during long walking
268 tests following 20 weeks of functional electrical stimulation.⁴ Nevertheless, Street et

269 al.³⁵ reported a third of participants gained clinically meaningful therapeutic effects,
270 whilst a third experienced a decline in walking over the same time frame. Given the
271 neurodegenerative nature of Multiple Sclerosis it seems unlikely that either device
272 could offer a therapeutic effect over the longer time frame investigated in our study.
273 However, as observed by Street et al.³⁵ it may be possible that a sub group of people
274 with Multiple Sclerosis have the potential to experience such effects and we
275 observed small positive therapeutic effects with ankle-foot orthoses at 12 but not 6
276 months. This finding suggests that changes may take longer than 6 months to
277 develop with ankle-foot orthoses. Further kinematic and neural control studies are
278 required to corroborate these findings and to understand the possible underlying
279 therapeutic mechanisms of these devices in people with Multiple Sclerosis.

280

281 There were no significant differences between the devices with regards to their
282 impact on the oxygen cost of walking. To our knowledge only one other study has
283 compared the ongoing orthotic effects of these devices on the energy and efficiency
284 of gait and reported no difference between these devices.⁹ Nevertheless, there were
285 different patterns of effects observed between the groups, with the functional
286 electrical stimulation group demonstrating small non-significant positive orthotic
287 effects throughout, and the ankle-foot orthoses group observing a greater positive
288 total orthotic effect ($-0.05 \text{ mL min}^{-1} \text{ kg}^{-1} \text{ m}^{-1}$; 14.7%). These results are difficult to
289 interpret. However, they may have been influenced by the lower baseline oxygen
290 cost of walking in the functional electrical stimulation group.

291

292 There was no difference between the groups with regards to the patient reported
293 outcomes, except for the Psychological Impact of Assistive Devices Score where

294 participants in the functional electrical stimulation group reported significantly higher
295 scores for all three subscales. Two previous studies evaluated the impact of
296 surface³⁴ and implantable⁴⁰ functional electrical stimulation on the Psychological
297 Impact of Assistive Devices Score. Scores for the functional electrical stimulation
298 group in the current study (Competence (1.53); Acceptance (1.00); Self Efficacy
299 (1.41)) were similar to those observed by Taylor et al.⁴⁰ (Competence (1.59);
300 Acceptance (1.34); Self Efficacy (1.44)). The Psychological Impact of Assistive
301 Devices Scale has been found to be predictive of device compliance and retention
302 and is responsive to device stigma.⁴¹ Higher scores observed in the functional
303 electrical stimulation group suggests that device acceptance may be greater than
304 ankle-foot orthoses. Although both devices aim to promote functional autonomy,
305 assistive technology can be viewed as a symbol of disability, a loss of independence
306 and altered self-image.⁴² Some participants in the ankle-foot orthoses group reported
307 that wearing their device emphasised their disability and this may have contributed to
308 the higher rate of device abandonment observed in this group. Squires et al.⁴³
309 suggests that assistive technology needs to meet both the physical and
310 psychological needs of an individual to ensure positive outcomes and continued use.
311 Future studies therefore need to consider the psychological acceptance of a device
312 in addition to its impact on walking outcomes.

313

314 Against a background of financial constraints there is a need for evidence of the cost
315 benefits of interventions. Our study indicates that although the upfront costs of
316 functional electrical stimulation are greater than usual care (ankle-foot orthoses), it
317 may be considered as a potentially cost-effective treatment option for foot drop and
318 offers a value for money alternative in Multiple Sclerosis. The incremental cost

319 effectiveness ratio for year one and two for functional electrical stimulation were
320 below the National Institute for Health and Care Excellence's conventional
321 thresholds of £20,000 (€22962)-£30,000 (€34443) per quality-adjusted life year.²⁸ No
322 previous studies have examined cost effectiveness of functional electrical stimulation
323 exclusively within Multiple Sclerosis or compared the cost effectiveness of these two
324 devices. Two previous economic evaluations which examined the cost effectiveness
325 of functional electrical stimulation in a mixed neurological population reported
326 incremental cost-effectiveness ratios of £25,235 (€28972.30) over one year,
327 reducing to £12,431 (€14272) over five years¹⁰ and £15,406 (€17688) compared to
328 physiotherapy.¹¹ An economic report undertaken in 2009 found that functional
329 electrical stimulation was likely to be cost-effective, although data were almost
330 exclusively from studies recruiting stroke participants.⁴⁴ The results of our current
331 economic analysis concur with these previous investigations and suggests that
332 further improvements in cost-effectiveness of the device could be gained with greater
333 compliance, thus offsetting the upfront costs and allowing the benefit of treatment to
334 accrue over the longer term.

335

336 This study has several limitations. Despite this study being powered to detect
337 change, the relatively small number of participants recruited and the high overall
338 dropout rates, with a greater loss from the ankle-foot orthoses group, make it difficult
339 to draw definitive conclusions. In addition, the participant, assessor and treatment
340 provider were not blinded, thus ascertainment bias is likely, although such bias may
341 be less relevant with objective outcomes, such as gait speed.⁴⁵

342

343 The multi-centre design of this study enhances the generalisability of results.
344 However, although the ankle-foot orthoses prescription was standardised, variations
345 did occur across sites. Ankle-foot orthoses specification can influence biomechanical
346 aspects of gait, thus impacting on walking performance outcomes⁴⁶ and device
347 retention. The ankle-foot orthoses prescription employed was based on stroke
348 guidelines and it is not clear whether this prescription was the most appropriate for
349 people with Multiple Sclerosis, particularly those presenting with a less severe foot
350 drop where such a rigid design may have resulted in higher drop outs. Further
351 investigation is required to identify the most appropriate and acceptable prescription.
352 We excluded participants with stance phase instability and reduced passive range of
353 ankle motion, therefore, findings are only applicable to those with mainly swing
354 phase impairments.

355

356 Although the 6-minute Walk Test has been found to be an accurate walking
357 performance test to assess the benefits of assistive technology for foot drop in
358 Multiple Sclerosis⁴⁷, the validity and reliability of our primary outcome, the 5-minute
359 self-selected walk test, has not been established. This is a significant limitation of
360 this study.

361

362 The inclusion of an economic analysis is a strength. However, analysis did not
363 consider the impact on other healthcare resources, the time horizons were short, and
364 the differences detected in quality-adjusted life years for both devices were small.
365 Therefore, despite undertaking sensitivity and scenario analyses, the results should
366 be treated with caution.

367

368 Results from this randomised trial which to the best of our knowledge is the first and
369 largest study undertaken comparing the clinical and cost effectiveness of two
370 interventions for foot drop in Multiple Sclerosis over 12 months has provided
371 evidence that functional electrical stimulation is a comparable to ankle-foot orthoses
372 with regards to its impact on walking speed and patient reported outcomes. Although
373 this study suggests that functional electrical stimulation may also provide a value for
374 money alternative to usual care, a larger study which includes follow up of device
375 drop outs, and the employment of long-term modelling to explore the cost and
376 quality-adjusted life years of both interventions over the lifetime of a person with
377 Multiple Sclerosis, is required before definitive conclusions can be drawn with
378 regards to the cost effectiveness of functional electrical stimulation. Further
379 investigation as to how both interventions impact on walking, from a biomechanical,
380 muscle activation, neural control and personal perspective is also recommended.
381 The results from this study will nevertheless begin to inform clinical decisions and
382 contribute towards future policy decisions regarding the management of foot drop,
383 ultimately improving outcomes for people with Multiple Sclerosis.

384

385 **Clinical messages**

- 386 • Ankle-foot orthoses and functional electrical stimulation have comparable
387 positive orthotic effects on gait speed in Multiple Sclerosis.
- 388 • Despite higher initial upfront costs for functional electrical stimulation, it offers
389 a value for money alternative to usual care.
- 390 • More people stopped using ankle-foot orthoses than functional electrical
391 stimulation over twelve months.

392

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401

402 **Declaration of Conflicting Interests**

403 The author(s) declared no potential conflicts of interest with respect to the research,
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405

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564 **Table 1.** Demographic characteristics of participants.

| | AFO | FES | <i>p</i> |
|---------------------------------------|------------|-------------|----------------------|
| n | 38 | 41 | |
| Mean age [years] | 51.4[11.2] | 50.4 [10.4] | 0.684 ^a |
| Gender % Male | 52.6% | 20.0% | 0.006 ^c * |
| Type of MS | | | |
| Primary Progressive | 21.1% | 15.0% | 0.6647 ^c |
| Secondary Progressive | 26.3% | 20.0% | |
| Relapsing Remitting | 42.1% | 45.0% | |
| Unknown | 10.5% | 20% | |
| Mean time since diagnosis [years] | 10.2[10.3] | 7.6[8.6] | 0.205 ^b |
| Mean Extended Disability Status Scale | 5.3[1.3] | 4.9[1.4] | 0.136 ^b |

565 Abbreviations- n: number; AFO: ankle-foot orthoses; FES: functional electrical stimulation;
566 MS: Multiple Sclerosis.

567 Data values are mean [SD] for continuous variables and n (%) for categorical variables
568 unless otherwise stated. Between group differences for demographic data (a: t-test, b: Man-
569 Whitney, c: chi-square, *: significant).

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571 **Table 2:** Means and SD for the primary and secondary outcome measures in the intervention and usual care group at 0,3,6 and 12 months.

| | Baseline (0) | | 3 mo | | 6 mo | | 12 mo | | ANOVA Results | | | |
|--|--------------|------------|-------------------------|-------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------|----------|------------------------|-----------------------------|
| | AFO | FES | AFO | FES | AFO | FES | AFO | FES | Group | Time | Group/Time interaction | Group/with v without device |
| 5minSSWT (without) m/s | 0.62[0.21] | 0.73[0.27] | 0.69[0.23] ^a | 0.75[0.26] ^a | 0.65[0.25] ^{b,c} | 0.78[0.27] ^{b,c} | 0.71[0.25] ^d | 0.73[0.26] ^d | P=0.005* | P<0.001* | P=0.028* | P=0.714 |
| 5minSSWT (with) m/s | 0.61[0.22] | 0.74[0.25] | 0.72[0.22] ^a | 0.81[0.26] ^a | 0.68[0.27] ^{b,c} | 0.83[0.27] ^{b,c} | 0.73[0.24] ^d | 0.79[0.24] ^d | | | | |
| 25ftWT (without) m/s | 0.86[0.34] | 0.94[0.34] | 0.89[0.30] | 0.95[0.30] | 0.98[0.29] | 0.93[0.29] | 0.96[0.31] | 0.95[0.30] | P=0.043* | P=0.279 | P=0.310 | P=0.571 |
| 25ftWT (with) m/s | 0.83[0.30] | 0.97[0.33] | 0.90[0.27] | 1.00[0.29] | 0.88[0.29] | 0.99[0.29] | 0.98[0.29] | 1.00[0.29] | | | | |
| O ₂ cost (without) mLmin ⁻¹ kg ⁻¹ m ⁻¹ | 0.34[0.16] | 0.29[0.14] | 0.22[0.18] | 0.31[0.21] | 0.36[0.17] ^e | 0.31[0.26] ^w | 0.35[0.21] ^{f,g} | 0.33[0.20] ^{f,g} | P=0.177 | P=0.002* | P=0.093 | P=0.989 |
| O ₂ cost (with) mLmin ⁻¹ kg ⁻¹ m ⁻¹ | 0.35[0.16] | 0.28[0.12] | 0.31[0.14] | 0.28[0.11] | 0.38[0.18] ^e | 0.28[0.23] ^e | 0.35[0.32] ^{f,g} | 0.29[0.15] ^{f,g} | | | | |
| MSIS-29 (physical) | 37.0[13.3] | 35.7[18.1] | 33.8[14.3] ^h | 33.9[16.1] ^h | 31.6[13.0] | 34.0[17.7] | 33.8[15.2] | 34.2[17.4] | P=0.836 | P=0.040* | P=0.819 | |
| MSIS-29 (psych) | 14.0[8.9] | 13.0[8.3] | 13.8[8.1] | 12.6[7.9] | 11.6[6.8] | 13.0[8.1] | 12.5[7.2] | 12.2[7.2] | P=0.056 | P=0.987 | P=0.873 | |
| MSWS-12 | 33.8[8.3] | 30.4[12.1] | 29.5[10.3] ⁱ | 27.2[12.0] ⁱ | 31.2[9.4] ^j | 27.9[11.0] ^j | 28.9[11.9] | 29.9[12.4] | P=0.202 | P=0.002* | P=0.243 | |
| EQ-5D-VAS | 67.7[16.5] | 70.2[19.3] | 67.7[18.7] | 72.5[17.5] | 66.0[19.0] | 71.5[21.4] | 68.8[18.9] | 74.3[15.5] | P=0.169 | P=0.257 | P=0.795 | |
| MFIS | 11.5[4.1] | 11.7[5.3] | 11.3[4.0] | 11.1[4.9] | 11.0[4.2] | 11.2[4.9] | 11.3[4.8] | 11.9[4.5] | P=0.888 | P=0.233 | P=0.433 | |
| ABC | 50.2[18.9] | 54.4[23.6] | 51.2[19.4] | 56.7[21.4] | 52.6[20.5] | 56.4[20.9] | 52.2[23.5] | 53.7[20.3] | P=0.378 | P=0.934 | P=0.741 | |
| PIADS C | | | | | | | 0.85[1.01] | 1.53[1.05] | P=0.0016* | | | |
| PIADS A | | | | | | | 0.38[0.97] | 1.41[0.98] | P=0.001* | | | |
| PIADS SE | | | | | | | 0.45[0.67] | 1.00[0.68] | P=0.006* | | | |

572 Abbreviations- mo: months; AFO: ankle foot orthoses; FES: functional electrical stimulation; 5minSSWT: 5 minute self-selected walk test: m/s;
573 meters per second: 25ftWT: 25 foot walk test; O₂ cost (mLmin⁻¹kg⁻¹m⁻¹); oxygen cost of walking per unit distance walked: MSIS-29 (physical);
574 Multiple Sclerosis Impact Scale-29 physical sub scale: MSIS-29 (psych); Multiple Sclerosis Impact Scale-29 psychological sub scale: MSWS-

575 12; Multiple Sclerosis walking scale-12: EQ-VAS; Euroqual questionnaire visual analogue scale; MFIS; modified fatigue impact scale; ABC:
576 activities and balance confidence scale; PIADS C: psychological impact of assistive devices scale competence sub scale; PIADS A:
577 adaptability subscale; PIADS SE: self-esteem subscale; *: statistically significant difference detected; ^a: ANOVA sig time effect 0-3months,
578 $p < 0.001$; ^b: ANOVA sig time effect 0-6 months, $p = 0.029$; ^c: ANOVA sig time effect 3-6 months, $p = 0.028$; ^d: ANOVA sig time effect 3-12 months,
579 $p = 0.09$; ^e: ANOVA sig time effect 3-6 months, $p = 0.07$; ^f: ANOVA sig time effect 0-12 months, $p = 0.011$; ^g: ANOVA sig time effect 3-12 months,
580 $p = 0.001$; ^h: ANOVA sig time effect 0-3 months, $p = 0.045$; ⁱ: ANOVA sig time effect 0-3 months, $p < 0.001$; ^j: ANOVA sig time effect 3-6 months,
581 $p = 0.035$.

582 **Table 3:** Estimated means (SE) of initial, ongoing and total orthotic and therapeutic effects of
 583 AFO and FES on the 5minSSWT, 25ftWT and the oxygen cost of walking.

| | AFO | | | FES | | |
|---|------------|------------|--------------------|------------|------------|--------------------|
| | without | with | Δ | without | with | Δ |
| IO | | | | | | |
| 5minSSWT(m/s) | 0.63(0.04) | 0.61(0.04) | -0.02 | 0.73(0.04) | 0.74(0.04) | +0.01 |
| 25ftWT(m/s) | 0.86(0.06) | 0.83(0.05) | -0.03 | 0.85(0.05) | 0.87(0.05) | +0.03 |
| O ₂ cost (mLmin ⁻¹ kg ⁻¹ m ⁻¹) | 0.34(0.03) | 0.35(0.03) | +0.01 | 0.29(0.02) | 0.28(0.02) | -0.01 |
| OO (3mo) | | | | | | |
| 5minSSWT(m/s) | 0.67(0.04) | 0.70(0.04) | +0.03 | 0.76(0.05) | 0.81(0.05) | +0.05 ^a |
| 25ftWT(m/s) | 0.86(0.05) | 0.87(0.05) | +0.01 | 0.95(0.05) | 0.99(0.05) | +0.04 |
| O ₂ cost (mLmin ⁻¹ kg ⁻¹ m ⁻¹) | 0.33(0.03) | 0.31(0.03) | -0.02 | 0.32(0.03) | 0.29(0.03) | -0.03 |
| OO (6mo) | | | | | | |
| 5minSSWT(m/s) | 0.61(0.04) | 0.65(0.04) | +0.04 | 0.76(0.04) | 0.81(0.04) | +0.05 ^a |
| 25ftWT(m/s) | 0.84(0.05) | 0.82(0.05) | -0.02 | 0.92(0.05) | 0.97(0.05) | +0.05 ^a |
| O ₂ cost (mLmin ⁻¹ kg ⁻¹ m ⁻¹) | 0.35(0.03) | 0.38(0.03) | +0.03 | 0.33(0.04) | 0.32(0.04) | -0.01 |
| OO (12mo) | | | | | | |
| 5minSSWT(m/s) | 0.66(0.04) | 0.67(0.04) | +0.02 | 0.71(0.05) | 0.76(0.05) | +0.05 ^a |
| 25ftWT(m/s) | 0.88(0.06) | 0.90(0.06) | +0.02 | 0.91(0.05) | 0.96(0.05) | +0.05 ^a |
| O ₂ cost (mLmin ⁻¹ kg ⁻¹ m ⁻¹) | 0.38(0.05) | 0.39(0.05) | +0.01 | 0.39(0.05) | 0.36(0.05) | -0.03 |
| TO (12mo) | | | | | | |
| 5minSSWT(m/s) | | | +0.05 ^a | | | +0.03 |
| 25ftWT(m/s) | | | +0.04 | | | +0.02 |
| O ₂ cost (mLmin ⁻¹ kg ⁻¹ m ⁻¹) | | | -0.05 | | | +0.07 |
| Th (6mo) | | | | | | |
| 5minSSWT(m/s) | | | -0.02 | | | +0.03 |
| 25ftWT(m/s) | | | -0.02 | | | -0.02 |
| O ₂ cost (mLmin ⁻¹ kg ⁻¹ m ⁻¹) | | | +0.01 | | | +0.04 |
| Th (12mo) | | | | | | |
| 5minSSWT(m/s) | | | +0.03 | | | -0.02 |
| 25ftWT(m/s) | | | +0.02 | | | -0.03 |
| O ₂ cost | | | +0.04 | | | +0.10 |

584 Abbreviations- AFO; ankle foot orthoses; FES: functional electrical stimulation; Δ = effect of
 585 estimated means; IO: initial orthotic effect; OO: ongoing orthotic effect; TO (12mth): total
 586 orthotic effect at 12 months; Th (12mth): therapeutic effect at 12 months; mo: months;
 587 5minSSWT: 5-minute self-selected walk test; m/s: meters per second; 25ftWT: Timed 25 foot
 588 walk; O₂ cost (mL min⁻¹ kg⁻¹ m⁻¹); oxygen cost of walking per unit distance walked; ^a indicates
 589 a mean change in walking speed of ≥ 0.05 m/s, considered to be clinically significant.

591 **Table 4:** Treatment costs, quality-adjusted life years and incremental cost effectiveness
 592 ratio's for both devices over both one and two years. (year two costs represent the
 593 cumulative total of year one and year two costs).

| Year 1 | | | | | |
|-----------|---|-------------|-----------------|-----------|--------------------|
| Treatment | Total cost per year including equipment and staff costs (£/€) | Total QALYs | Inc. cost (£/€) | Inc. QALY | ICER (£/€) |
| AFO | 579.76/665.62 | 0.65 | | | |
| FES | 1,228.02/1409.89 | 0.68 | 648.26/744.27 | 0.03 | 25,588.96/29378.68 |
| Year 2 | | | | | |
| Treatment | Total cost per year including equipment and staff costs (£/€) | Total QALYs | Inc. cost (£/€) | Inc. QALY | ICER (£/€) |
| AFO | 723.00/830.08 | 1.31 | | | |
| FES | 1,446.83/1661.11 | 1.36 | 723.83/831.03 | 0.05 | 14,285.92/16401.66 |

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595 Abbreviations- AFO; ankle foot orthoses; FES: functional electrical stimulation; inc:
 596 incremental; QALY: quality adjusted life year; ICER: incremental cost effectiveness ratio.
 597 Values presented are British pounds and euros.

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613 **Figure 1:** Consort diagram.

614 Abbreviations: AFO: ankle-foot orthoses, FES: functional electrical stimulation

