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The Effectiveness of Peroneal Nerve Functional Electrical Simulation for the Reduction of Bradykinesia in Parkinson's Disease: A Feasibility Study for a Randomised Control Trial.

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Abstract

Objectives

To assess the feasibility of a multi-site randomized controlled trial to evaluate the effect of functional electrical stimulation on bradykinesia in people with Parkinson's disease.

Design

A two-arm assessor blinded randomised controlled trial with an 18 weeks intervention period and 4 weeks post-intervention follow-up.

Setting

Two UK hospitals; a therapy outpatient department in a district general hospital and a specialist neuroscience centre.

Participants

64 participants with idiopathic Parkinson's disease and slow gait <1.25ms^{-1}.

Interventions

Functional Electrical Stimulation delivered to the common peroneal nerve while walking in addition to standard care compared with standard care alone.

Main measures

Feasibility aims included the determination of sample size, recruitment and retention rates, acceptability of the protocol and confirmation of the primary outcome measure. The outcome measures were 10m walking speed, Unified Parkinson's Disease Rating Scale (UPDRS), Mini Balance Evaluation Systems Test, Parkinson's Disease Questionnaire-39, EuroQol 5-dimension 5-level, New Freezing of Gait questionnaire, Falls Efficacy Score International and falls diary. Participants opinion

on the study design and relevance of outcome measures were evaluated using an embedded qualitative study.

Results

There was a mean difference between groups of 0.14ms^{-1} (CI 0.03, 0.26) at week 18 in favour of the treatment group, which was maintained at week 22, 0.10ms^{-1} (CI -0.05, 0.25). There was a difference in UPDRS motor examination score of -3.65 (CI -4.35, 0.54) at week 18 which was lost at week 22 -0.91 (CI -2.19, 2.26).

Conclusion

The study design and intervention were feasible and supportive for a definitive trial. While both the study protocol and intervention were acceptable, recommendations for modifications are made.

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Introduction

Difficulty in walking is a major factor in reduced quality of life for people with Parkinson's Disease. Walking is often unsafe with falls being a significant problem. Cioni et al[1]. identified that people with Parkinson's have significantly reduced muscle activity in the lower extremity distal muscles, particularly affecting the tibialis anterior muscle. Functional electrical stimulation is a means of producing an active muscle contraction controlled to provide functional movement to assist everyday tasks. It is a standard intervention for correction of dropped foot for individuals who have multiple sclerosis or stroke[2, 3]. Electrical stimulation is applied to the common peroneal nerve using skin surface electrodes placed over the head of the fibula and the anterior tibialis muscle. The stimulation is timed to the gait cycle using a footswitch, causing dorsiflexion when the heel is taken from the ground. This increases the safety of gait by reducing falls, improving walking speed and efficiency and is associated with an improvement in quality of life.

Mann et al.[4] hypothesized that functional electrical stimulation used to produce dorsiflexion may assist the initiation of stepping and overcome freezing in gait in people with Parkinson's Disease. In this observational study, 10 people who exhibited freezing used functional electrical stimulation for two months. Participants showed reduce freezing and fewer trips and falls, while gait speed and stride length were increased. Improvements were maintained for four weeks after ending stimulation. In a study by Popa and Taylor[5] 11 people with Parkinson's used functional electrical stimulation for two weeks. Participants demonstrated improvements in a range of outcomes but most notable was the increase in walking speed measured without functional electrical stimulation, increasing by a mean of 0.29ms^{-1}.

These findings lead us to a new hypothesis, that functional electrical stimulation may be an effective intervention to reduce bradykinesia. We therefore proposed a multicentre, parallel arm randomized controlled trial to determine the clinical and cost effectiveness of peroneal nerve functional electrical stimulation for the reduction of bradykinesia for people with Parkinson's, with secondary objectives assessing the effect on akinesia, hypokinesia, balance and falls and quality of life.

In preparation for the full randomized control trial, this study tested the feasibility of protocol and assessed the following objectives:

1. Estimate the recruitment, willingness to be randomized and loss-to-follow rates.
2. Determine participant views on obstacles to recruitment and retention.
3. Determine the participant views on what would constitute a meaningful primary outcome measure.
4. Estimate the variability and correlations of outcome measures in order to inform the sample size calculation.
5. Develop resource use data collection methods to inform a future cost-effectiveness analysis.
6. Estimate the time frame of a full trial.

Method

The study was a feasibility randomised controlled trial and compared standard care with functional electrical stimulation in addition to standard care. The study period of 22 weeks from randomisation, comprised an intervention period of 18 weeks and a 4-week follow up. The study was reviewed by the South West - Cornwall & Plymouth Research Ethics Committee (IRAS project ID: 192222, REC reference: 16/SW/0041). The Sponsor was Salisbury NHS Foundation Trust. The study was funded by the National Institute for Health Research under their Research for Patient Benefit funding stream (PB-PG-1014-35012). The study was registered with the International Standard Randomised Controlled Trial Number Registry (SRCTN17609599). Recruitment was from May 2016 to November 2017.

Participants were recruited by study centres in Salisbury and London. Participants were identified by members of the Movement Disorders Teams, via publicity on the Parkinson's Society web site and other local publicity. All potential participants were given an information sheet and asked to contact the research team if they wished to be assessed. Following telephone screening, potential participants were invited to a screening session. Following consent, participants were assessed against the inclusion criteria and if found suitable, invited to join the study. Participants returned to the clinic for baseline assessments after which randomisation was performed using

computer generated block (variable size) randomisation, prepared by the study statistician and administered by the clinical trials unit.

The selection criteria were assessed by the blinded assessors and principle investigators at each centre.

Inclusion criteria were; aged 18 years and above, idiopathic Parkinson's, Hoehn and Yahr stages I to IV under medication, bradykinesia demonstrated by a 10m walking speed <1.25ms^{-1} and difficulty with one or more aspects of their gait (reduced dorsiflexion or eversion in the swing or weight acceptance phase of gait, akinesia or hypokinesia demonstrated by walking with a short stride length), able to walk 10m with appropriate walking aids independently, able to obtain standing from sitting independently, medically stable and able to understand and comply with the treatment and assessments.

Exclusion criteria were; treatments other than standard oral drug therapy, untreated or refractory epilepsy (seizure in last 3 months), pregnancy, active medical implanted devices, other neurological conditions known to cause dropped foot, severe osteoarticular pathology, malignancy or dermatological conditions in the area of the electrodes and major cognitive impairment.

Both groups received standard care consisting of medication, attendance at medical clinics, exercise classes or visits from specialist nurses. Each participants Parkinson's medication was recorded at each clinic visit and used to derive a levodopa equivalent daily dose. Contacts with health-related services were recorded in a study diary. No additional interventions were given to the control group.

The treatment group received the Odstock Dropped Foot Stimulator- ODFS®Pace[5], which was fitted to the leg the treating clinician identified as having the greatest deficit in dorsiflexion and eversion (Appendix 1). The current was set at a sufficient intensity to cause an active comfortable muscle contraction, correcting any deficit present in dorsiflexion and eversion. The participants were taught how to fit the device, how to identify the correct movement of the foot and how to adjust the position of the electrodes and intensity to produce this movement. The participant returned to the clinic the next day or soon after and were asked to demonstrate that they were able to use the

device and further training given if required. The participant returned to the clinic 6 weeks later to check that they were continuing to use the device effectively and any required adjustments made or further training given. Participants returned to the clinic at 18 weeks for a final assessment by the treating clinician and retrieval of the device. Any additional contacts with the FES clinic were recorded. Treating clinicians were experienced FES trained physiotherapists or clinical scientists working in the clinical FES service for stroke, multiple sclerosis and other neurological conditions at each centre.

Both groups were assessed by an assessor blinded to group allocation at weeks 0, 6, 18 and 22. All assessments were made in the "on phase" of Parkinson's, without the ODFS®Pace being worn and at the same time of day. The proposed primary outcome measure for future trial was walking speed over 10m[4]. A single instruction to "walk briskly but safely" was given. The secondary outcome measures were; the Unified Parkinson's Disease Rating Scale[6], the Parkinson's Disease Questionnaire 39[7], EuroQol 5 dimension 5 level[8], the 'new' freezing of gait questionnaire[9], stride length[10], a falls diary[11], the Falls Efficacy Score – International[12,], the Mini Balance Evaluation Systems Test[13] and a resource use questionnaire and diary designed for this study. The effectiveness of blinding was assessed after each participants completion of the protocol by asking the assessor to report if they had been unblinded.

To assess the participants opinion of which outcome measures were most relevant to their experience of the effect of the treatment, a questionnaire was devised, called the "change questionnaire" (Appendix 2). An embedded qualitative study was used to study the participant's experience of intervention and trial participation, using semi-structured telephone interviews (Appendix 3).

Statistical methods

The sample size calculation was based on estimating recruitment & retention rates, estimation of participant variability (SD) in outcome measurements and correlation between outcomes at baseline and subsequent time-points. A total recruitment of 68 participants would enable estimation of a recruitment rate circa 50% with a 90% confidence interval (CI) +/-7%, a retention to follow-up rate circa 60% with 90% CI +/-10%, a between participant standard deviation for outcome variable with upper limit of 90% CI of 1.17 times observed value and a within-participant correlation for outcome variable circa 0.7 with a lower 90% confidence interval of 0.54 (based on 60% of

68 participants supplying data). A conservative estimate of R of 0.7 is based on an observed R of 0.85 in observational studies on the same patient population.

As a feasibility study, it was not powered to detect a minimal clinically important difference in primary outcome. However, we have used the data to calculate preliminary estimates (with 95% confidence intervals) of effect size for outcome measures at each measurement time point. For each continuous outcome we have used multiple regression to calculate the mean difference in outcome between trial groups adjusted for study centre and baseline. For outcome measures with accepted minimum clinically important difference in the literature, we have estimated the odds ratio comparing treatment with control groups using logistic regression, adjusting for study centre. An intention-to-treat approach has been used with no imputation for missing data. No p-values have been presented, consistent with this being a feasibility study. Correlation relationships between items in the change questionnaire were investigated using Pearson's correlation coefficients with 90% confidence intervals calculated using bootstrapping (1000 samples).

Results

The recruitment process is shown in a CONSORT flow diagram (figure 1). 64 participants were recruited, 94% of the target. The recruitment rate was 1.8 participants per centre per month and a participant retention rate of 80% was achieved. Assessor blinding was maintained for 81% of participants. Two treatment group participants required additional clinical contacts (3 extra clinic sessions in total). 14 serious adverse events occurred; six in the control group and eight in the treatment group. None were related to the intervention or protocol. Two device-related adverse events occurred. Both were minor cases of skin irritation from the electrodes.

A summary of the participant's characteristics is given in table 1. The groups were well matched for demographics, co-morbidities and outcome measure characteristics. While, on average, the treatment group were receiving a slightly higher dose of levodopa than the control group at the week 0, changes in levodopa dose through the study were similar in both groups. (table 2). Participation in exercise classes was also slightly higher in the treatment group. The stimulation parameters used are shown in table 3. The median number of steps taken with the device by

the intervention group (intervention dose) was 89,261 (IQR 39,327 to 153,591) over 18 weeks. A summary of ankle muscle strength is given in table 4. All participants exhibited some degree of ankle weakness.

25 participants in the functional electrical stimulation group completed the change questionnaire at week 18 (Tables 5 and 6). The most frequently identified factor moderately or considerable improved was walking speed n=11 participants. The opinion on what was the most important factor was split across 9 factors, the most frequently identified being confidence walks can be completed. Discussion in a group of participants confirmed that confidence was the most important factor. Confidence is not well aligned with the outcome measures used in the study. However, change in self-reported confidence was found to be strongly correlated with self-reported change in walking speed r_s=0.874, which also correlated with self-reported change in overall walking ability r_s= 0.904, indicating that walking speed was an acceptable surrogate measure.

The standard deviation of the proposed primary outcome measure, walking speed at baseline was 0.33 (90%CI 0.28, 0.37) ms^{-1}. The correlation of walking speed at 18 weeks with baseline was 0.72 (90%CI 0.59, 0.82). Two scenarios for sample size calculations with walking speed at 18 weeks as the primary outcome measure were made:

1. Based on the estimated values of standard deviation and correlation with baseline: minimum clinically important difference=0.1 ms^{-1}, SD=0.33, r=0.72, 90% power and 20% missing data: n=278
2. Based on upper 90% confidence limit of standard deviation and lower 90% confidence limit of correlation with base line: minimum clinically important difference=0.1 ms^{-1}, SD=0.37, r=0.59, 90% power and 20% missing data: n=470. This is a conservative approach.

To obtain a sample size of 278 to 470, between 5 and 9 centres, each recruiting at a rate of 1.8 per month for 30 months, the recruitment and 6 months of data collection would be completed in 36 months.

Recruitment methods were acceptable. The information sheet was considered clear. While most participants accepted the need for randomization, it was considered a barrier by some and it was suggested the control group should try the intervention at the end of the study. Other barriers included travel difficulties and some found the measurement sessions long and tiring. The postural stability tests in the Unified Parkinson's Rating Scale and Mini Balance Evaluation Systems Test were unpopular but accepted once participants built trust in their assessor.

The amount the device use varied between participants. However, several participants reported that they received significant effects from intermittent use of functional electrical stimulation, achieving improved walking without the device for a period of time after it was used. The period of improved walking varied from participant to participant from a few hours to a few days. One participant reported;

> "Not used (functional electrical stimulation) a lot. It's like re-calibrating. Once a week is enough. An amazing difference. Can't praise it enough".

However, other participants chose to use the device every day reporting that their walking was safer with functional electrical stimulation, reducing the risk of falls and improving their confidence. Another participant reported;

> "I can do more things, increased confidence. My husband doesn't need to be by my side all the time when using functional electrical stimulation".

Resource use questionnaire and diaries were developed and tested. While these performed reasonably well there was a higher than expected missing data rate (25%). It was also not possible to compare this information with data taken from health records for many participants because health care was received from different hospitals to the two study centres.

Preliminary estimates of effect size

Table 7 reports the means and standard deviations at baseline of each outcome measure. Additionally, the mean, 95% confidence interval of the difference between the groups and standardized effect size is reported at 6, 18 and 22 weeks. Figure 2 shows the change in 10m walking speed over the course of the study. For outcome measures that have established values for minimum clinically important difference, odds ratios (adjusted for site) are given in table 8. The results from the falls diary are given in table 9.

Discussion

This study has demonstrated the feasibility of a multi-site fully powered randomised controlled trial to determine the effect of functional electrical stimulation on bradykinesia in Parkinson's. Preliminary findings add support to the hypothesis that functional electrical stimulation may have a clinically meaningful effect on bradykinesia, demonstrated by increased walking speed after device use. Additionally, some participants benefited from the use of the device as an orthosis, increasing the safety of their walking at the time it was used. However, some caution should be used in interpreting these results. As functional electrical stimulation produces an active movement, sensation from the stimulation and requires active participation in its use, it is not possible to blind the user to group allocation. It therefore cannot be ruled out that there may be an element of placebo effect. However, the intervention period of 18 week may be considered long enough for any initial Hawthorn effect to have passed.

To determine if a follow-on study was justified, we set the following criteria. Firstly, the intervention must be acceptable to people with Parkinson's. Table 6 indicates that the majority of participants would recommend the intervention to another person with Parkinson's. However, it was observed that participants who lived with family who could assist with donning and doffing the device, were more successful than those who lived alone. In particular, tremor was reported as a hindrance to independently donning and doffing the device. Carers or partners should be encouraged to be involved with application of the device and methods to support independent use of the device should be included in future studies.

The second criterion to proceed to the next study was to achieve a sufficient retention rate. Schulz & Grimes proposed that the minimum retention rate for trial validity is 80%[16]. This criterion was achieved.

The third criterion was that eligibility criteria were appropriate. The original protocol for the study had set a walking speed limit for inclusion of $0.8ms^{-1}$. This is the minimum threshold for community walking and allowed sufficient 'head room' to demonstrate an effect on bradykinesia. However, in the early stages of the study it was found that many people with Parkinson's were excluded because they walked too fast, despite apparent reduced ankle movement and other gait deficits. There was therefore a significant risk that the sample was not representative of people with Parkinson's that might benefit from the intervention and so walking speeds limit was increased to

1.25ms^{-1} (The speed needed to safely use a pelican crossing[14]). The modified selection criteria enabled an improved recruitment rate and it is recommended for the future study.

The fourth criterion was that the treatment pathway was appropriate. The study used the same clinical pathway used for provision of functional electrical stimulation for correction of dropped foot in stroke or multiple sclerosis[5]. While the pathway worked well it was noted that two centres tended to use slightly different stimulation parameters (table 3). While it is not known if this effected outcomes, it is recommended that there is greater co-ordination between sights in a future study to ensure a consistent approach to intervention dose.

The fifth criterion was that the research protocol was acceptable to the participants. Generally, this worked well although some participants found the assessment sessions fatiguing. It is recommended that sessions are restricted to 90 minutes in duration and that treatment and assessment sessions are held on different days.

The final criterion is that there be an indication that a clinically meaningful effect may be achievable. It is of note that the 95% CI for the estimate of mean difference in walking speed between groups at 18 weeks did not include 0 and the mean difference was greater than the value for a substantial clinically meaningful change. This is a strong indication that a follow-on study is justified.

Clinical Message

- Weakness of the muscles that control the movement of the ankle is a common occurrence in Parkinson's
- Functional electrical stimulation to the common peroneal nerve may be a feasible and clinically effective non-invasive method to improve mobility of people with Parkinson's
- Functional Electrical Stimulation may act as an assistive device, improving walking at the time it is used and also as a training device, improving walking for a period after it is used

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Suppliers

The ODFS Pace was supplied by Odstock Medical Limited (OML), Salisbury District Hospital, Salisbury, UK.

Statement of competing interests

Paul Taylor is Clinical Director of Odstock Medical Limited (OML), the company that supplied the devices used in this study. OML is majority owned by Salisbury NHS Foundation Trust, the organization that hosted this study. Paul Taylor holds stocks in OML. No other author has financial or conflicting interests to declare.

Authors Roles

PNT: Chief investigator, project conception, study design, organisation, monitoring, treating clinician, writing of first draft, guarantor.

TS: Blinded assessor, organisation, manuscript review

BB: Blinded assessor, organisation, manuscript review

DP: Salisbury medical supervision, study design, participant recruitment

JL: study design, participant recruitment

SN: people with Parkinson's representative, study monitoring

PS: study design, manuscript review

MD-H: Qualitative researcher, study design, participant interviews, analysis and manuscript review

EM: Health economics design, analysis and manuscript review

CS: Physio lead, study design, treating clinician and manuscript review

VS: Principle investigator and medical supervisor in London, study design, organisation and manuscript review.

PT: Statistician, study design, data analysis, manuscript review

Supplementary materials

Supplementary materials may be obtained from the chief Investigator Paul Taylor (p.taylor@salisburyfes.com)

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Table 1. Descriptive statistics at baseline

	Control (n=32)	Treatment (n=32)
Site n (%)		
Salisbury	16 (50%)	17 (53%)
London	16 (50%)	15 (47%)
Age mean (SD)	71.3 (7.8)	69.3 (8.7)
Gender n (%)		
Male	23 (72%)	23 (72%)
Female	9 (28%)	9 (28%)
Age at diagnosis (years) Mean (SD)	61.5 (9.6)	60.3 (10.9)
Hoehn and Yahr Scale score n (%)		
I. Unilateral only	3 (9%)	4 (13%)
II. Bilateral – no balance impairment	16 (50%)	15 (47%)
III. Mild to moderate	10 (31%)	12 (38%)
IV. Severe disability	3 (9%)	1 (3%)
Co-morbidities n (%)		
0	6 (19%)	8 (25%)
1	11 (34%)	12 (38%)
2	9 (28%)	6 (19%)
3	4 (13%)	4 (13%)
4+	2 (6%)	2 (6%)
Description of gait at screening (walking in an open gym, assessed by the blinded assessor)		
Slow walking n (%)	29 (91%)	30 (94%)
Reduced dorsiflexion n (%)	25 (78%)	24 (75%)
Reduced eversion n (%)	20 (63%)	22 (69%)
Short strides n (%)	15 (47%)	18 (56%)
Freezing n (%)	6 (19%)	5 (16%)
Festination n (%)	4 (13%)	3 (9%)
Current living situation		
Living alone	6 (19%)	7 (22%)
Living with family or others	26 (81%)	25 (78%)
Current occupation		
Retired	26 (81%)	24 (75%)
Paid work	3 (9%)	5 (15%)
Not working due to PD or other reason	3 (9%)	3 (9%)
Falls in past 6 weeks		
None	26 (81%)	26 (81%)
One	4 (13%)	0 (0%)
Two +	2 (6%)	5 (16%)

Table 2. Levodopa equivalent daily dose and participation in physiotherapy and exercise classes. Mean, standard deviation and number of participants who had an increased or reduced dose in comparison to week 0, at weeks 6, 18 and 22. The number of participants in classes at each stage.

	Week 0	Week 6	Week 18	Week 22
Control				
Levodopa equivalent daily dose [mg]	773 (344)	779 (345)	817 (367)	813 (356)
Increase dose from week 0 [n]		2	8	9
reduced dose from week 0 [n]		0	2	1
Participating in physiotherapy [n]	3	4	6	5
Participating exercise classes [n]	7	8	8	6
Treatment				
Levodopa equivalent daily dose [mg]	917 (570)	904 (547)	974 (635)	1009 (658)
Increase dose from week 0 [n]		5	5	8
reduced dose from week 0 [n]		2	3	4
Participating in physiotherapy [n]	4	1	2	2
Participating exercise classes [n]	10	11	6	8

Exercises classes included swimming, tai chi, yoga, dance, Pilates, PD Warrior® and falls prevention classes.

Table 3 Median and Interquartile range of stimulation parameters at week 0.

	Stimulated side	Current (mA) [IQR]	Rising ramp (ms) [IQR]	Extension (ms) [IQR]	Falling ramp (ms) [IQR]	Waveform	Frequency (Hz) [IQR]
All	Right 13 Left 16	40 [30, 50]	100 [50, 150]	150 [100, 150]	50 [50. 150]	Symm 25 Asym 4	40 [40, 40]
Salisbury	Right 8 Left 9	36 [30, 46]	150 [100,150]	150 [150, 150]	50 [50, 50]	Symm 17 Asym 0	40 [40, 40]
London	Right 5 Left 7	42 [33, 57]	50 [0, 50]	150 [87, 200]	150 [87, 150]	Symm 8 Asym 4	40 [40, 40]

IQR = Interquartile range, Symm = symmetrical biphasic waveform, Asym = Asymmetrical waveform. The stimulation pulse width was set at 180µs. Participants were taught to adjust the pulse width to produce a comfortable muscle contraction.

Table 4 Ankle power measured using the modified Medical Research Council scale. The table reports the number of ankles recorded with each MRC score and the percentage of the cohort with that score at base line. 64 participants (right and left legs = 128)

Ankle movement	Modified MRC score						
	1	2	3	4-	4+	5	Both ankles = 5
Plantarflexion n (%)	0 (0%)	2 (2%)	12 (9%)	22 (17%)	55 (43%)	37 (29%)	11 (17%)
Dorsiflexion n (%)	0 (0%)	4 (3%)	19 (15%)	35 (27%)	50 (39%)	20 (16%)	2 (3%)
Eversion n (%)	1 (1%)	12 (9%)	23 (18%)	43 (34%)	36 (28%)	13 (10%)	0 (0%)
Inversion n (%)	0 (0%)	7 (5%)	19 (15%)	34 (27%)	49 (38%)	19 (15%)	2 (3%)

1 = flicker, 2 = full active movement gravity eliminated, 3 =Full active movement against gravity, 4- = full range of movement against gravity plus resistance using 2 fingers, 4+ = full active range of movement against gravity plus resistance using the hand, 5 = full muscle power. MRC = Medical Research Council. n = number of ankles, except for "both ankles = 5" where it is the number of participants who had an MRC score of 5 in both ankles.

Table 5. Change Questionnaire. The participant's perception of aspects of their walking that had changed over the course of the study and the aspect they considered to be the most important to them. Collected from the treatment group at week 18.

	Considerably Worse	Moderately Worse	Slightly Worse	No Change	Slight Improvement	Moderate Improvement	Considerable Improvement	Most Important	Total Score
(score)	(-3)	(-2)	(-1)	(0)	(1)	(2)	(3)		
	Number of participants								
Walking speed	1	0	2	8	3	4	7	1	27
Overall walking ability	0	1	1	8	5	5	5	2	27
Walking distance	0	0	1	11	5	2	6	0	26
Stride length	0	1	0	10	4	7	3	0	25
Walking effort	0	1	1	10	5	4	4	3	22
Confidence you can complete walks you undertake	1	0	3	7	6	3	5	4	21
Fear of falling while walking	1	1	0	11	4	3	5	2	20
Overall quality of life	0	1	0	13	5	2	4	1	19
Independence	1	0	1	12	4	4	3	2	17
Taking part in normal activities OUTSIDE your home	1	0	2	11	3	5	3	0	17
Balance while walking	1	1	3	5	9	5	1	0	14
Trips and falls	0	0	5	10	5	2	3	3	13
Taking part in normal activities INSIDE your home	0	0	2	16	2	2	3	1	13
Freezing	1	3	1	13	2	2	3	2	5
Tremor	0	2	2	19	1	0	1	0	-2

PD FES Trial STEPS

Table 6. Change Questionnaire. The number of participants in the treatment group who wished to continue using Functional Electrical Stimulation or who would recommend the treatment to another person with Parkinson's.

	Definitely	Probably	Not sure	Probably not	Definitely not
If you had the opportunity, would you continue using FES after the STEPS study?	12	3	2	4	4
Would you recommend FES to someone else who had Parkinson's?	18	3	3	0	1

FES = Functional Electrical Stimulation

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Table 7. Summary of outcome measures. Means at base line and difference between groups at 6, 18 and 22 weeks

Outcome measure	Control group Mean (SD)	Treatment group Mean (SD)	Mean difference between groups adjusted for baseline and site (95% CI) [standardized effect size]		
	baseline		6 weeks	18 weeks	22 weeks
10mWT [ms^{-1}]	0.95 (0.33)	0.93 (0.33)	0.12 (0.02, 0.23)[1] [0.37]	0.14 (0.03, 0.26)[1] [0.43]	0.10 (-0.05, 0.25)[1] [0.31]
Stride Length [m]	0.52 (0.15)	0.50 (0.14)	0.06 (0.02, 0.11)[1] [0.43]	0.05 (0.001, 0.10)[1] [0.35]	0.05 (-0.1, 0.11)[1] [0.33]
Timed up and go test [s]	23.1 (17.9)	22.7 (19.5)	-4.67 (-9.05, -0.29)[1] [-0.25]	-1.58 (-9.71, 6.56)[1] [-0.08]	2.37 (-10.07, 14.82)[2] [0.13]
Timed up and go dual task test [s]	32.8 (22.3)	33.1 (31.8)	-1.05 (-10.71, 8.62)[1] [-0.04]	-5.50 (-12.09, 1.10)[1] [-0.20]	5.45 (-11.96, 22.97)[2] [0.20]
MDS-UPDRS Non-motor aspects of ADL	14.9 (8.5)	14.0 (6.6)	0.80 (-1.13, 2.73)[2] [0.11]	0.07 (-2.72, 2.87)[2] [0.01]	0.99 (-1.63, 3.62)[2] [0.13]
MDS-UPDRS Motor aspects of ADL	20.2 (8.8)	21.5 (7.3)	-1.96 (-4.04, 0.12)[1] [-0.24]	-1.90 (-4.35, 0.54)[1] [-0.24]	-0.35 (-2.95, 2.26)[1] [-0.04]
MDS-UPDRS Motor examination	43.7 (12.5)	42.4 (10.7)	-2.83 (-6.95, 1.29)[1] [-0.24]	-3.65 (-8.97, 1.67)[1] [-0.32]	-0.91 (-6.21, 4.40)[1] [-0.08]
MDS-UPDRS Motor complications	7.7 (5.1)	6.5 (4.1)	-0.99 (-2.69, 0.71)[1] [-0.21]	-0.44 (-2.61, 1.73)[1] [-0.09]	0.24 (-1.65, 2.12)[2] [0.05]
PDQ39 Mobility	58.4 (23.1)	58.6 (24.4)	-2.32 (-9.51, 4.86)[1] [-0.10]	-2.32 (-10.73, 6.10)[1] [-0.10]	-1.95 (-11.97, 8.07)[1] [-0.08]
PDQ39 ADL	42.1 (27.8)	43.0 (19.4)	-1.29 (-7.84, 5.26)[1] [-0.05]	-2.99 (-11.52, 5.55)[1] [-0.13]	-0.99 (-11.45, 9.46)[1] [-0.04]
PDQ39 Summary	35.2 (17.0)	35.7 (14.9)	0.40 (-3.52, 4.31)[2] [0.03]	-0.22 (-5.69, 5.25)[1] [-0.01]	1.77 (-4.12, 7.65)[2] [0.11]
EQ-5D-5L Index	0.58 (0.23)	0.61 (0.23)	0.06 (-0.01, 0.13)[1] [0.26]	0.03 (-0.04, 0.10)[1] [0.14]	0.05 (-0.03, 0.13)[1] [0.22]
EQ-5D-5L VAS	64.8 (21.6)	64.3 (17.3)	4.75 (-2.54, 12.04)[1] [0.24]	7.17 (-1.68, 16.02)[1] [0.37]	7.85 (-1.30, 16.99)[1] [0.40]
New freezing of Gait questionnaire	15.9 (8.9)	17.1 (9.0)	-3.81 (-6.73, -0.90)[1] [-0.43]	-0.48 (-3.46, 2.50)[1] [-0.05]	-0.89 (-4.41, 2.64)[1] [-0.10]
Falls efficacy Scale - international	37.0 (13.2)	37.2 (10.1)	-1.18 (-4.78, 2.41)[1] [-0.10]	-2.74 (-6.77, 1.30)[1] [-0.23]	-1.73 (-5.89, 2.43)[1] [-0.15]
Mini BESTest	14.8 (5.5)	15.6 (5.1)	1.64 (0.23, 3.04)[1]	0.83 (-0.89, 2.56)[1]	0.52 (-9.3, 1.97)[1]

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			[0.31]	[0.16]	[0.10]

[1] = difference in favor of the Treatment Group, [2] = difference in favor of the Control Group

SD = Standard Deviation, CI = Confidence Interval, 10mWT = 10m walking test, MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale, ADL = Activities of Daily Living, PDQ39 = Parkinson's Disease Questionnaire 39 quality of life measure, EQ-5D-5L = Euroquol 5 dimension, 5 level quality of life measure. Mini BESTest = Mini Balance Evaluation Systems Test.

Table 8. Summary of outcome measures. Proportion of participants where improvement exceeded the minimal clinically important difference (MCID) and odds ratios comparing treatment group to control group at week 6, 18 and 22 weeks

Outcome	Week 6	Week 18	Week 22
10m Walking speed SCID = 0.1 ms^{-1}			
Control	7 (26%)	8 (30%)	8 (32%)
Treatment	21 (66%)	12 (50%)	15 (58%)
Odds ratio (95% CI)	5.51 (1.77, 17.15)[1]	2.34 (0.72, 7.64)[1]	2.98 (0.94, 9.47)[1]
UPDRS Non-Motor aspects of ADL MCID =2.64			
Control	14 (52%)	12 (44%)	9 (36%)
Treatment	10 (31%)	11 (46%)	8 (31%)
Odds ratio (95% CI)	0.42 (0.14, 1.22)[2]	1.05 (0.35, 3.18)[1]	0.79 (0.25, 2.55)[2]
UPDRS Motor aspects of ADL MCID =3.05			
Control	2 (7%)	3 (11%)	4 (16%)
Treatment	7 (22%)	7 (29%)	4 (15%)
Odds ratio (95% CI)	3.64 (0.67, 19.92)[1]	3.39 (0.70, 16.48)[1]	0.95 (0.21, 4.30)[2]
UPDRS Motor Examination MCID =2.5			
Control	8 (30%)	11 (41%)	12 (48%)
Treatment	18 (56%)	12 (50%)	8 (31%)
Odds ratio (95% CI)	3.07 (1.04, 9.08)[1]	1.57 (0.50, 4.93)[1]	0.46 (0.15, 1.49)[2]
PDQ39 Summary Score MCID =1.6			
Control	15 (56%)	12 (44%)	17 (68%)
Treatment	15 (47%)	13 (54%)	17 (65%)
Odds ratio (95% CI)	0.70 (0.25, 1.97)[2]	1.55 (0.50, 4.75)[1]	0.88 (0.28, 2.84)[2]
EQ-5D-5L Index score MCID =0.1			
Control	6 (22%)	6 (22%)	8 (32%)
Treatment	14 (44%)	5 (21%)	8 (31%)
Odds ratio (95% CI)	2.72 (0.87, 8.55)[1]	0.95 (0.25, 3.66)[2]	0.92 (0.27, 3.11)[2]
EQ-5D-5L VAS score MCID =5.23			
Control	7 (26%)	5 (19%)	5 (20%)
Treatment	14 (44%)	9 (38%)	12 (46%)
Odds ratio (95% CI)	2.35 (0.75, 7.35)[1]	2.86 (0.78, 10.57)[1]	3.54 (0.99, 12.68)[1]
Mini BESTest MCID =1.6			
Control	8 (30%)	12 (44%)	8 (32%)
Treatment	16 (50%)	12 (50%)	10 (39%)
Odds ratio (95% CI)	2.38 (0.81, 7.04)[1]	1.29 (0.42, 3.91)[1]	1.34 (0.42, 4.28)[1]

[1] = difference in favor of the Treatment Group, [2] = difference in favor of the Control Group

10mWT = 10m walking test, MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale, PDQ39 = Parkinson's Disease Questionnaire 39 quality of life measure, EQ-5D-5L = Euroquol 5 dimension, 5 level quality of life measure, Mini BESTest = Mini Balance Evaluation Systems Test.

Table 9. The median number of falls and proportion of participants who had a fall.

Falls	**Falls 0-18 weeks post randomization Control n=27 FES n=23**	**Falls 18-22 weeks post randomization (intervention withdrawn) Control n=24 FES n=26**
All falls		
Control (median(IQR))	2.0 (3.0)	0.0 (1.3)
0 falls	10 (37%)	14 (58%)
>0 and <3 falls	9 (33%)	5 (21%)
3.0+ falls	8 (30%)	5 (21%)
FES (median(IQR))	3.0 (10.8)	0.0 (2.7)
0 falls	9 (39%)	15 (58%)
>0 and <3 falls	3 (13%)	5 (19%)
3.0+ falls	11 (48%)	6 (23%)
Odds ratios adjusted for site (95% CI)		
>0 and <3 falls	0.37 (0.08, 1.82)[1]	0.95 (0.22, 4.03)[1]
3.0+ falls	1.52 (0.42, 5.46)[2]	1.08 (0.26, 4.44)[2]
Injurious falls		
Control (median(IQR))	0.9 (1.8)	0.0 (0.0)
0 falls	13 (48%)	21 (88%)
>0 falls	14 (52%)	3 (13%)
FES (median(IQR))	0.0 (1.0)	0.0 (0.0)
0 falls	15 (65%)	24 (92%)
>0 falls	8 (35%)	2 (8%)
Odds ratios adjusted for site (95% CI)		
>0 falls	0.49 (0.15, 1.63)[1]	0.52 (0.07, 3.65)[1]

[1] = difference in favor of the Treatment Group, [2] = difference in favor of the Control Group,

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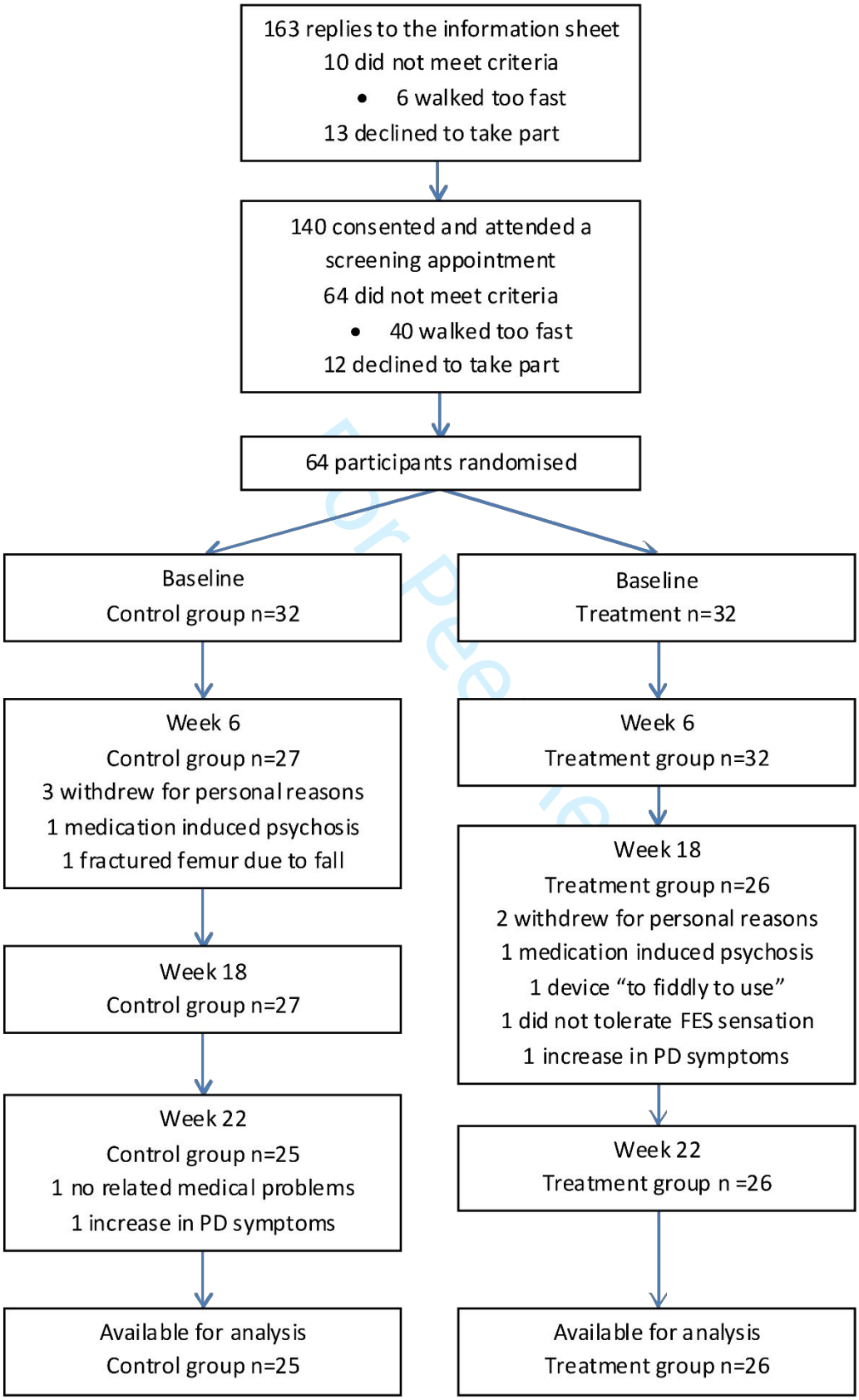
Figure 1. CONSORT diagram



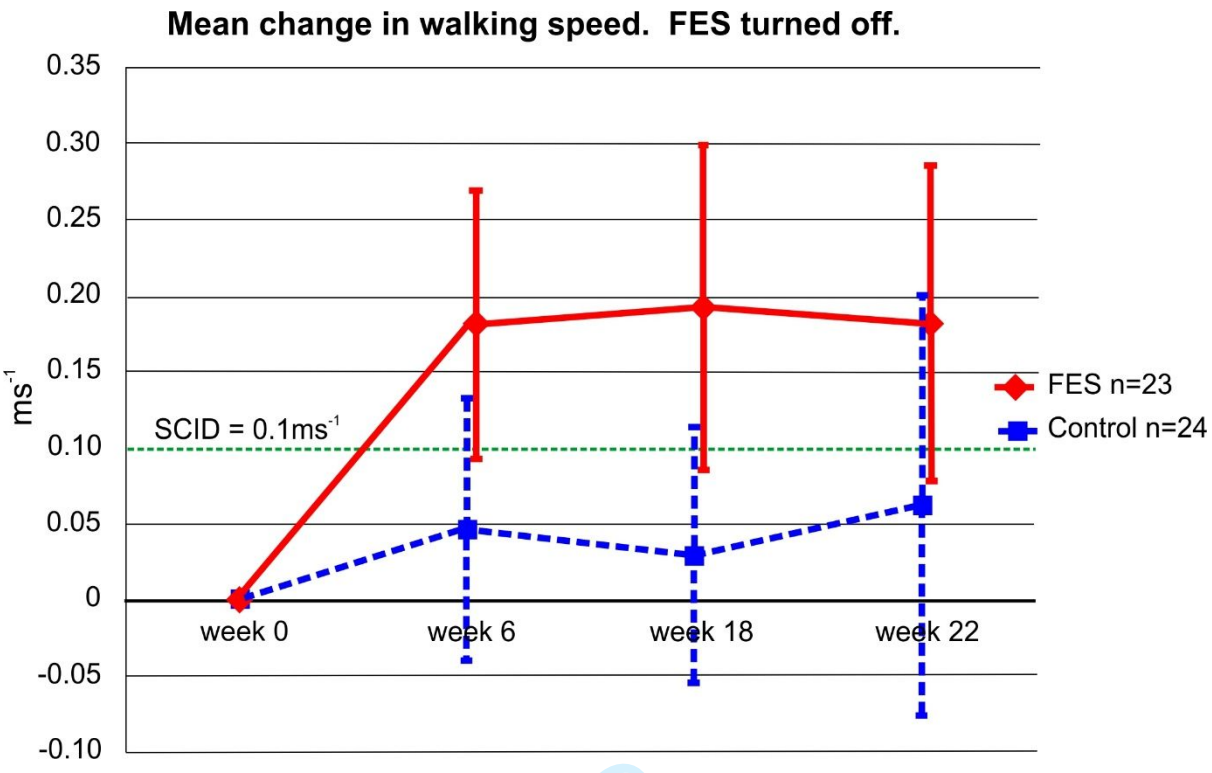


Figure 2. The mean change in 10m walking speed relative to baseline.

Error bars are 95% confidence intervals. SCID = Substantial Clinically Meaningful Change = 0.1ms^{-1}. FES= Functional Electrical Stimulation. Data is not adjusted for baseline or site and includes only participants with complete data sets. Functional electrical stimulation was withdrawn at week 18.

Appendix 1

The Odstock® Dropped Foot Stimulator (ODFS®) Pace

The Odstock Dropped Foot Stimulator (ODFS®) Pace is a single channel footswitch triggered nerve stimulator intended to assist dorsiflexion and eversion in the gait of people who have dropped foot due to an upper-motor neuron lesion. Self-adhesive electrodes are placed on the skin over the common peroneal nerve at its most superficial point, over the head of fibula (figures 1 and 2). Stimulation causes dorsiflexion and eversion. Electrode positions may also be chosen over the common peroneal nerve as it passes through the popliteal fossa or over the motor point of the anterior tibialis and toe extensors. By choosing electrode positions and stimulation parameters, the movement produced can be modified to best address the patient's gait deficit. For example, placing one electrode over the nerve in the popliteal fossa may increase knee and hip flexion by inducing a flexion withdrawal reflex. The stimulation is timed using a foot switch placed in the shoe (figure 3). Stimulation begins when weight is taken from the switch and ends just after heel contact, lowering the foot to the ground (figure 4). Stimulation feels like pins and needles. Most people quickly become used to the sensation.

Common peroneal stimulation has two principle effects. Firstly dorsiflexion is provided through the swing phase, reducing the risk of the foot catching on the ground. The second effect is the positioning of the foot at heel strike. Through the provision of eversion the foot is positioned so that weight bearing is through the midline of the foot, improving ankle stability in the stance phase. Both effects have an important role in reducing the incidence of falls.

The stimulators parameters can be adjusted to suit the gait of each individual. The intensity of the stimulation (current 10 to 100mA) is set by the clinician while stimulating with a pulse-duration of 180µs. The device user can fine tune the strength of the contraction by adjusting the pulse duration (3 to 360 µs).

Figure 4 shows the stimulation envelope delivered by the device. The rising ramp controls the rate at which the stimulation reaches its maximum. A longer ramp produces a slow contraction, which may be less likely to course a stretch reflex, increasing spasticity. It also allows time for push-off and is often perceived as more comfortable.

However, fast walkers require a shorter ramp to ensure dorsiflexion occurs soon enough to pick up the foot in the swing phase. A typical value for the rising ramp is 150ms.

The extension time is the period after heel strike that the stimulation remains on before ramping down. This mimics the natural action of the tibialis anterior muscles, lowering the foot to ground. The muscle also pulls the knee forward and hence can reduce knee hyper-extension. A typical value for the extension is 150ms.

Falling ramp is the time taken for the stimulation to fall to zero at the end of the envelope. It can be used to fine tune the effect of the extension time. A typical value for the falling ramp is 50ms.

Time out period is the maximum stimulation time. A typical value for the time out period is 2.5s

The stimulation frequency (20 to 60Hz) is the number pulses per second delivered by the stimulator. Lower frequencies may produce less muscle fatigue and can sometimes lower the spastic tone in the leg. Higher frequencies can produce a stronger, brisker response and may produce a better withdrawal reflex. A typical values for frequency is 40Hz.

The device offers a choice of stimulation waveforms. An asymmetrical bi-phasic waveform consists of a short positive pulse followed by a longer but lower intensity negative current flow. This waveform produces a stronger effect under the active (negative polarity) electrode than the indifferent electrode (positive polarity). This is useful to tune the motor response, emphasising eversion if the active electrode is over the head of fibular or dorsiflexion with less eversion if the active is over the tibialis anterior. A symmetrical waveform uses the same pulse shape as the symmetrical wave form but reverses the polarity of alternate pulses. In this setting both electrodes have equal stimulation effect. This waveform is believed to produce less skin irritation and is also useful for producing a balance of eversion and inversion.

The ODFS Pace is a CE marked and FDA approved medical device, and is recommended for routine clinical use in the UK by NICE. It is produced by Odstock Medical Limited.

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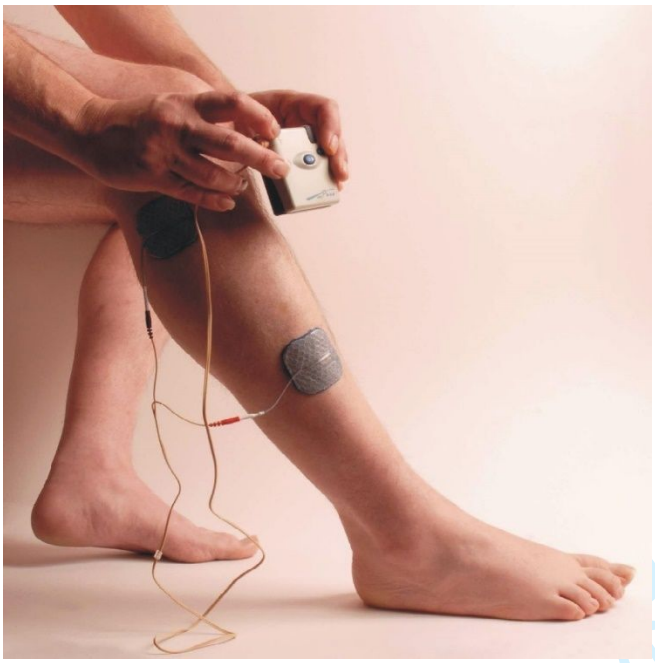

Figure 1. The ODFS® Pace

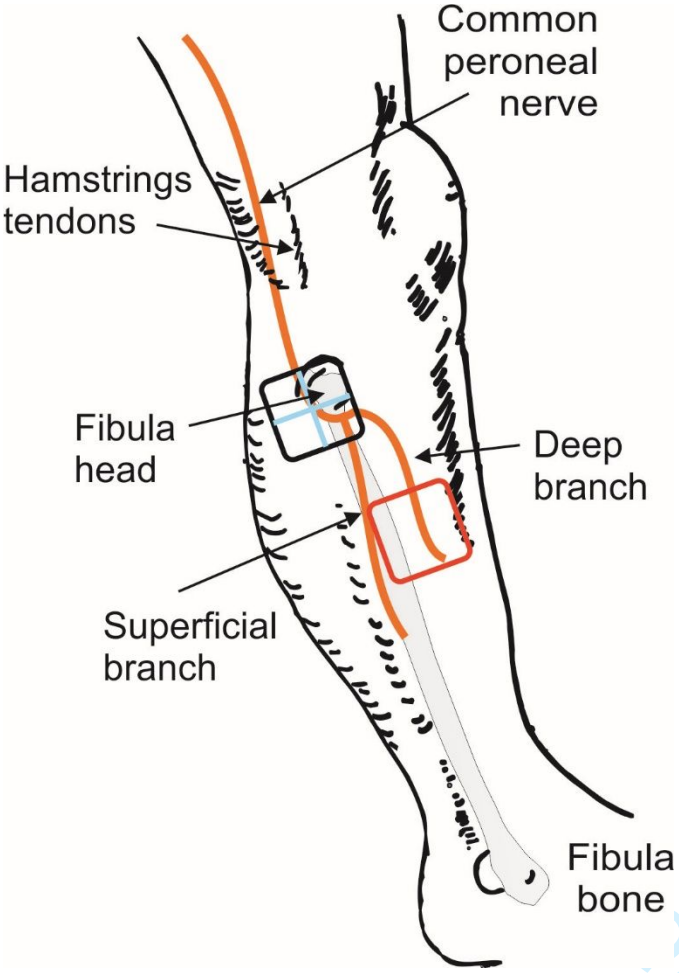

Figure 2. Electrode positions shown relative to the underlying common peroneal nerve. The nerve bifurcates at head of fibula. The superficial branch innovates the peroneus longus and brevis. These muscles produce eversion of the ankle. The deep branch innovates the tibialis anterior, extensor digitorum longus and brevis, extensor hallucis longus and peroneus tertius. These muscles produce dorsiflexion with inversion. By choosing the electrode position, different proportions of each nerve are stimulated varying the movement of the foot and ankle. The aim is to produce dorsiflexion with a small degree of eversion.

Figure 3. The device is controlled using a pressure sensitive footswitch placed on the underside of an insole.

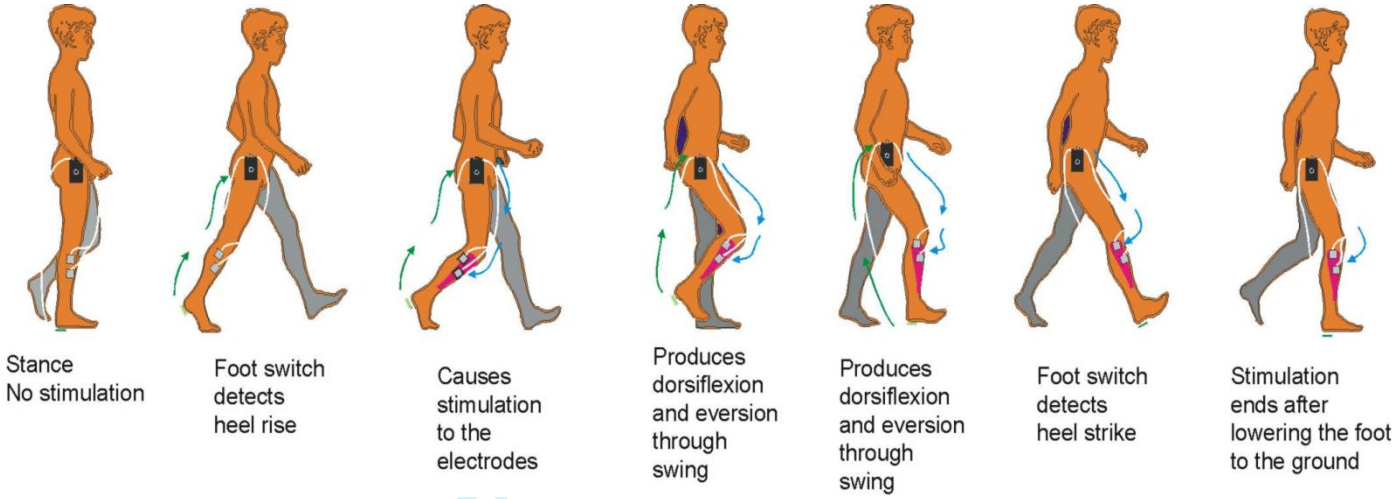

Figure 4. The operation of the ODFS® Pace.

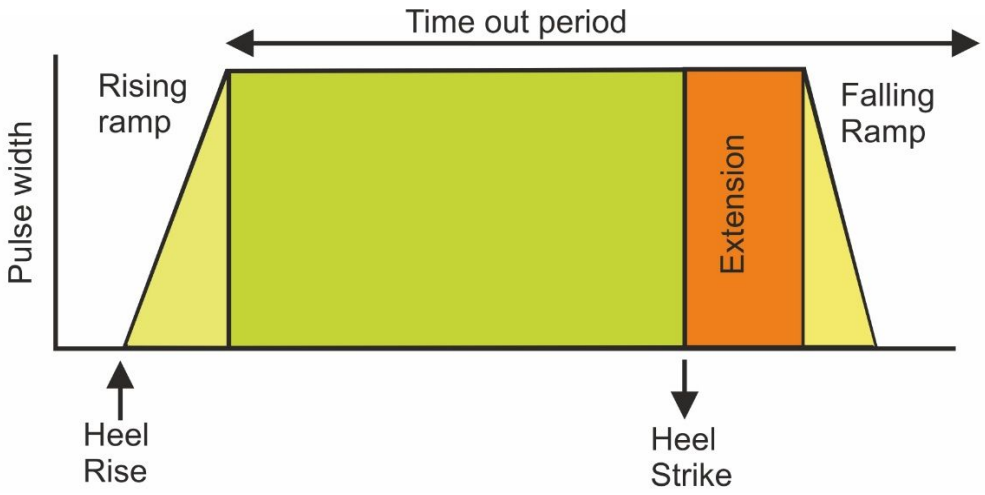

Figure 5. The stimulation envelope.

Appendix 2

The Change Questionnaire

This questionnaire was devised to assess the participant's opinions on what aspects of their walking, described as factors, may have been affected by using Functional Electrical Stimulation (FES). Each factor was chosen to represent a domain of a formal outcome measures used in the study. The participants were asked to rate how much a factor had changed and also which factor was most important to them. The results from the questionnaire were used to verify the choice of principle outcome measure for the subsequent study, ensuring it would be meaningful to people who have Parkinson's. The questionnaire also asked if participants wanted to continue with the treatment and if they would recommend it to another person.

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STEPS Change Questionnaire

Participant Number	Date

Each phrase or word below describes a factor that may be affected by using FES. For each factor please put an "X" in the appropriate box to show whether you feel there has been some improvement or if things have been getting worse since starting FES and by how much. Once you have answered all 15 questions please put an "X" in the box on the right hand side to indicate which single factor you think is most important to you.

		-3	-2	-1	0	1	2	3	
	Factors	Considerably Worse	Moderately Worse	Slightly Worse	No Change	Slight Improvement	Moderate improvement	Considerable Improvement	**MOST IMPORTANT FACTOR**
1	Walking speed								
2	Walking distance								
3	Walking effort								
4	Independence								
5	Trips and falls								
6	Confidence you can complete walks you undertake								
7	Freezing								
8	Balance while walking								
9	Stride length								
10	Tremor								
11	Taking part in normal activities **INSIDE** your home								
12	Taking part in normal activities **OUTSIDE** your home								

Continues over leaf….

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		-3	-2	-1	0	1	2	3	
	Factors	Considerably Worse	moderately Worse	Slightly Worse	No Change	Slight Improvement	Moderate improvement	Considerable Improvement	**MOST IMPORTANT FACTOR**
13	Fear of falling while walking								
14	Overall walking ability								
15	Overall quality of life								

If you had the opportunity, would you continue using FES after the STEPS study?

Definitely not ☐ Probably not ☐ Not sure ☐ Probably yes ☐ Definitely yes ☐

Would you recommend FES to someone else who had Parkinson's?

Definitely not ☐ Probably not ☐ Not sure ☐ Probably yes ☐ Definitely yes ☐

Please add any comments you have about the FES device, the STEPS study, the treatment you received or the facilities at the hospital. Thank you for completing this questionnaire.

Checked Y/N Clinician Name_____ Signature_____ date_____

Appendix 3

Qualitative study Interview Schedules

Four semi-structured interview schedules for different stages of the study and groups of people:

1. Pre-intervention interview for people who agreed to take part in the study
2. Pre-intervention interview for people who do not wish to take part in the study, but are happy to take part in the interview
3. Post-intervention interview for participants who stayed in the study for the entire period
4. Post-intervention interview for participants who withdraw from the study before the study end, but are happy to take part in the interview

Key questions and suggested prompts to be used as needed (example of prompts provided for interview schedule 1)

1) Pre-intervention interview for people who have agreed to take part in the study

1. Introduction and explanation of the aims of the interview and opportunity to ask any questions

2. Please tell me about your current mobility and walking?
   - *Impact of current PD symptoms on walking*
   - *Impact of any problems with walking on daily activities*
   - *Impact of any problems of walking on quality of life*
   - *Falls history*
   - *Concerns about falling*

3. Please talk through what influenced your decision to take part in the study?
   - *Key aspects that helped you to decide to take part in the study*

4. What were your initial thoughts about the paperwork you received about the study?
   - *The way the paperwork was received*
   - *Thoughts about the information sheet*
     - *Length*
     - *Writing style*
     - *Detail of information*
   - *The opportunity to ask more questions*
   - *The instructions on completing and returning the reply slip*
   - *How the information could be improved for a future study*

5. What were your views of the first assessment?
   - *Views on the initial contract by the research team*
   - *Organisation of the assessment*
   - *Place of the assessment*
   - *Length of time the assessment took*
   - *Thoughts about the different types of measures*

6. What are your views about being randomised into one of two different groups?

7. Were the next steps of the study made clear to you?

8. If we were to run a larger study, what do you think we should do differently for regarding the recruitment to the study?

9. Is there anything else you would like to add about taking part in the study so far?

2) Pre-intervention interview for people who do not wish to take part in the study, but are happy to take part in the interview

1. Introduction and explanation of the aims of the interview and opportunity to ask any questions

2. Please tell me about your current mobility and walking?

3. Please talk through what influenced your decision not to take part in the study?

4. What were your initial thoughts about the paperwork you received about the study?

5. If we were to run a larger study, what do you think we should do differently for this stage of the study?

6. Is there anything else you would like to add about your involvement in the study?

3) Post-intervention interview for participants who stayed in the study for the entire period

1. Introduction and explanation of the aims of the interview and opportunity to ask any questions

2. Please tell me about your current mobility and walking?

3. Have there have been any changes to your mobility and walking since taking part in the study?

4. What is the impact of the changes you have experienced since taking part in the study?

5. What was your view of the 6, 18 week and 22 week assessments?

6. ONLY ASK GROUP 2 WHO RECEIVED FES: Please can you tell me what you felt about receiving the FES treatment?

7. What influenced your decision to stay in the study for the required time?

8. What was your overall view of taking part in the study?

9. Is there anything about the study that you think may put other people taking part?

10. If we were to run a larger study, what do you think we should do differently for this stage of the study?

11. Is there anything else you would like to add about taking part in the study?

4) Post-intervention interview for participants who with withdraw from the study before the study end, but are happy to take part in the interview

1. Introduction and explanation of the aims of the interview and opportunity to ask any questions

2. Please tell me about your current mobility and walking?

3. Please tell me why you decided to withdraw from the study?

4. Before you withdraw from the study, were there any changes to your mobility and walking?

5. What is the impact of the changes you have experienced since taking part in the study?

6. ONLY ASK GROUP 2 WHO RECEIVED FES: Please can you tell me what you felt about receiving the FES treatment?

7. ONLY ASK PEOPLE WHO TOOK PART IN A FOLLOW-UP ASSESSMENT: What was your view of the 6 and 18 week assessments?

8. What was your overall view of taking part in the study?

9. Is there anything about the study that you think may put other people taking part?

10. If we were to run a larger study, what do you think we should do differently for this stage of the study?

11. Is there anything else you would like to add about taking part in the study?