The Effectiveness of Peroneal Nerve Functional Electrical STimulation (FES) for the Reduction of Bradykinesia in Parkinson's Disease: A Pragmatic Feasibility Study for a Single Blinded Randomised Control Trial (STEPS).

RfPB: PB-PG-1014-35012

Short title for the project: Can Electrical Stimulation of Muscles be Used to Improve Walking for People with Parkinson's Disease?

Study Protocol

V2. 6.0

Post submission

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REC reference: 16/SW/0041

REC approval date: 3rd March 2016

IRAS project ID: 192222

World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ISRCTN17609599
Date of registration in primary registry	5th April 2017
Portfolio CPMS ID	30475
Secondary identifying numbers	RfPB: PB-PG-1014-35012 IRAS project ID: 192222 REC reference: 16/SW/0041
Source(s) of monetary or material support	Research for Patient Benefit (RfPB) funding stream of the National Institute for Health Research (NIHR)
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Public title	STEPS
Scientific title	The Effectiveness of Peroneal Nerve Functional Electrical **ST**imulation (F***E***S) for the Reduction of Bradykinesia in **P**arkinson's Disease: A Pragmatic Feasibility **S**tudy for a Single Blinded Randomised Control Trial (STEPS).
Countries of recruitment	UK
Health condition(s) or problem(s) studied	Bradykinesia in Parkinson's Disease
Intervention(s)	Functional Electrical Stimulation delivered to the common peroneal nerve Normal care (no intervention)
Key inclusion and exclusion criteria	• Inclusion criteria: • aged 18 years and above idiopathic Parkinson's disease

Data category	Information
	• Hoehn and Yahr stages I to IV • difficulty with gait (includes any deficit in dorsiflexion or eversion, bradykinesia, festination, akinesia or • hypokinesia) • able to walk 10m with appropriate walking aids but without assistance from another person • able to obtain standing from sitting without the assistance of another person • medically stable • able to understand and comply with assessment procedures • able to give informed consent Exclusion criteria: • able to walk 10m in less than 8.0s (walking speed >1.25ms^{-1}) indicating non limited functional walking • other treatment than standard drug therapy (FES, deep brain stimulation, duodopa, apomorphine) • atypical or secondary parkinsonism or parkinsonism related to other neurodegenerative diseases • dropped foot due to any neurological condition other than Parkinson's Disease • untreated or refractory epilepsy • pregnancy • cardiac pacemaker, or other active medical implanted devices • denervation of the common peroneal nerve • malignancy or dermatological conditions in the area of the electrodes • major cognitive impairment; dementia.
Study type	A Pragmatic Feasibility Study for a Single Blinded Randomised Control Trial
Date of first enrolment	19th May 2016
Target sample size	68
Recruitment status	Active
Primary outcome(s)	• Patient identification, recruitment, willingness to be randomised and loss-to-follow rates
Key secondary outcomes	• Participant views on what would constitute a meaningful outcome measure.

Data category	Information
	• Participants views on the recruitment information and process • Participant views on obstacles to recruitment and retention in study. • To obtain estimates of likely time frame and costs for full RCT. • To obtain estimate of variability of primary outcome measure for sample-size calculation • To obtain estimate of within-subject outcome measure correlation for sample-size calculation • To design data collection tools for outcome and resource use data to improve completion and response rate in the full RCT

Abbreviations

10mWT	10 meter Walk Test
ANCOVA	ANalysis of COVAriance
EQ-5D-5L	EuroQol 5 dimension 5 level generic health related quality of life questionnaire
FES	Functional Electrical Stimulation
FES-I	Falls Efficacy Score – International questionnaire
Group 1	The group who receive normal care
Group 2	The intervention group (FES)
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
HSIC	Health and Social care Information Centre PIC
Mini-BESTest	Mini Balance Evaluation Systems Test
MRC	Medical Research Council scale for grading muscle strength
NFOG-Q	New Freezing Of Gait Questionnaire
OML	Odstock Medical Limited
OPCS	Office_of_Population_Censuses_and_Surveys classification of interventions and procedures
PAG	Participant Advisory Group
Pen CTU	Peninsula Clinical Trials Unit
PD	Parkinson's Disease
PDQ39	Parkinson's Disease Questionnaire 39 – PD related quality of life
PI	Principal Investigator

pwPD	People with Parkinson's Disease
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
UPDRS	Unified Parkinson's Disease Rating Scale

Plain English Summary

People with Parkinson's disease (PD) often have difficulty in walking, which causes them to walk slowly and fall, leading to a reduced quality of life. Functional Electrical Stimulation (FES) can be used to produce useful movements in under active muscles, by applying small electrical impulses to their nerves, using a small battery powered device worn on the leg.

In previous small studies, we have shown that patients are able to walk faster and have reduced PD symptoms after using FES. We want to carry out a larger study to investigate whether FES would be beneficial to patients in the longer term when compared to routine care and whether it would be value for money for the NHS. Before setting up a larger study, we need to run a smaller study to ensure we design the full study properly. We especially want to know how many people will complete the study and the reasons why some people don't.

Sixty-eight people who have PD will be randomly allocated to have either FES with routine care or routine care alone. Over 22 weeks we will measure the changes in walking speed, falls, quality of life and PD symptoms. We also want to determine if we are asking the right questions, and if the study methods are acceptable. We will interview participants to find out what they think about the study and whether there are things we should improve.

A Patient Advisory Group has been formed from participants of the earlier studies. They have contributed to the design of this research and will advise on all aspects of the study.
Our results will be used to plan the larger full study. They will be made available to other people doing research into Parkinson's Disease and summarised on the Parkinson's Society website.

Abstract

Functional Electrical Stimulation (FES) is a means of producing functional movement in paralysed muscle where the paralysis results from neural damage in the brain or cervical / thoracic spine. Its most common clinical application is to correct dropped foot following stroke and multiple sclerosis, where the common peroneal nerve is stimulated to cause the foot to lift (dorsiflexion) in the swing phase of gait. Three observational studies have investigated the use of FES in people who have walking difficulty due to Parkinson's disease (PD) and have shown clinically meaningful improvements in walking speed, freezing and step length19,20,21. In two of these studies the improvements were maintained after the device was subsequently turned off, indicating that FES had had a training effect on gait. These changes were associated with improved functional walking and reduction in the symptoms of PD. Participants in these studies have reported that the intervention had a useful impact on their daily lives and it was an intervention that they may choose to use as a long term mobility aid.

A feasibility study is proposed to determine recruitment, willingness to be randomised, loss-to-follow-up rates, the appropriate outcome measures, and methods of data collection, for a subsequent Randomised Controlled Trial (RCT) to evaluate the effectiveness and cost-effectiveness of FES in a standard clinical setting. In order to obtain a realistic estimate of probable loss-to-follow-up rate, the feasibility study will follow the design we currently envisage for the subsequent full RCT.

Sixty-eight people with gait deficit due to idiopathic PD will be recruited. A gait deficit is defined as a self-selected brisk walking speed of less than 1.25 metres per second (ms^{-1}) and reduced dorsiflexion or eversion in the swing phase of gait. All participants will continue with usual care; in general this comprises medication, attendance at medical clinics or visits from PD nurses; exercise therapy may be accessed by individuals although this is not routinely prescribed. Participants will record usual care during the 22 week study. The participants will be randomly allocated to one of two groups.

- Group 1 (control group) will not receive any additional intervention over their usual care.
- Group 2 (FES) will use the device in addition to their usual care.

The standard clinical application protocol established for the provision of FES in other neurological groups will be followed for Group 2, who will be taught to use the device over two clinic appointments with follow up 6 and 18 weeks. Both groups will be assessed at weeks 0, 6, 18 and 22, (4 weeks after withdrawal of the device from group 2), by an assessor blind to the group allocation.

The primary aim is to determine recruitment and retention rate. We will record the outcome measures currently envisaged for the future RCT, enabling refinement of data collection methods, and determine their acceptability to the participants. Results will also be used to derive estimates of sample size for the RCT. Semi-structured interviews will be used to explore the experience of the participants in the study and the relevance of the outcome measures to the participants.

The findings of the feasibility study will be used to underpin the design of the subsequent RCT, ensuring the design is costed appropriately, practical, adequately powered and utilises outcome measures relevant to the lives of the participants.

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V2.5

Introduction

Parkinson's disease (PD) affects about 127,000 people in the UK and is the 2nd most prevalent neurodegenerative condition after Alzheimer's disease[1]. Difficulty in walking has been identified as a major factor in reduced quality of life for people with Parkinson's Disease (pwPD)[2]. The studied intervention is most likely to be effective in those people moderately affected (Hoehn and Yahr stage II and III, 36% of people with PD (pwPD[36]) and in those who are younger (80% are under the age of 80[37]) indicating a target UK population of about 38,000.

Parkinsonian gait is characterized by bradykinesia (slowness of movement), hypokinesia (reduced movement size), festination (rapid but very short strides) and akinesia (difficulty in initiation of movement leading to freezing in gait). Walking is often unsafe with falls being a significant problem. It is reported that 39% of pwPD are recurrent fallers, experiencing a mean of 20.8 falls per year[3]. These issues can lead to pwPD reducing their overall activity, which can lead to reduction in fitness levels and reduced health status[4]. Reduced mobility also leads to reduced participation and it is common for pwPD to become socially withdrawn[5].

Symptoms of people with mild to moderated PD are often well controlled by drug therapies designed to modify the amount and action of dopamine in the brain[6]. However the drug therapies are not without side effects, for example dyskineasia (involuntary muscle movements), confusion, hallucinations and delusions, mood swings, psychological changes, sleepiness, fainting or dizziness. These side effects can limit the benefit received or result in a reduction in adherence with treatment. Further, the time for which the medication is effective can be limited, both in the short term (the amount of time each day) and the long term (the total period the drug is effective). Another intervention often used in conjunction with drug therapies is physiotherapy exercise. A recent meta-analysis of physiotherapy randomised controlled trials concluded that clinically meaningful changes were obtained in walking speed ($0.04ms^{-1}$), balance (3.71 points improvement on the Berg balance scale) and in PD symptoms (Unified Parkinson's Disease rating scale total score reduction -6.15 points)[7]. While benefits from exercise can be obtained, they are often limited and long term commitment and intensity are required that may not be possible for all pwPD, particularly for those with greater disability. There is therefore a need for additional treatment options for pwPD.

Functional electrical stimulation (FES) is a means of producing an active muscle contraction controlled in such a way to provide functional movement to assist everyday tasks. It is most frequently used for correction of dropped foot for individuals who have brain or spinal cord damage with preserved nerve and muscle integrity[8, 9, 10, 11, 12, 13, 14, 15, 16, 17]. FES is approved for use in the NHS for correction of dropped foot due to central neurological origin[14]. 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 foot switch placed in the shoe, causing the foot to be lifted when the foot is taken from the ground. The practical

assistance this produces increases the safety of gait by reducing falls[8, 15], improves walking speed[12, 17] and is associated with an improvement in quality of life measures[9, 15]. Further, longitudinal studies have shown that FES users who have had a stroke can also receive a training effect, demonstrated by increased walking speed without FES after several months of FES use[12, 16, 17]. FES is used as a long term practical assistive device with a median duration of use of 4.0 years for people with multiple sclerosis[17].

It has been identified by Cioni et al. that pwPD have significantly reduced muscle activity in the lower extremity distal muscles[18]. Particularly affected is the tibialis anterior muscle, the main dorsiflexion muscle and hence FES could be used to improve this function. The first investigation of the use of FES in PD was by our research group. Mann et al.[19] hypothesised that FES when used to produce dorsiflexion may be useful intervention to assist the initiation of stepping, overcome freezing in gait. In an observational study, 10 pwPD who exhibited freezing in gait used an FES device for a period of 2 months. Any participant who had a dropped foot was excluded from the study so that the effect on freezing could be studied in isolation. The study showed that FES use was associated with reduced episodes of freezing, increased gait speed, increased stride length and reduced incidence of trips and falls. Further, it was found that there was a training effect, demonstrated by improved gait parameters, four weeks after FES was withdrawn.

We further investigated the immediate effect FES on freezing of gait in a study where nine pwPD used the same FES device as above but this time at a single assessment (Djuric-Jovicic et al[20]). Participants were asked to walk along a given path comprising of standing up from the chair, passing through narrow doorways and turning. This was done with regular walking and walking while carrying tray with a glass of water (dual-task). The gait sequences with and without FES were recorded using gait analysis. Results showed that when FES was used the duration of the double support phase of gait was decreased and variability of stride duration and stride length was also reduced. Two participants did not experience freezing in places along the path where they had experienced problems without FES.

More recently we performed a study with 11 pwPD who had a Hoehn and Yahr scores of 2 or 3 (Popa and Taylor[21]). In contrast to the earlier studies, participants were chosen who exhibited gait deficits related to reduced dorsiflexion or inversion in the swing phase of gait. Outcome measures were the 10m Walking Test, the Tinetti balance scale, the modified Parkinson's Disease quality of life questionnaire (PDQL), the short Parkinson's evaluation scale/scales for outcomes in Parkinson's disease (SPES/SCOPA) scale and compliance. The focus of this study was the training effect from FES and hence all tests were carried out with FES switched off. Nine participants completed the protocol. After 2 weeks of FES there was a mean increase in walking speed of 0.29ms^{-1} ($p = 0.008$). (Figure 1) The mean step length also increased by 0.09 m ($p = 0.007$) and mean cadence increased by 19.8 steps min^{-1} ($p = 0.045$). The Tinetti balance score increased by 2.9 ($p = 0.006$) demonstrating improved balance. There was a significant change in the PD Symptoms score of the PDQL of 4.9 ($p = 0.013$) and also a reduction in the SPES/SCOPA score of -5.7 ($p = 0.005$) indicating a reduction in the impact of PD. Perera et al.[22] determined that for older adults a substantial clinically meaningful change in walking speed is 0.1ms^{-1}. This was achieved by all but one of the participants who completed the protocol, the remaining volunteer exceeding a minimal meaning change (>0.05ms^{-1}). Further, of the 5 participants whose initial walking speed was sufficiently reduced so that they could be categorized as limited to either household walking only (< 0.4ms^{-1}) (2 out of 5), most limited

community walking (0.4 to 0.58 ms^{-1}) (1 out of 5) or least limited community walking (0.59 to 0.79 ms^{-1}) (remaining 2 out of 5), all changed their functional walking category[23]. Four of the five participants who wanted to continue FES use were in this group suggesting the intervention has greatest impact on the slower walkers.

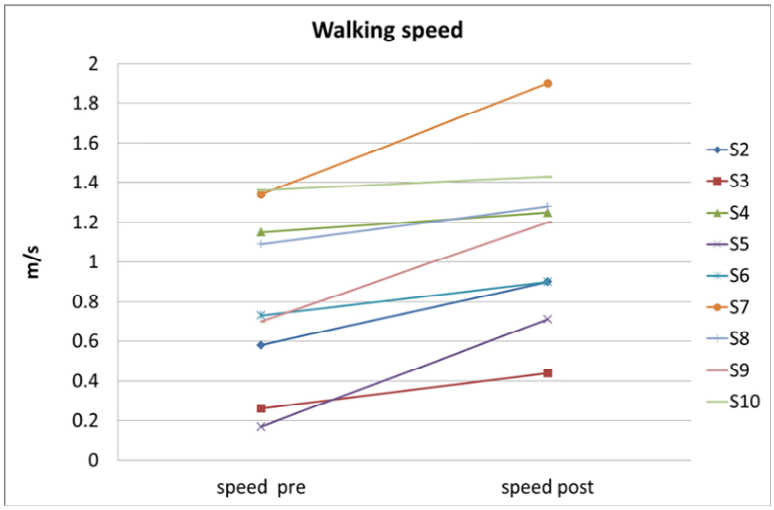


Figure 1. Change in walking speed after using FES for 2 weeks

One study has examined the neurological effect of FES in PD. Popa et al. used electrical stimulation of the wrist, finger and thumb extensors in 10 pwPD and compared the effect in a group of neurologically unimpaired volunteers[24]. Both groups received 30 minutes of stimulation each day for 10 days. The PD group demonstrated increased speed of hand movements at the end of the intervention period, increasing the number of times the hand was opened and closed in one minute by 21%. Cortical excitability was measured using Transcranial Magnetic Stimulation (TMS), which showed a reduction in excitation threshold over the study period. This increased excitability of the motor cortex may account for the increase in voluntary movement.

These studies suggest that the application of electrical stimulation of the common peroneal nerve timed to the swing phase of gait is feasible and that the technique may provide long term assistance, extending mobility as the disease process progresses. A randomised controlled trial using a clinically realistic protocol is now needed to determine the clinical effectiveness of this technique.

In our recent observational study the most notable effect was on bradykinesia demonstrated by an increase in walking speed by all participants who completed the protocol (figure 1). This mean increase in walking speed (0.29ms^{-1}) was substantially larger than that reported in a meta-analysis of physiotherapy interventions (0.04ms^{-1})[7]. Walking speed is accepted as a good indicator of overall gait quality and is also known to correlate well with the level of functional walking activity[23]. Further, difficulty in walking has been identified as a major contributor to reduced quality of life and falls for pwPD[2, 34]. Therefore the purpose of the subsequent full RCT is to evaluate the effect of FES on bradykinesia, in people with PD who have reduced functional walking ability demonstrated by the change in walking speed compared with normal care. For inclusion in the study a maximum walking speed of 1.25ms^{-1} has been chosen. The mean brisk walking speed of pwPD is reported to be 1.47ms^{-1} (confidence interval 1.30 to 1.64ms^{-1})[48]. Hence, by choosing a threshold below the lower confidence limit sufficient headroom is allowed to demonstrate an increase in walking speed.)

Currently normal care is medication that aims to boost or maintain the level of dopamine within the brain.

Aims and objectives

The envisaged research questions for the subsequent full RCT would be:

- What is the effect of the use of a FES on the mobility of pwPD compared with current routine care?

This will be assessed by examining the effect on:

- Bradykinesia (the speed of movement assessed from walking speed)
- Akinesia (freezing)
- Hypokinesia (reduced movement size assessed from stride length)
- Balance, the incidence of falls and the fear of falling
- The impact of PD symptoms and quality of life
- Is FES cost-effective compared to standard care?

Before a full RCT can be undertaken there are matters that must be addressed. Firstly, the present experience of FES with pwPD is restricted to small, non-controlled studies of short duration from a single specialised centre. A pragmatic effectiveness study would require a longer treatment period, be multi-centred and participants would have less frequent interaction with the clinical staff. It is not known what effect these changes will have on recruitment and retention. Secondly, some of the outcome measures we might consider for the RCT are untested in the PD and FES context. Experience is needed to ascertain their suitability for the RCT. Finally, while it is reported that walking difficulty is of importance to pwPD, it is not known if walking speed per se is the most representative outcome measure of walking difficulty for pwPD. A feasibility study would allow an exploration of the experience of FES users to identify what might be the most appropriate outcome measures for the full RCT. We therefore propose a feasibility study to determine the following objectives:

1. Recruitment (including identification of participants), willingness to be randomised and loss-to-follow rates that must be accommodated in a full RCT design & its implementation.
2. Participant views on obstacles to recruitment and retention in study.
3. Participant views on what would constitute a meaningful primary outcome measure.
4. To obtain an estimate of the variability of outcome measures to inform sample-size calculation
5. To obtain an estimate of the within-subject outcome measure correlations to inform sample-size calculation.
6. To develop and refine resource use data collection methods to inform a future cost-effectiveness analysis. This will included to decrease the amount of missing resource use data and identify the main cost drivers of the intervention.
7. To obtain estimates of likely time frame and costs for a full RCT.

Method

Design

A two arm RCT is proposed for the full subsequent RCT (figure 2), the design of which will be mirrored in the feasibility study to best assess obstacles to recruitment & retention. The study is single blinded with a trial period of 22 weeks from randomisation, comprising of an intervention period of 18 weeks and a 4 week post intervention follow up. This research study will run over a 25 month period.

Group 1 (Control): This group will not receive any intervention from the study but will continue with their standard care.

Group 2 (FES): This group will wear the stimulator and use it with sufficient intensity to cause an active muscle movement of dorsiflexion and eversion for 18 weeks, followed by 4 weeks without FES.

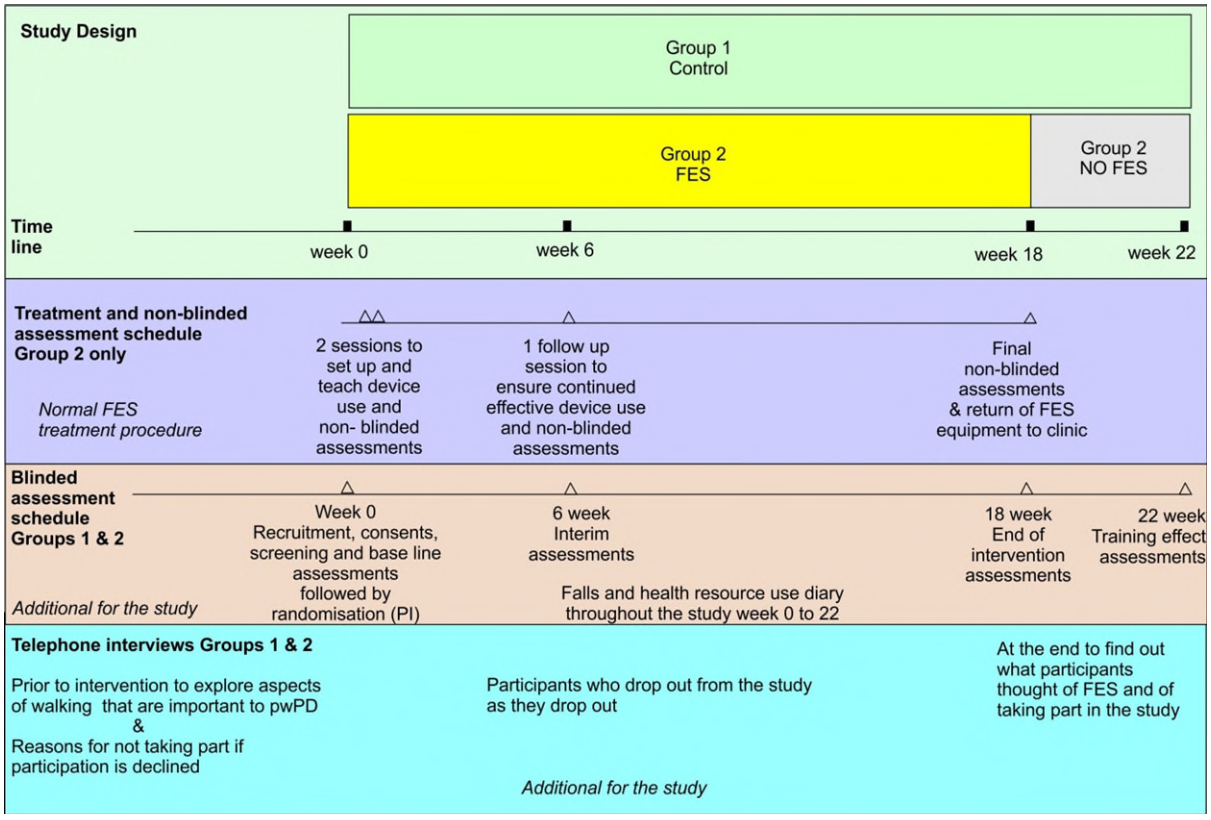


Figure 2. Trial design.

Recruitment, study entry and randomisation
Participants will be recruited to two study centres, one in Salisbury and one in London. The centres will recruit from contrasting rural and urban populations. The Salisbury centre has a long established FES service while the London centre is more recently established.

Participant identification
Potential participants will be identified by members of the Movement Disorders Teams in Salisbury NHS Foundation Trust and the National Hospital for Neurology and Neurosurgery and also the research practitioners of the Wessex (PIC-Participant Identification Centres; Bournemouth,

Southampton, Basingstoke and Bath) from hospital records and from contact in routine clinic appointments. The PICs will confirm a diagnosis of idiopathic Parkinson's Disease and screen for medical contraindications, but not make a formal assessment of mobility other than observing that walking is effected by PD and is slower than normal. Potential participants will be given a recruitment pack containing an information sheet describing the study, a reply slip and a pre-paid addressed envelope to return the reply slip in. The information sheet will contain the research team's details so that potential participants can contact the relevant study centre by phone, e-mail or pre-paid post if they have any questions about the study. Those willing to take part in the study will be able to indicate on the reply if they wish to:

- take part in the study
- do not want to take part in the study, but are happy to take part in an interview to discuss their reasons to help future research
- do not want to take part in any part of the study (and therefore do not need to return the reply slip).

PICs will be asked to record how many pwPD were considered for the study and how many information sheets were given out. The Participant information sheet will also request that people who do not wish to take part also contact the research team at either study centre and give their permission for their contact details to be passed to the qualitative researcher. The qualitative researcher will contact the individual to perform a short telephone interview to determine their reasons for not taking part in the study.

A further source of recruitment is the Parkinson's Society, which has agreed to publicise the study, subject to their own research governance procedures. The trial information sheet will be made available via their web page. PwPD who are interested in taking part will be asked to contact the nearest study centre. If a large number of pwPD contact the centres, participation will be on a first come, first served basis. The study will also be advertised on posters displayed in research active GP surgeries. The poster will instruct interested parties to contact the study centres directly.

Consent and randomisation

PwPD who express an interest in the study will be invited to one of the study centres. The study will be explained to them and any questions that they have about the study will be answered. If they agree to take part, formal consent will be taken by the PI or blinded assessor. The full inclusion and exclusion criteria will then be assessed.

Inclusion criteria:

- aged 18 years and above (no upper age limit)
- idiopathic Parkinson's disease
- Hoehn and Yahr stages I to IV under medication (see table 1)
- difficulty with one or more aspects of their gait (clinical observation by experienced clinician)
    - reduced dorsiflexion or eversion at any point in the swing or weight acceptance phase of gait,
    - bradykinesia demonstrated by a measured 10m walking speed of less than 1.25ms^{-1}
    - festination demonstrated by walking with short rapid strides
    - akinesia demonstrated by exhibiting freezing episodes while walking. This may be in restricted areas such as doorways.
    - hypokinesia demonstrated by walking with a short stride length
- able to walk 10m with appropriate walking aids but without assistance from another person
- able to obtain standing from sitting without the assistance of another person.

- medically stable defined as no significant changes in the participants condition over the last 3 months
- able to understand and comply with the treatment and assessment procedures
- able to give informed consent
- able to start using FES within 2 weeks

Exclusion criteria:

- able to walk 10m in less than 8.0s ()
- other treatment other than standard drug therapy (deep brain stimulation, duodopa, apomorphine)
- atypical or secondary parkinsonism or parkinsonism related to other neurodegenerative diseases
- pyramidal and/or extrapyramidal systems injuries
- untreated or refractory epilepsy (fits in last 3 months)
- pregnancy
- cardiac pacemaker, or other active medical implanted devices
- denervation of the common peroneal nerve or other neurological condition known to cause dropped foot
- severe osteoarticular pathology that involves the calf bones, knee and tibio-tarsal joints or other condition that significantly effects walking
- malignancy or dermatological conditions in the area of the electrodes
- major cognitive impairment; dementia.

Gait speed will be assessed using the 10metre walk test (see Outcome Measures section). Their route into the study, whether from receiving an information sheet from a movement disorders clinic or via the PD Society website, will be recorded. If their diagnosis is not confirmed as idiopathic Parkinson‘s disease, permission will be asked for the researcher to contact the volunteer’s GP or consultant to confirm the diagnosis. If this is the case the baseline measurements and randomisation will be delayed until conformation is received. If not suitable for the study the participant will thanked for their interest and there will be no further involvement for them in the study.

After it has been identified that the participant fits the selection criteria, the base line assessments will be taken by the blinded assessor. For a list of outcome measures taken at base line please see the Outcome Measures Section. Additionally the following descriptors will also be recorded:

- Date of birth and gender
- Date of diagnosis of PD
- Modified Hoehn and Yahr Scale score (see table 1)
- Other medical conditions
- Current medication
- A description of their gait
- Ankle muscle strength (MRC), ankle passive and active range of motion.
- Falls history
- Usual walking distance range
- The participant’s view if what they consider to be the main problem with their walking
- Use of assistive devices
- Social situation and ADL (activities of daily living) assistance requirement, need for assistance with FES equipment (if allocated to group 2)

Once complete, the online database (Pen CTU) will be accessed by the local PI or other member of the team not blinded to the allocation and the participant informed of their group allocation. If allocated to group 1 the participant will be given an appointment for the next clinical assessment appointment (6 weeks). If allocated to group 2 the participant will be given two appointments to begin treatment in the FES clinic.

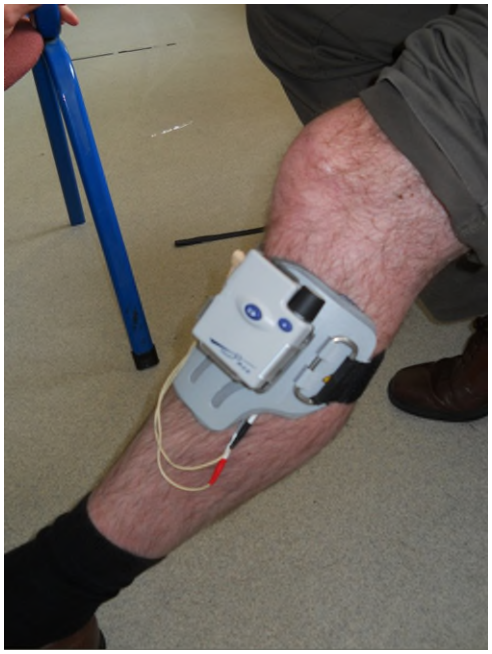
Following consent, but prior to group 2 receiving the intervention, a purposive sample of 24 participants will be contacted by the qualitative researcher to participate in a brief semi-structured interview asking about aspects of walking that are important to them, reasons for taking part, expectations, any reservations they might have and their views about randomisation.

Stage	Modified Hoehn and Yahr Scale
1	Unilateral involvement only
1.5	Unilateral and axial involvement
2	Bilateral involvement without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

Table 1 Hoehn and Yahr Scale[26]

Intervention
The ODFS® Pace and leg cuff

The Odstock Dropped Foot Stimulator (ODFS®) Pace is a small (72 x 64 x 28 mm 112gm) battery powered single channel FES device used to correct dropped foot in gait. The device uses self-adhesive skin electrodes over the common peroneal nerve at the point it passes over the fibula bone and where the nerve enters the anterior tibialis muscle. These electrodes can be mounted on the inside of a leg cuff, enabling repeatable daily placement of the electrodes so ensuring a consistent effects from the stimulation each time the device is used (figure 3). The device is controlled by a pressure sensitive foot switch placed within the shoe. Stimulation begins when weight is taken from the switch and ends just after weight is retuned and hence dorsiflexion is provided through the swing phase of gait. In addition to dorsiflexion, common peroneal nerve stimulation also causes eversion and this significantly increases the stability of the ankle at heel strike. Stimulation feels like pins and needles and most people quickly become used to the sensation. The device is equipped with a foot step counter which will be used to monitor stimulation 'dose' and compliance with the protocol. The device is CE marked.



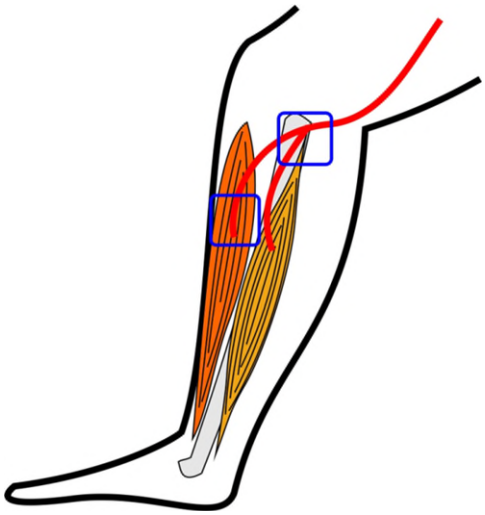


Figure 3a. 3b.
a) The ODFS Pace and leg cuff, b) the cuff mounted electrodes relative to the underlining common peroneal nerve, fibula bone, tibialis anterior (dorsiflexion) and peronei longus (eversion) muscles.

Stimulator configuration and clinical application

The device will be fitted to the leg the treating clinician identified as having the greatest deficit in dorsiflexion and eversion. The current will be set at a sufficient level to cause an active comfortable muscle contraction, correcting any deficit present in dorsiflexion and eversion. The participant/carers will be taught how to fit the device, how to identify the correct movement of the foot and how to adjust the position of the cuff and stimulation intensity to produce this movement. The participant will return to the clinic the next day and will be asked to demonstrate that they are able to use the device. Any further training will be given as required. Walking speed with and without the device will be recorded in accordance with the standard clinical protocol used in the Salisbury FES clinic[5]. The participant will return to the clinic 6 weeks after the baseline measurements to check that they are continuing to use the device effectively and any required adjustments made or further training given. They will be asked to contact the clinic if they experience any problems. Contacts will be recorded.

End of Study

The ODFS and leg cuff will be returned to the study centre at week 18.

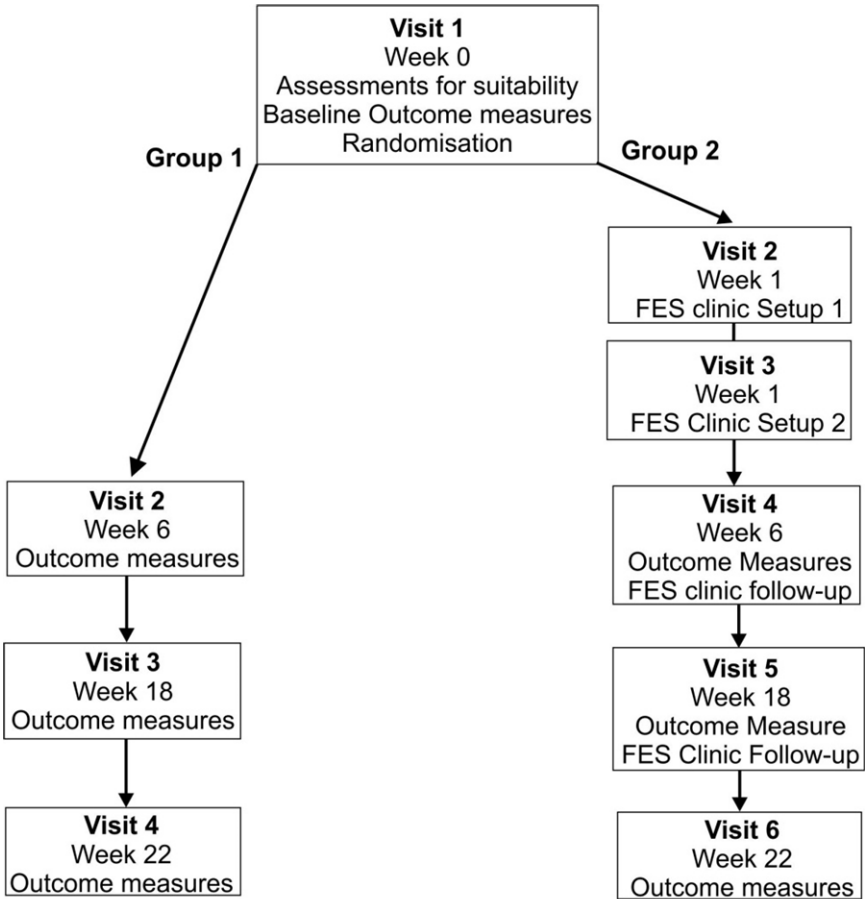


Figure 4 Study visits. (Week 0 assessment may be split over 2 visits if conformation of diagnosis of idiopathic PD is required from the GP or medical consultant.)

All outcome measurements will be performed in the same period each day relative to the participant's medication routine. Assessments will be made on the same day as the group 2 treatments sessions but before the treatment session has taken place. All assessments except those done wearing the device (group 2 only) will be made by the blinded assessor. Participants in group 2 will be asked to attend the assessment session not wearing the device. This will be checked by the clinic receptionist on arrival at the clinic. They will be asked to wear clothing that covers the area of the leg where the FES device is worn so that any residual marks cannot be seen (clipped leg hairs, electrode gel, pen marks used to help position the cuff etc.) Assessment sessions will take place in a separate location to the treatment sessions to maintain blinding of the assessor.

Primary outcome for the feasibility study

Recruitment and retention rate

- This will be calculated from records of the number of pwPD:
    - Who are identified as candidates and referred to the study
    - Who consent to join the study
    - Who are assessed
    - Who are found to be suitable for the study
    - Who complete the protocol
    - Who complete the treatment protocol

- The reasons for not joining the study or completing the protocol.

A qualitative evaluation of participant's experience of FES and study participation.

Outcome measure for the Subsequent RCT

Both groups will be assessed by the blinded assessor at weeks 0, 6, 18 and 22. Assessments at week 22 are 4 weeks after FES use has stopped. Outcome measures for group 2 made with the device switched on will be taken by the treating clinician at week 0, 6 and 18 only. We will attempt to measure outcomes on all participants even if they are no longer using the FES (group 2) or have obtained the FES from another source (group 1).

Primary outcome Subsequent RCT (provisionally).

Effect on bradykinesia.

- Walking speed over 10m (10mWT) with device turned off [5]. The measurements will be made in an open gym over smooth flooring. 1m before and after the 10m will be allowed for acceleration and deceleration giving a total walk length of 12m. A single instruction to "walk briskly but safely" will be given. Two measurements will be taken and the second measurement used for analysis. The first walk is used to eliminate the warm up effect. The difference between the groups will be compared using 4 samples. (weeks 0, 6, 18, 22)

Secondary Outcomes for subsequent RCT

Effect on the impact of PD motor symptoms and activities of daily living

- Unified Parkinson's Disease Rating Scale[28] (weeks 0, 6, 18, 22)

Effect on disease specific health related quality of life

- PDQ39 Parkinson's Disease Questionnaire 39[29] (weeks 0, 6, 18, 22)

Effect on general health related quality of life

- EQ-5D-5L (EuroQol questionnaire 5 dimension 5 level) This generic quality of life measure and has been validated for use in PD, will be used to calculate QALY (Quality Adjusted Life Years)[33, 47] (weeks 0,6,18, 22)

Effect on Akinesia

- The 'new' freezing of gait questionnaire (NFOG-Q)[30] (weeks 0, 6, 18, 22)

Effect on Hypokinesia

- Stride length while performing the 10mWT with device turned off[19, 21] (weeks 0, 6, 18, 22)

Effect on balance, falling and fear of falling

- Effect on falls – Falls diary recorded with device turned on or off recorded in the trial diary[8,15,47]. (throughout the study)
- Falls Efficacy Score – International questionnaire[31,47] (weeks 0, 6, 18, 22)
- Mini-BESTest (Mini Balance Evaluation Systems Test)[39]

Assessments done by the treating clinician (non-blinded)

Effect on walking when the stimulator is turned on will be assessed by the treating clinician. This is standard clinical procedure in the Salisbury FES Clinic.

- Stride length in 10mWT with device turned on (week 1, 6, 18)
- 10m walking speed (10mWT) with device turned on (week 1, 6, 18)
- Borg rating of perceived effort scale[45] (week 1, 6, 18)

The measurements will be made in an open gym over smooth flooring. 1m before and after the 10m will be allowed for acceleration and deceleration giving a total walk length of 12m. A single instruction to "walk briskly but safely" will be given. Four measurements will be taken, the first two without FES, the third with FES and the fourth without FES. The second and third measurements will be used for analysis. The first walk is used to eliminate the warm up effect. The fourth walk will be compared with walk two to measure immediate short term carry over effect. At the end of each walk the participant will be asked to rate the effort of the walk using the 10 point visual analogue Borg scale [45].

Choosing the primary outcome measure for subsequent RCT

- Change questionnaire. To assist in the choice of primary outcome measure participants in group 2 will be asked to complete a short custom designed questionnaire that asks them to rate the change they have experienced in different aspects of walking and Parkinson's Disease since using FES . They will be asked to indicate, which in their opinion, is the most important effect. Administered by the treating clinician at the end of treatment. (week 18)

Resource use data collection:

In this feasibility study we will develop resource use data collection tools to prepare the future economic evaluation.

- Intervention delivery case report forms. We will design case report forms to collect resource required to deliver the intervention. These forms will collect information on the staff grade and time required to inform and train the patient to use FES at both visits. We will also record on trial forms when staff had been trained to administer FES at participating centres, and whether new staff required further training. The study team already developed a standard training packaged that is delivered at a fixed cost in centres requiring training. Staff at current participating centres have been trained.

- Health Resource Use Questionnaire. This questionnaire will be included within the follow-up data collection forms and it will be custom designed for the study in consultation with the PAG. It will be used to identify and record patient reported resource use and will be facilitated by the blinded assessor at the 6, 18 and 22 weeks. These questionnaires will include questions about NHS community based resources (GP and nurse practice visits), social and other services, hospital visits to A&E, outpatient and inpatient admissions, and which hospitals were attended, prescribed and over the counter medication use, time off work and leisure activities and informal care.

- Review of medical notes. At the end of the study, the blinded assessor at each study centre will review hospital records to collect secondary care resource use for patients from date of randomisation to 22 weeks follow-up. This information will be collected onto study-specific case report forms and entered on the study database. Case report forms will collect secondary care visits at trial centres by type of visit: A&E, outpatient visits, and inpatient and day case. A&E forms will include attendance date, reason for attendance and whether patient was admitted to hospital. Outpatient forms will include appointment date and clinic, procedures received and procedure and diagnosis codes if known. Inpatient and day case visits included admission and discharge dates, whether admission was elective, number of nights in critical care ward, reason for admission, major diagnostic or surgical procedures, and OPCS procedure and Healthcare Resource Group (HRG) codes when available.

- Resource use log. Participants will be asked to record contacts with the NHS, social services and other health related services in the trial diary. This will be used as "aid memoir" when completing the Health Resource Use Questionnaire in clinic at follow-up, but not as the resource use end point measure. The same log will be used to record falls (see "Effect on balance, falling and fear of falling" section above).The diary will be returned to the study centre at each assessment. (weeks 6, 18, 22)

An embedded qualitative study to participant's experience of FES and trial participation in the feasibility study

In order to explore participant's views of the study and suggest changes for future research, a series of semi-structured interviews will be conducted before and after participants take part in the feasibility study. The interviews will be carried out by a research at the University of Southampton and will be independent of the treating clinicians or blinded assessors. The interviews held prior to the intervention will explore what aspects of Bradykinesia and gait are important to the participants, participants' views on the recruitment process and recruitment information, and factors that influenced decisions to take part in the study. The interviews held after the feasibility study will explore the effect of the intervention on the participants, their view of the impact or importance of any changes experienced and overall experience of taking part in the study. This will involve exploring participants' views of the factors that they believe may influence retention in the study and adherence to the study with protocol. As participants will be recruited from two centres it is anticipated that the majority of interviews will be telephone interview. However, as Parkinson's disease can affect a patient's speech, participants will be offered the choice of a face-to-face

interview in their home or another location (i.e. a room at one of the centres) if they feel they are unable to take part in a telephone interview.

All suitable candidates who fulfil the feasibility study inclusion criteria will be invited to take part in the qualitative study. To ensure a diverse sample of participants views are explored within the interviews, a purposive sample of participants will be selected to take part in the pre and post telephone interviews from the sample of participants who agreed to take part in this phase of the study. It is anticipated that 24 participants take part in interviews both pre and post study. In addition to interviewing the people who take part in the study, ethical approval will be sought to invite participants who have been given an information pack but decline to take part in the study (but state that they are happy to be contacted on the reply slip) or begin the study and then withdraw to take part in an interview to determine their reasons. This will involve not more than six participants giving a total of 54 interviews overall.

Each interview will take no longer than 40 minutes and will use an interview schedule outlining the main topics with a series of sub-questions and prompts, derived with the assistance of the Patient Advisory Group. There will be a total of four different interview study for the different stages of the study and groups of participants we would like to interview:

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 with withdraw from the study before the study end, but are happy to take part in the interview

Participants will be asked to complete a separate consent form to the main study as this will outline key aspects related to the qualitative study, such as the interviews (telephone or face-to-face) being recorded using a digital recorder, transcribed verbatim and anonymous quotes used in publications and presentations etc. For the telephone interviews, participants will be send a copy of the consent form prior to the date of the telephone interview and asked to sign it and return it in a pre-paid envelope. They will have the opportunity to contact the researcher leading the qualitative work and ask any questions about the study or consent process. On the day of the telephone interview, the researcher will read out loud the signed consent form and ask verbal consent to clarify that the participant is still in agreement with all aspects of the consent form. For face-to-face interviews, the researcher will obtain consent on the day of the interview. The participant will be given the opportunity to ask any questions about the study and will be asked to complete a consent form before taking part in the interview. Prior to the interview, participants will also be sent a copy of the interview topics to enable them to start thinking about the answers they will give in the interview. If during the interview the participant becomes tired, the interviewer will offer the participant the option of discontinuing the interview and recommencing it at another time.

The analysis for all interviews will involve the stages outlined by Braun and Clarke (2006) consisting of familiarisation of the data through reading and re-reading the transcripts, generating the initial codes, identifying and reviewing themes, defining and naming the themes, and developing these

provide the set of suggestions and considerations to inform a further trial. The QSR NVivo software package will be used to assist in the process of the coding and analysis.

Blinding

All assessments except those done with the device turned on and post protocol focus groups will be made by an assessor blinded to group allocation. Blinded assessments will be made on the same day as the treatment sessions prior to the treatment session taking place. Participants in group 2 will be asked to attend the assessment session not wearing the device.

Compliance / dose

Use of the stimulator will be monitored using the stimulators internal usage log. This will be used to count the number of steps taken with electrical stimulation and the length of time spent walking with the device turned on.

Sample size

The sample size calculation for the current feasibility study is configured in terms of estimating recruitment & retention rates, along with the estimation of between subject variability (SD) and within-subject correlation, both required to estimate the sample-size for the repeated measures ANCOVA design envisaged for the subsequent full RCT. A total of 68 participants will enable estimation of:

1. A recruitment rate circa 50% with a 90% confidence interval +/-7%.

2. A retention to follow-up rate circa 60% with 90% confidence interval +/-10%.

3. A between subject standard deviation for outcome variable with upper limit on 90% +/- 10% of true value.

4. A within-subject correlation I for outcome variable circa 0.7 with 90% confidence interval *+/- 10%. (*Using a conservative estimate of R of 0.7, based on an observed R of 0.85 in observational studies on the same patient population. Since the time frame for the proposed full RCT will be longer than that of the observational studies (18 weeks as opposed to 8 weeks), we might reasonably expect a lower correlation over time.

Sample size calculations from NCSS PASS v.11

Randomisation

Randomisation will be administered centrally by the clinical trials unit using web based computer generated random allocation. Randomisation will take place after the first set of outcome measures has been taken. Block randomisation will be used to ensure equal numbers of participants in each group at each centre.

Data management

The data from case report forms and participant questionnaires will be collected on paper forms and entered into an on-line electronic database by the blinded assessor or treating clinician who collected it. Electronic records will be anonymised by use of a participant identification number. Data entry by the blinded assessor and treating clinician is preferred as they will have full understanding of the data they are entering and hence are less likely to make errors. The paper records will be retained to allow checking for data errors. The database will be designed, implemented and verified by the Clinical Trials Unit (PenCTU).

Analysis

The primary objective of the feasibility study is to obtain estimates of the recruitment & retention rates and measures of variability and correlations for the primary outcome measure, of sufficient quality to underpin robust sample-size estimation for the subsequent RCT. As this is a feasibility study, analysis of outcome measures will focus on descriptive statistics relating to rates for eligibility, retention, adherence to protocol, planned outcome measures and data completeness, both overall and by group allocation. As specified in the sample size calculations, 90% confidence intervals will be used to assess the precision of these estimates. No imputation methods will be used if there are missing data. Participants will be analysed in the group they were randomised to. Measures assessing the feasibility and patient acceptability will be reported along with cost estimates for the RCT. All statistical analyses will be undertaken by the project statistician. For the full RCT we currently anticipate undertaking between group comparisons of walking speed (assuming that will be the primary outcome measure) using ANCOVA with baseline walking speed as a covariates.

This is a feasibility study for a subsequent larger RCT, and as such has not been powered to detect a full range of clinically important differences in primary outcome. Indeed one of the main aims of this feasibility study is to inform a sample size calculation for the future trial. However we will use the data from the study to calculate preliminary estimates (with 95% confidence intervals) of effect size for outcome measures at each measurement time point. This will:

- Help us develop and test the methods of statistical analysis for the subsequent trial,
- Help to assess the plausibility of the effect size that will be used in the sample size calculation for the future trial and
- Help in informing the decision on the timing of the primary end point for the future trial.

In calculating preliminary estimates of effect size we will use an intention-to-treat approach, take into account study centre, and use the baseline of each outcome measure as a covariate.

Health economic analysis

In this feasibility study we aim to design and pilot the data collection methods for the future economic evaluation. We would expect that FES would have life time health benefits and costs that would carry on beyond the time frame of the trial. The future economic evaluation will include a within trial cost-utility analysis and an analytical economic decision model to capture life time health benefits and costs deriving from the intervention.

In this feasibility study, the economic analysis will be intention to treat and we will mainly report descriptive statistics overall and by group allocation when informative for the future trial. We will:

- Apply UK preference based tariffs for the EQ-5D-5L questionnaire responses to derive utility scores at baseline and follow-up time point. Inspect the distributions of these scores for baseline imbalances, and floor and ceiling effects. Derive quality adjusted life years (QALYs), using the area under the curve approach[46].

- Develop the data collection tools for a within trial economic evaluation. This will include collecting patient reported resource use from questionnaires and hospital visits data from a review of medical notes. We aim to determine:
    - Rates of missing data, overall and by group allocation, in self-reported and medical notes resource use data collected, in particular for the categories of community based resources, secondary care, total NHS resources, personal and social services use, and productivity losses.

    - Check resource use collected from medical records against self-reported data at trial centres. It is possible that secondary care resource use data collection for the future economic model will be collected from Hospital Episode Statistics (HES) data provided in a tailored data extract from the Health and Social care Information Centre (HSIC). Given the time lag required from hospital attendance through to obtaining a HES extract from the HSIC, it is not feasible, within this feasibility study, to check whether HES data and self-report data match and which method would be gold standard. In this study we will be able to check whether self-reported hospital visits at the study centre match centre's medical records data.

    - Identify potential cost drivers for this intervention.

- Consider the components of the standard staff training courses available to administer FES and the number of staff trained at each session. Standard training is currently provided at £229 per trainee. We will ascertain whether other costing tariffs would be appropriate to value resource use in an NHS roll out of the training package.

Qualitative analysis

For the qualitative phase, the transcribed interviews will be analysed using thematic analysis. Thematic analysis is a flexible approach that provides a systematic means of identifying meaning within the data. This will involve stages outlined by Braun and Clarke (2006)[35] consisting of, familiarisation with the data through reading and re-reading the transcripts, generating the initial codes, identifying and reviewing themes, defining and naming the themes, and verification of final themes. The QSR NVivo® software package will be used to assist in the process of coding and analysis.

Success Criteria

Our first criterion for progression to a full RCT is the acceptability of the proposed intervention to study participants. This is an intervention that can only make a difference if people are happy using it. This research aim is addressed in the proposed qualitative component. Subject to that, the prospect of successful progression of the research question to full trial will be based on a review of the feasibility study outcomes by the Project Management team in discussion with the Participant Advisory Group (PAG) and Study Steering Group. The team will review all aspects of the recruitment and retention experience and the degree of consensus achieved in identifying an appropriate

primary outcome measure for a full RCT. In detail successful progression to full trial will be based on evidence of:

- The willingness of potential participants to participate in the trial through to final assessment, in sufficient numbers to underpin a fully powered RCT. We are aiming for a minimum of 80% retention of participants through to final assessment, this being a reported threshold below which trial validity may be compromised[44]. Failure to achieve this target would not constitute 'failure' as such, rather it will trigger a search for the cause and refinement of trial procedures where required to mitigate such loss. To that end, the concurrent qualitative aspects of the research will explore participants' perceptions of this key aspect of the study. This would be an important factor in subsequent trial design (sample size and number of participating centres).
- Achieving a clear consensus amongst participants as to the most meaningful outcome measure(s) for the subsequent study.
- Obtaining robust estimates of the variability and correlation measures required for sample-size calculation.

In addition, the review will consider whether:

- Eligibility criteria were acceptable and adequately defined.
- Treatment pathways were acceptable and adequately defined.
- Outcome measures and data collection methods were feasible and adequately defined.
- Processes of patient identification and recruitment were feasible and adequately defined.
- Patient information materials are fit for purpose or in need of refinement.

Study Management

Day to Day management will be by the CI Paul Taylor. Monthly team meetings will be held between the blinded assessor, treating clinician and PI to review recruitment, practical issues and adverse incidences at each centre. The CI will produce a 6 monthly report summarising the progress of the project, which will be circulated to the whole research team, Patient Advisory Group and Steering Group.

The full Research team (applicants, recruited researcher and treating clinician) will meet formally every 6 months to discuss the progress report and plan any required actions. Additional meetings will be held in the start-up period of the project to finalise the protocol, prepare and agree study documentation and research ethics/governance applications. Where appropriate, meetings will be held by skype.

A steering committee will be formed consisting of independent PD experts, including people who have PD and their carers. The committee will meet every twelve months throughout the project and communicate via electronic media as required through the project. The committee will receive

project progress reports every 6 months. The team will advise on development of the protocol, review the progress of the study and final report.

Our Patient Advisory Group (PAG) will provide us with important patient perspectives on all aspects of the project. The group will meet at regular intervals and particularly in the start-up phase of the project and in advance of the steering group meetings. At these meetings the protocol and study documents will be presented to the committee members and discussion facilitated to determine the PAG member's opinions. Where appropriate, documents will be sent in advance of the meeting to allow more time for understanding of the material. PAG members will be offered training in research methods and the details of the study by the PI. They will also be given the INVOLVE pack and their expenses for attending meetings and reviewing documents will be paid. The PAG will advise on recruitment strategies and help with any problems that we encounter. They will also highlight important questions to be included in the interviews and advise on project documentation, information and publicity material. Sheila Nell, the local PD Society representative, and a member of our PAG will be part of the trial steering committee and advise on the overall conduct of the study.

Where appropriate, electronic media will be used to facilitate meetings, where geographical distance may be a barrier to efficient use of time.

Ethical considerations

Ethical review will be applied for through IRAS (integrated Research Application System. The CI will be responsible for preparation of this submission and any subsequent substantial amendments. The CI will also be responsible for registration of the trial with the ISRCTN (International Standard Randomised Controlled Trial Number).

There are small risks associated with electrical stimulation which are no greater than when FES is applied in the clinic with patients of other neurological conditions for which the technique is well established. These may include discomfort from the sensation of stimulation and irritation of the skin. All the usual procedures used in the clinic will be followed minimise the risk of these adverse effects. If a participant experiences any significant adverse reaction, treatment will be stopped. To enable "attention to treat" analysis, the participant will be asked to attend any reaming assessment sessions.

Adverse and serious adverse events

All adverse events (events that result in minor injury or discomfort to the participant or other individual associated with the study) will be recorded and reported to the CI together with any action taken by the team members. The CI will decide if any further action is required.

Serious adverse events (events that cause injuries requiring medical intervention or death) will be reported to the CI who will immediately inform the sponsor and ethics committee. If the serious adverse event is device related, the MHRA will also be informed. The PI in consultation with these parties and the co-applicants will decide whether to suspend the study.

Early termination of the study

The study would be terminated in the unlikely event of the product being evaluated being withdrawn from the market. If an identical or very similar study were published negating the need for this study, termination would be considered. Termination may also be considered in the event of a serious adverse event.

Project time line

The project will formally run for 25 months with a 6 month lead up to allow time for obtaining ethical approval, other research governance activities, recruit the blinded assessor and to finalise data collection paper work. The first month of funded project will be used for training, final testing of data collection forms and PIC visits. Recruitment will start at month 3 and will run for a maximum of 16 months, assuming a minimum recruitment rate of 1 participant per week but with project capacity of up to 2 a week being possible. The final 3 months of the study will be used for data analysis and reporting. Figure 3 shows a Gantt chart for the project.

Dissemination

The study results will be submitted to a peer reviewed journal. A synopsis of the results will be presented to the participants at a feedback event and in writing through the post. The synopsis will also be posted on the department web page www.salisburyfes.com. We will present the results at the Parkinson UK research meeting and at the International Functional Electrical Stimulation Society conference.

Criteria for authorship will be participation in all or part of the following:

- contribution to the study protocol / grant application,
- execution of the study,
- analysis of the results
- contribution to writing publication

Access to data and confidentiality

All information collected during the course of the research will be kept strictly confidential. Each participant will be given a unique code that does not contain any personal details. All data collected will be anonymised and confidentiality will be maintained at all times.

Participants clinical records recorded within this study will stored in accordance with the Hospitals' procedures. Ammonised research records will be kept in a secure location for a period of 10 years.

Access to the study raw data will be restricted to the named co-applicants and research staff working on this study. Collated data will be made available to investigators outside the team after the study is completed and disseminated on request to the CI.

Audit of research governance

The trial sponsor will perform an annual audit of the studies research governance procedures.

Provision of post study intervention

FES is not a standard treatment for pwPD and is not currently funded by most areas. If at the end of the study period the treating clinician and the participant believe that it is in the participant's best interest to re-commence FES (following the 4 week period of treatment withdrawal) the clinician will pursue funding for continued FES treatment from the NHS. If this is not available, participants will be offered the opportunity to self-fund their continued use of FES through Odstock Medical Limited.

Statement on competing interests

The lead applicant and CI, Dr Paul Taylor was the inventor of the original Odstock Dropped Foot Stimulator (ODFS®), co-inventor of the ODFS® Pace and is named on the patents for the devices[40,41,42.] The patents are assigned to Salisbury NHS Foundation Trust. In 2005 he was co-founder of Odstock Medical Limited (OML), the first company set up by an NHS foundation Trust in England. The company produces and markets the FES equipment and provides clinical FES services to the NHS. 86% of OML is owned by Salisbury NHS foundation Trust and its Charitable Trust and OML pay the Trust a licence fee for use of the IP. At the time of the setup of OML Dr Taylor was allocated 150 shares, which he paid for at a rate of 1p per share. Shares do not pay a dividend, are not saleable and would only have a value in the unlikely event of OML being sold by the Trust. Dr Taylor remains a Salisbury NHS Foundation Trust employee with 40% of his time being seconded to OML for provision clinical, training and R&D services. To avoid any perception of bias the following arrangements will be put in place.

- The Steering Group will be chaired by another member of the team, independent of OML, to be agreed at the first Steering group meeting, before the start of the study
- The study data will be securely held in the on-line database by PenCTU and verified by other members of the team
- The analysis of the results will be by the study statistician, health economist and qualitative researcher, who are independent of Salisbury NHS Foundation Trust
- Reports and publications will be agreed by and only by the research team, PAG and Steering group

Month	6	5	4	3	2	1		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Pre start date activities Research ethics submission and acceptance Obtain R&D permission and Trust Sponsorship Obtain permission from the PD Society for trial publicity Recruit blinded assessors and Health Economist Recruit PIC sites through the Wessex CRN network Develop supporting material for PICS Develop outcome measures data base and randomisation system (Plymouth CTU) Apply for ISRCTN RCT and UPDRS registration							PROJECT STARTS																									
Assessor training Testing of forms, databases and recruitment material																																
Initial PIC visits																																
PIC follow up visits and monitoring																																
Participant recruitment																																
Participants active trial																																
Analysis																																
Report submitted + feedback events																																
Steering group meetings																																
Patient Advisory Group meetings																																
Research group (applicants plus treating clinician and blinded assessor) meetings																																
Month	**6**	**5**	**4**	**3**	**2**	**1**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**

Figure 4 Project Gantt chart

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3-4
Protocol version	3	Date and version identifier	1,8 and on page footer
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____1, 2_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____, 8, 9, 10, 11___
	6b	Explanation for choice of comparators	_____10____
Objectives	7	Specific objectives or hypotheses	_____11____
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	___12 - 25__

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___12_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	____13, 14___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____15 – 16__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	_____26_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	_____15, 22___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____12_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____17 - 21_
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____12, 17___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____22_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____13_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____22_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____22_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____22_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	_____22_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____17 -21__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____18___
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____22-23___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____23-24_____
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	_____23-24_____
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	_____23-24_____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____n/a_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____26____

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	26
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25-26
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	26
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	26
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	27
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	28
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	27
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	27
	31b	Authorship eligibility guidelines and any intended use of professional writers	27

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____27_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____separate document_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.