The Efficacy of Peroneal Nerve Functional Electrical STimulation (FES) for the Reduction of Bradykinesia in Parkinson's DiSease: An Assessor Blinded Randomised Controlled Trial

(STEPS II)

Assessment of electrical stimulation to improve movement for people who have Parkinson's disease

PROTOCOL

Version 2.1 22.10.2025

IRAS number:	**330866**
ISRCTN:	**13120555**
FUNDER'S reference:	**NIHR131791**

This protocol has regard for the HRA guidance and order of content.

This study has received ethical approval from Yorkshire & Humber – Sheffield Research Ethics Committee.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and in accordance with the UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018), the principles of Good Clinical Practice (GCP) and the Sponsor's (and any other relevant) SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: 	Date (dd/mm/yyyy): 26.03.2024
Name (please print): Tumi Kaminskas	
Position: Head of Research	

Chief Investigator:

Signature: 	Date (dd/mm/yyyy): 28/07/2023
Name: (please print): Paul Taylor	

Senior Trial Statistician:

Signature: 	Date (dd/mm/yyyy): 28/07/2023
Name: (please print): Siobhan Creanor	

PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
AM08-NSA07	2.1	22.10.2025	Abbey Tufft	Clarification added to primary objective wording in Sections 3.1, 3.3 and Table 1 that the primary objective/outcome measure relate to change in walking speed between baseline and Week 18. Section 6 updated with the names of the eight participating centres. Section 8.3.2.2 updated to include collection of Beech Band and CUE1 device use as walking aids; clarification added that these should be removed when the participant is carrying out study assessments. Section 11 updated to re-categorise 'partial withdrawal' as 'discontinuation'.
AM06-SA01	2	24.03.2025	Abbey Tufft and Maggie Donovan-Hall	Increased Group 1 and Group 3 qualitative sample size to a maximum of 50 and 25, respectively. Reduced the number of qualitative interviews for Group 1 from 2 (Week 18 and Week 22) to one (Week 22). Added clarity that qualitative Group 2 sample could be sourced from partial withdrawals or full withdrawals, provided that the participant consents to this on the withdrawal form.
AM05-NSA05	1.5	21.10.2024	Abbey Tufft	Updated 'Section 12 Participant withdrawal' to specify withdrawal categories (pre-randomisation, partial, full or lost to follow-up) and clarification that if the participant withdraws pre-randomisation they should be replaced. Post-randomisation withdrawals do not need to be replaced. Participant may choose to withdraw from part of the study. Updated 'Section 8.9 Payment' that participant receives £20 voucher for each blinded assessment completed; one voucher, with a maximum value of £100, will be posted to the participant at the end of their time on the study. Travel expense reimbursement process specified; the participant submits this to the site at the end of the study. Site will reimburse the participant and claims the cost back from the Sponsor.

AM03-NSA03	1.4	11.07.2024	Abbey Tufft	Specified in Section 5.1.2 that trial statistician will remain blinded until the SAP is signed off. Updated site information in Section 6 due to site withdrawals. Additional information in Section 8.7 stating that if a participant attends a visit on a day where they are struggling to complete all assessments, the APA stepping task may be omitted followed by the miniBESTest, if required. Questionnaires may be posted to the participant the week prior to the assessment to reduce burden. Protocol deviations forms should still be completed for missing data. Added Produodopa to Apomorphine/ Duodopa exclusion criteria in iii., Section 7.2., and 8.3.2.1 as it is considered a substitute/ extension of Duodopa.
AM02-NSA02	1.3	25.03.2024	Abbey Tufft	Updated Sponsor contact details due to changes in personnel. Added clarification that self-referral forms will trigger an automated email to PenCTU. Increased the time of screening visit from 75 minutes to 90 minutes. Removed North Bristol NHS Trust as a site.
AM01_NSA01	1.2	08.11.2023	Abbey Tufft	Added ISRCTN number to the header. Updated Section 15.2 Data Handling and Record Keeping with the location of data storage for REDCap Community databases. Added confirmation of ethical approval statement to title page. Removed reference to Dorset as a PIC site. Correction of minor spelling mistakes and formatting errors. Added section ’19.3 Communication with trial participants’ to detail updates participants will receive throughout the study.

KEY TRIAL CONTACTS

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Trial Steering Committee –	Associate Professor Emily Henderson (Chair and Independent Expert)

Independent members	Mrs Catriona Keerie (Independent Statistician) Dr Julie Jones (Independent Expert) Mrs Victoria Lynne Wright (PPI member) Dr Martin Rumsby (PPI member)
Data Monitoring Committee- Independent members	Dr Alison Yarnall (Chair and Independent Expert) Ms Lucy Bradshaw (Independent Statistician) Mrs Sarah Lauchlan (Independent Expert)

For enquiries about the STEPS-II trial, email: **steps2.penctu@plymouth.ac.uk**

i. LIST OF CONTENTS

ii. LIST OF ABBREVIATIONS

10mWS	10metre Walking Speed
10mWT	10metre Walking Test
ADL	Activities of Daily Living
AFO	Ankle Foot Orthoses
APA	Anticipatory Postural Adjustment
ACPIN	Association of Charted Physiotherapist Interested in Neurology
AE	Adverse Event
AR	Adverse Reaction
CASE	Compiler Averaged Causal Effect
CA	Co-Applicant
CCG	Clinical Commissioning Group
CE	"Conformité Européenne" (French for "European Conformity")
CI	Chief Investigator
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COM	Centre Of Mass
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
DAR	Device-related adverse reaction
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EMBASE	Excerpta Medica dataBASE
EQ5D5L	EuroQol 5 dimension 5 level health elated quality of life scale
FES	Functional Electrical Stimulation
FES-I	Falls Efficacy Scale - International
FTE	Full Time Equivalent
GCP	Good Clinical Practice
HDAS	Healthcare Database Advanced Search
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
IFESS	International Functional Electrical Stimulation Society
IPG	Interventional Procedure Guidelines

ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Registered Clinical/social sTudy Number
IMU	Inertial Measurement Unit
LEDD	Levodopa Equivalent Daily Dose
L	Left
MAR	Missing at Random
MCAR	Missing Completely at Random
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Multiple Imputation
miniBESTest	mini Balance Evaluation Systems Test
MNAR	Missing Not at Random
N-FOG	New Freezing of Gait Questionnaire
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NMES	Neuro-Muscular Electrical Stimulation
OML	Odstock Medical Limited
ODFS	Odstock Dropped Foot Stimulator
PAG	Patient Advisory Group
PCI	Phase Coordination Index
pCRF	Paper Case Report Form
PDQ39	Parkinson’s Disease Questionnaire 39 (quality of life)
PD	Parkinson's Disease
PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
pwPD	people with Parkinson's Disease
QC	Quality Control
QA	Quality Assurance
N	No
R	Right
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RfPB	Research for Patient Benefit
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SDAR	Serious Device-related Adverse Reaction
SD	Standard Deviation
SDV	Source Data Verification
SoECAT	Schedule of Events Cost Attribution Tool
SOP	Standard Operating Procedure
SSI	Site Specific Information
STEPS	The Effectiveness of Peroneal Nerve Functional Electrical ST imulation (FES) for the Reduction of Bradykinesia in Parkinson's Disease: A Pragmatic Feasibility Study for a Single Blinded Randomised Control Trial
SUS	System Usability Score
SUDSAR	Suspected Unexpected Device-related Serious Adverse Reaction
TENS	Transcutaneous Electrical Stimulation
TIDieR	Template for Intervention Description and Replication
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TUG	Timed Up and Go test
MDS-UPDRS Scale	Movement Disorder Society Unified Parkinson's Disease Rating
UKCRC	UK Clinical Research Collaboration
Y	Yes

iii. TRIAL SUMMARY

Full title	The Efficacy of Peroneal Nerve Functional Electrical STimulation (FES) for the Reduction of Bradykinesia in Parkinson's DiSease: An Assessor Blinded Randomised Controlled Trial
Short title	Assessment of electrical stimulation to improve movement for people who have Parkinson's disease
Trial acronym	STEPS II
Trial design	A multi-centre, two-group, parallel, assessor-blinded, superiority, individually randomised controlled trial comparing FES in addition to usual care to usual care alone
Primary protocol objectives	To compare change in whole body bradykinesia of people with PD (pwPD) between baseline and 18 weeks post-baseline using FES with usual care versus usual care alone.
Secondary protocol objectives	1. Determine if any effects remain for up to four weeks after FES is withdrawn. 2. Investigate the effect of FES on other aspects of Parkinsonian gait and living life with PD, to inform the need and design of future research. To achieve this, we will produce the first estimates of effect size of FES on secondary outcome measures for: I. Hypokinesia II. Akinesia III. Falls and balance IV. Activities of daily living V. Activity VI. Quality of Life VII. Cost/utility VIII. The effect on gait while using FES 3. Determine how pwPD and their carers perceive the usefulness and practical experience of FES use and its therapeutic effect. 4. Determine the safety of FES in pwPD 5. Investigate potential mechanisms of action of FES in PD, by determining: I. short-term (up to 6 weeks) changes in inter-limb coordination, APA and limb bradykinesia while stepping and walking II. the link between putative mechanisms of action and their relationship to walking speed at 6 and 18 weeks, through causal mediation analysis III. changes over time in the strength of muscles directly targeted and not targeted by the intervention
Study population	People with Parkinson's disease (pwPD)
Trial participants	234 participants recruited in total, 117 per randomised group.
Inclusion criteria	• aged 18 years and above (no upper age limit) • idiopathic Parkinson's disease

	• Hoehn and Yahr stages I to IV • difficulty in walking due to Parkinson's Disease bradykinesia, defined as a measured 10mWS of less than 1.25ms^{-1} (time to complete 10mWT >8s). Participants asked to walk "briskly but safely". • able to walk 50m with appropriate walking aids, but without assistance from another person. Appropriate aids include walking sticks, tri or quad sticks, Ankle Foot Orthoses (AFOs) and similar devices. • able to obtain standing from sitting without the assistance of another person • able to understand and comply with the treatment and assessment procedures • able to give informed consent
Exclusion criteria	• receiving, or scheduled to start, deep brain stimulation, within the next 6 months • scheduled to start apomorphine, duodopa, or produodopa within the next 6 months (those who are currently taking produodopa, duodopa and apomorphine are eligible) • pyramidal and/or extrapyramidal systems injuries • untreated or refractory epilepsy with seizures in the last 3 months • pregnancy or planned 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 conditions that significantly affect walking • malignancy or dermatological conditions in the leg that would be stimulated • major cognitive impairment; dementia • under treatment for an unresolved deep vein thrombosis in the leg that would be stimulated • participating in another interventional clinical trial (observational studies are permitted)
Summary of clinical outcome measures	• Ankle proprioceptive 2-point sensory discrimination • Gradient discrimination sensory test • 10mWT (time taken, stride length, description of gait, phase coordination index (PCI)) • Timed up and Go (TUG) • Dynamometry • Unified PD Rating Scale (MDS-UPDRS) Section 3 • Anticipated Postural adjustment (APA) test • Mini Balance Evaluation Systems Test (MiniBESTest) • Step count from StepWatches

	• Resources use (clinician time and consumables used)
Summary of patient reported outcome measures	• Social situation, Activities of Daily Living (ADL) and view on walking • Walking aid use • Usual walking distance (m) during 'on' and 'off' medication periods • Participation in exercise classes/physiotherapy • Medication changes (Levodopa equivalent daily dose (LEDD)) • New Freezing of Gait Questionnaire (N-FOG) • MDS-UPDRS Sections 1A, 1B and 2 • Falls Efficacy Scale-International (FES-I) questionnaire • Parkinson's Disease Questionnaire 39 (PDQ-39) • EQ-5D-5L • Falls diary • Borg Rating of Perceived Exertion (RPE) score (0-10) • Device-related adverse reactions • Systems Usability Scale (SUS) • FES experience questionnaire
Intervention duration	18 weeks
Follow up duration	4 weeks post week 18
Planned trial period	52 months
Intervention	Functional Electrical Stimulation (FES). The CE-marked ODFS Pace is a small, battery-powered, single channel FES device used to correct dropped foot. Electrical stimulation is applied to the common peroneal nerve using skin surface self-adhesive electrodes placed over the head of fibula and the anterior tibialis muscle. Intervention participants will be asked to walk every day with the device and use the device whenever they feel it assists their walking. The clinical pathway established for multiple sclerosis and stroke patients will be used, with clinical (unblinded) FES set-up sessions at Weeks 1 and 2 and FES follow-up sessions at Weeks 6 and 18. The intervention is used in addition to usual care.
Comparator (usual care)	Treatment as Usual
Qualitative sub-study research questions	• What are the views and experiences of individuals and with Parkinson's using FES within the RCT? • What are the views and experiences of family members or carers of the individuals with Parkinson's using FES within the RCT?
Qualitative sub-study design	A qualitative study using telephone or online video (i.e., Zoom or Teams) semi-structured interviews with both individuals with PD using FES and their family members or carers.

Qualitative sub-study sample size	Group 1 (FES intervention)- up to 50 participants Group 2 (Discontinued FES)- up to 15 participants Group 3 (family members/carers)- up to 25 participants

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL SUPPORT GIVEN
NIHR Efficacy and Mechanism Evaluation (EME) Programme	Total research costs (not including NHS Support & Treatment Costs): £1,529,668.61 Total NHS Support Costs: £8,244.00 Total NHS Excess Treatment Costs: £168,480.00 Total Non-NHS Excess Treatment Costs: £0.00 Total NIHR grant: £1,539,450.73

v. ROLE OF TRIAL SPONSOR AND FUNDER

This trial is funded by the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The Sponsor for this study, Salisbury NHS Foundation Trust, assumes overall responsibility for the initiation and management of the trial in accordance with the UK Policy Framework for Health and Social Care Research.

The Sponsor and funder will not have direct involvement in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The trial was designed by the Chief Investigator and co-applicants with support from the NIHR Research Design Service and the Peninsula Clinical Trials Unit.

vi. ROLE OF THE COORDINATING CLINICAL TRIALS UNIT (CTU)

The Sponsor of the study has allocated tasks associated with overall trial management and data management to the Peninsula Clinical Trials Unit (PenCTU). PenCTU's management of the trial includes the delivery of site initiation training and monitoring. A detailed breakdown of tasks undertaken by PenCTU on behalf of the CI and trial Sponsor is described in a formal written Sponsor agreement and Task Allocation Matrix.

vii. ROLES OF TRIAL OVERSIGHT COMMITEES AND GROUPS

The Trial Management Group (TMG) is chaired by the Chief Investigator and includes representation from the Sponsor, statistics team, PenCTU and patient representatives. It also includes representation from co-investigators and lead for the qualitative component. The TMG will meet monthly to review trial progress and to ensure appropriate management of the trial, in accordance with the terms of reference for the Group.

Trial oversight will be provided by an independent Data Monitoring Committee (DMC) and a Trial Steering Committee (TSC).

The Trial Steering Committee (TSC) is an executive oversight body operating on behalf of the Sponsor and will make decisions as to the future continuation (or otherwise) of the trial. The TSC has an independent chair (Associate Professor Emily Henderson), independent clinician (Dr Julie Jones), two PPI representatives (Dr Martin Rumsby and Mrs Victoria Lynne Wright) and an independent statistician (Mrs Catriona Keerie). The TSC will meet every 6-7 months/at least yearly in accordance with an agreed set of terms of reference, detailed in the TSC Charter, to review the progress of the trial and will report to the Sponsor and Funder.

DMC meetings will be scheduled to precede TSC meetings so that DMC recommendations can be considered by the TSC as appropriate. The DMC has an independent Chair (Dr Alison Yarnall), independent statistician (Ms Lucy Bradshaw) and independent expert (Mrs Sarah Lauchlan). The DMC will meet every 6-7 months/at least yearly in accordance with an agreed set of terms of reference, detailed in the DMC Charter, to monitor study data and make recommendations to the TSC regarding any ethical or safety issues.

The roles, constitution and composition of the two committees will be in accordance with NIHR Research Governance Guidelines[1] and will be described in committee-specific charters produced by the CTU. Independence of committee members will be as defined in the NIHR Research Governance Guidelines.

viii. KEY WORDS:

Parkinson's Disease; Peroneal Nerve Functional Electrical Stimulation (FES); Bradykinesia

[1] NIHR Research Governance Guidelines: https://www.nihr.ac.uk/documents/research-governance-guidelines/12154

ix. PARTICIPANT JOURNEY FLOW CHART

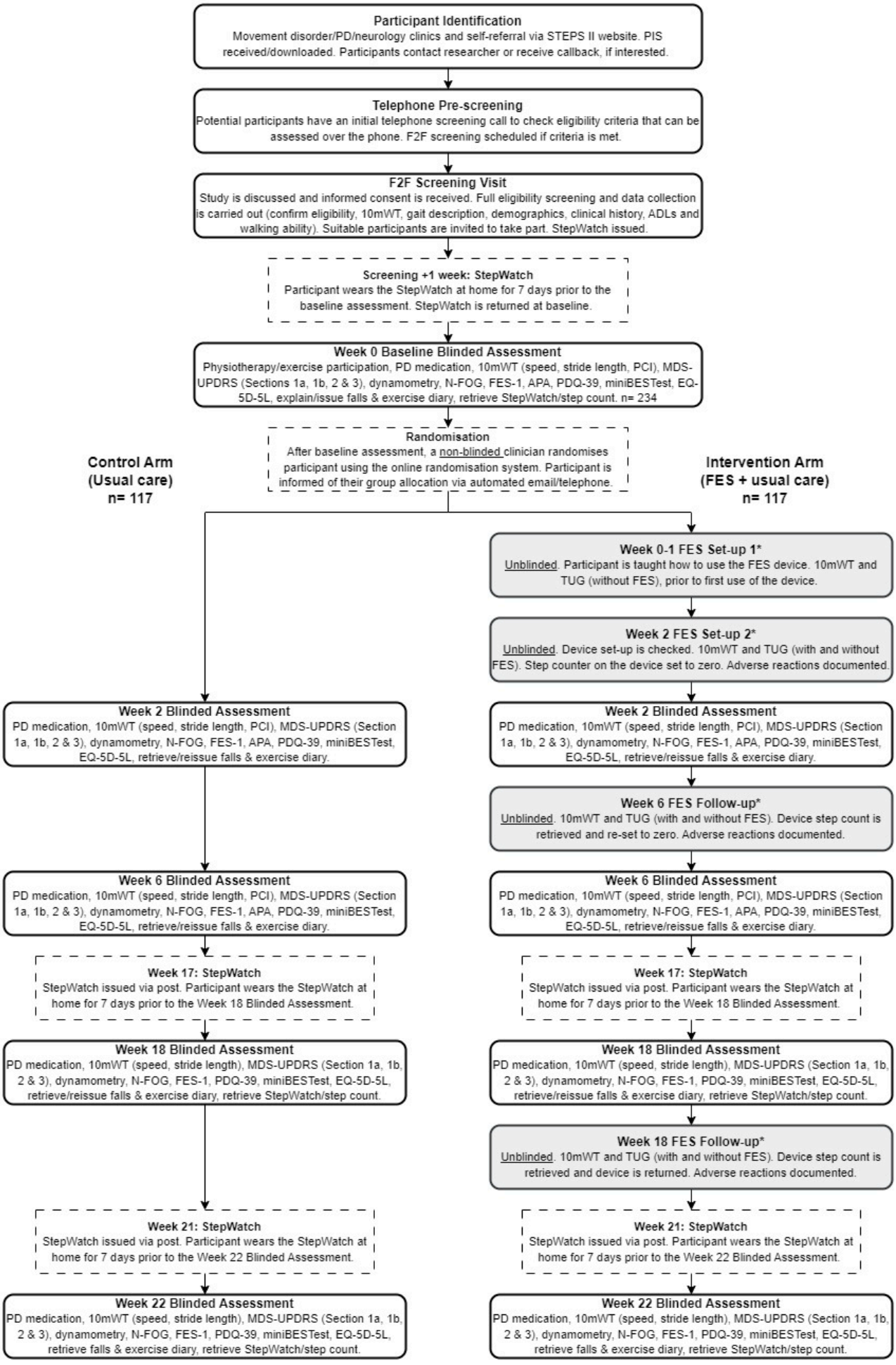

Figure 1: Participant pathway flowchart

*Routine FES treatment pathway

1. BACKGROUND & RATIONALE

1.1. Unmet health need

Difficulty in walking has been identified as a major factor in reduced quality of life for people with Parkinson's Disease (pwPD) and is considered a priority for treatment by pwPD[1]. Walking is often unsafe and 39% of pwPD are recurrent fallers, experiencing a mean of 20.8 falls a year[2], and falls reduction is a key priority for research[3]. These issues can lead to a reduction in overall activity, fitness, mobility, health status and participation in society; it is common for pwPD to become socially withdrawn[4].

Parkinsonian gait is characterised by bradykinesia (slow movement), hypokinesia (small movement size), festination (rapid short strides) and akinesia (difficulty in initiating movement) and freezing (sudden, short and temporary episodes of an inability to move feet forward). Walking is often asymmetric, showing deficits in inter-limb coordination and whole body coordination (i.e. the coordination between postural adjustments and leg movements)[6]. PwPD also have reduced muscle activity, particularly affecting their distal muscles and their ability to dorsiflex (foot lift) their feet[7]. These deficits are associated with slower walking speeds and freezing of gait[8]. Tasks that require precise inter-limb and body-limb coordination, such as turning, are particularly affected and frequently associated with falls[6].

1.2. Incidence & prevalence

Parkinson's Disease (PD) affects about 148,000 people in the UK and is growing in incidence, with approximately 18,000 new diagnoses in the UK each year[9,10]. While it is the second most prevalent neurodegenerative condition, after Alzheimer's disease, its incidence is growing faster than any other neurological condition[2,11]. It is possible that Functional Electrical Stimulation (FES) may be most clinically relevant in those moderately affected (36% of pwPD are in Hoehn and Yahr stages II or III[12]), and who are younger (80% of pwPD are under 80 years of age[13]), indicating a potential UK target population for this intervention of about 42,000 individuals.

1.3. Context of proposed research in terms of current practice

The symptoms of PD can be controlled by drug therapies designed to modify the amount and action of dopamine in the brain[14]. However, even with medication, pwPD still experience significant mobility and balance problems. Further, medication is limited in its effectiveness over the course of the day and over the course of the disease. Medication can also have significant side effects, sometimes leading to poor adherence.

Additional treatments are often used to supplement the effect of PD medication and include physiotherapy, exercise-based therapies, cueing strategies, music and dance therapies[15,16]. Other more recently introduced interventions include deep brain stimulation, trans-cranial or spinal cord stimulation[17]; these procedures are highly invasive, high-risk and high-cost. NICE guidelines limit their use to more advanced cases where standard pharmaceutical therapies are inadequate to control PD symptoms[16]. Despite these interventions, difficulty in walking is still identified as a major contributor to reduced quality of life and research into preventing falls and improving walking is a priority for pwPD[1,3,18].

1.4. Proposed innovation

Functional Electrical Stimulation (FES) uses externally applied electrical stimulation to induce functional movement in paralysed or weak muscles. It is commonly used for correcting dropped foot in stroke and multiple sclerosis (MS) patients by stimulating the common peroneal nerve timed to the swing phase of gait, causing dorsiflexion. It is a NICE recommended intervention for people with dropped foot[19] due to stroke or MS, and is used as an *assistive device*, meaning that the principal

benefit is received at the same time the device is being used. This has been demonstrated by increases in walking speed while using the FES device[20-22], which is a good indicator of gait quality and correlates with the level of functional walking[23]. FES use in stroke and MS is also associated with a reduction in the incidence of falls[24,25], reduced effort of walking[20,26] and improved quality of life[27,28].

When walking speeds are compared with and without the FES device on the same occasion, the difference in speed is referred to as an '*orthotic effect*'. The 'total orthotic effect' compares walking speed with the device switched on with unassisted walking at the beginning of treatment[20]. It has also been noted that FES can have a *therapeutic effect*, leading to an increase in walking speed when walking without the FES device, after the device has been used for a period of time. If this therapeutic effect is short-term, typically minutes to hours, it is referred to as a 'carryover effect' and is thought to relate to increased excitability of the neurological system and short-term adaptive changes[30]. If the therapeutic effect is maintained for a longer duration, it is referred to as a 'training effect' and may be due to additional mechanisms such as muscle strengthening and/or motor relearning[31]. Typically, the orthotic effect is reported to be more clinically significant than the therapeutic effect in people with MS or stroke. For example, in a case series of 111 people with dropped foot due to stroke who used a dropped foot stimulator for 18 weeks, the authors reported a mean total orthotic effect of 0.16ms^{-1} and a mean therapeutic effect of 0.08ms^{-1} [20]. In a case series of 153 people with a dropped foot due to multiple sclerosis and who used a dropped foot stimulator for 18 weeks, a mean total orthotic effect of 0.11 ms^{-1} was reported but no therapeutic effect was observed (mean 0.00 ms^{-1}) [32].

In the STEPS feasibility study involving pwPD[29], we observed different effects of FES on walking speed. The mean total orthotic effect on walking speed was 0.12 ms^{-1} after 18 weeks of FES use, fairly similar to that observed in the above case series in stroke and MS patients. However, the mean therapeutic effect was 0.17 ms^{-1}, indicating that the therapeutic effect is potentially greater for pwPD than for people who have had a stroke or have MS. Further, effects of FES in pwPD appear to occur after a relatively short period of FES use, with one study observing effects after two weeks of FES use[33]. In the STEPS feasibility study, improved mean walking speed was observed after 6 weeks, maintained at 18 weeks, and was still present but slightly reduced at 22 weeks (4 weeks after FES was withdrawn). Some intervention participants reported that intermittent use of FES resulted in longer-term benefits, in some cases lasting several days[29]. This could be characterised as a carryover effect, as improvements occurred after a short period of using stimulation, which then declined before being renewed by another short period of stimulation.

Because this initial observation in pwPD is a different treatment effect to that observed in FES users with other neurological conditions, such as stroke or MS, further research is needed to characterise the effect of FES on bradykinesia, determine its clinical utility in pwPD and understand potential mechanisms of action.

1.5. Potential mechanism of action: a whole body neurophysiological approach

In PD, selective loss of dopaminergic neurons that regulate sensorimotor behaviour, affects internally initiated movements more than movements generated in response to external cues[34]. Movements are associated with abnormal neuronal oscillatory activity in the basal ganglia and interconnected cortical and subcortical areas including areas such as the pedunculopontine nucleus, that are central to the control of walking. This activity entrains populations of neurons, affecting the ability of neurons to change their firing rate, a process that is critical for the control of movement amplitude, driving adaptive, plastic changes[35]. Deficits in adaptation and learning in pwPD will affect their ability to improve walking and hence additional interventions are needed. It has been shown that pwPD can adapt walking patterns in the short term, following split belt treadmill training, where one leg is forced to move at a different speed[36]. This demonstrates that walking can be potentially improved if there is the correct stimulus applied over a long-term basis; FES may provide such a stimulus, in a form that can be used daily without direct clinical supervision. A complex whole body movement such as

walking can be affected by many factors. We propose that FES in the short-term will target two determinants of walking speed, namely deficits in coordination while walking and deficits in limb bradykinesia.

Mechanistic hypothesis 1: FES leads to a short-term (within 2-6 weeks) improvement in inter-limb coordination and whole body coordination when assessed without FES.

Studies have showed that rhythmic sensory cues (e.g. visual and auditory) can lead to immediate improvements in movement amplitude. When applied during walking, they lead to improvements in walking speed and step length[37]. Such cues may be effective by engaging motor circuits that facilitate externally generated, goal-directed movements as opposed to circuits that facilitate internally generated, habitual movements[38]. This may result in a more normal movement-related oscillatory activity and thus potentially improved neuronal signalling and adaptation. FES produces larger and less variable movement of the ankle with each step and hence provides, through direct stimulation or the ensuing movement, regular somatosensory cues[39]. These may normalise oscillatory activity in the brain and allow adaptive mechanisms to occur that address the fundamental deficits in walking, enabling improvement of abnormal inter-limb coordination and whole-body coordination deficits. This study will therefore investigate the hypothesised behavioural adaptive effects of FES and may provide the justification to explore the neuronal effects of FES in future studies using techniques such as cortical-muscular coherence while walking.

Inter-limb coordination can be assessed by measuring the relative timing of stepping using the Phase Coordination Index (PCI), a measure that combines the accuracy and temporal consistency of stepping[40]. It is hypothesised that FES will improve the PCI, bringing it closer to a consistent 180° phase relationship between right and left stride duration. Whole body coordination can be assessed by measuring Anticipatory Postural Adjustment (APA) movements by tracking the motion of the centre of mass (COM) whilst walking or while performing stepping to targets tasks. Medio-lateral APA velocity is reduced in pwPD and this is more marked when stepping from a wide initial stance position[41]. A recent study has shown that Medio-lateral APA amplitude was increased while stepping with FES[5]. We hypothesised that FES use over a period of weeks will lead to a training effect, increasing the medio-lateral APA velocity when stepping to targets and while walking without FES.

Mechanistic hypothesis 2: Repetitive stimulation results in a decrease in bradykinesia in the targeted limb.

Limb bradykinesia has several potential causes and contributory factors[42]. Weakness in an agonist muscle is a key contributory factor in the pathophysiology of limb bradykinesia and could be due to changes in central drive and /or peripheral muscle atrophy. Peripheral atrophy requires 8-12 weeks of training to change, so any early (within 2-6 weeks) changes in strength may be putatively attributed to a change in central drive. Central causes of bradykinesia in PD include a reduction in the activation of premotor cortical areas including the supplementary motor area, over-activity in the cerebellum and enhanced oscillatory activity in motor areas. In addition, impaired sensory discrimination and somatosensory temporal discrimination thresholds are associated with limb bradykinesia and impaired balance in PD[43], suggesting an important role of sensory inputs and integration in limb bradykinesia pathophysiology[42]. Central changes with FES may arise from alterations in afferent feedback either due to direct stimulation of the common peroneal nerve with FES and/or due to more normal walking patterns induced by the direct motor effects of FES. Such afferent changes, potentially coupled with the volitional drive to the ankle dorsiflexors during functional movements, could induce plastic changes in central motor circuits and thus alter limb bradykinesia[44]. Changes in limb bradykinesia would be manifested by an improvement in ankle tapping speed in sitting and ankle velocity while walking without FES whilst changes in the non-affected limb would show less improvement. Early changes in dorsiflexor strength (i.e. within 2-6 weeks) are proposed as an additional indication of a change in central drive and will be compared across sides and compared to changes in non-targeted muscles

(hip abductors) to assess whether changes could be explained by alterations in habitual walking patterns. Causal mediation analysis will be performed to assess potential short-term mechanistic pathways (inter-limb coordination, APA while stepping and limb bradykinesia and strength) on change in the walking speed at 6 and 18 weeks. This will include an assessment of the impact of sensory discrimination abnormalities on improvements in walking speed. By week 18 it is hypothesised that there would be global changes in muscle strength reflecting an increase in walking speed and habitual walking time

1.6. Evidence of proof of concept

To investigate the use of FES to improve walking in pwPD, a systematic review was performed in December 2021. EMBASE, MEDLINE and CINAHL databases and Google Scholar were searched. The search terms were FES, TENS, NMES, electrical stimulation, walking, locomotion, walking speed, gait, bradykinesia, hypokinesia, freezing, Parkinson's disease, with variations. Forty publications were identified, from which only six relevant articles were identified[5,33,45-47,51]. No studies were RCTs or used blinded outcome measures. A search of trial registries did not find any current studies in this area.

In the earliest study, Mann[45] hypothesised that FES used to produce dorsiflexion may assist the initiation of stepping and overcome freezing. Ten pwPD used FES for two months, preceded by a one-month baseline phase and followed by one-month withdrawal of treatment. Results suggested that in the phase when FES was used there was a reduction of freezing, increased gait speed and stride length, both when FES was turned on and when it was turned off, in comparison to baseline. There was also a reduced incidence of falls in the treatment phase. There was evidence of a therapeutic effect, shown by maintained improvement in some gait parameters four weeks after FES was withdrawn. In the second study, the immediate effect of FES on freezing was investigated by Djurić-Jovičić[46]. Nine pwPD used FES at a single assessment and walked a path comprising standing up from the chair, passing through doorways and turning. Gait analysis showed the duration of the double support decreased and variability of stride time and length were reduced by FES. With FES, two participants did not freeze in places along the path where they had without FES. In the third study, nine pwPD who had reduced dorsiflexion or eversion while walking, used FES for two weeks[33]. Walking speed over 10m was measured at baseline and follow-up without FES. There was a statistically significant increase in mean walking speed of 0.29ms^{-1} (95% CI: 0.14 to 0.44) and in step length of 0.09m (95% CI: 0.03 to 0.14) compared to baseline, and mean Tinetti balance score improved by 2.9 points (95% CI: 1.1 to 4.7). There was a statistically significant improvement in the PD symptoms score of the modified PD quality of life questionnaire of 4.9 points (95% CI: 1.3 to 8.5) and a reduction in the short Parkinson's evaluation scale of -5.7 points (95% CI: -7.8 to -3.8), indicating a reduction in the impact of PD. Similar increases in mobility were reported in two case studies. In the first, two participants with Parkinson's plus syndromes, walked faster with FES after 6 sessions using the L300 Go dropped foot stimulator[51]. In the second, a 63 year-old with PD used a dropped foot stimulator for two months and experienced an 85% increase in walking speed[47]. In the final study, 14 pwPD used FES to the common peroneal nerve on a single occation[5]. Using kinematic gait analysis, it was shown that when FES was used, it led to an increase in the amplitude of the Anticipatory Postural Adjustments (APA) while stepping, indicating an improvement in movement control and balance.

These studies suggest that while FES may have a beneficial effect on freezing in pwPD, its primary effect may be on bradykinesia, demonstrated by increased walking speed and improved APA amplitude, with the effect persisting after FES use is stopped (i.e. a carryover effect). A meta-analysis of therapy interventions such as general physiotherapy, exercise, treadmill training, cueing, dance, and martial art, for mobility in pwPD[15] reported a mean increase in walking speed of 0.04ms^{-1}, substantially less than the 0.29ms^{-1} mean increase reported in our case series[33]. It is therefore

indicated that FES may be a clinically useful and efficient intervention for pwPD and should be further investigated.

In preparation for this trial, we successfully completed a 2-site randomised feasibility study (RfPB PB-PG-1014-35012) and, as well as assessing feasibility outcomes, collected the outcome measures envisaged for the subsequent definitive RCT[29]. In the feasibility study, 64 pwPD were randomly allocated 1:1 to receive either usual care or FES with usual care for 18 weeks, followed by 4 weeks of FES withdrawal. Outcome measures were recorded by blinded assessors at baseline, weeks 6, 18 and 22, while intervention participants were not wearing the FES device; assessments were made in the 'on' phase of PD (when medication is effective) and at the same time in relation to the participants' daily medication schedule. Blinding of assessors was maintained for 80% of participants. The mean between-group difference in walking speed was 0.14ms^{-1} (95% CI: 0.03 to 0.26) at week 18 in favour of the intervention group, which was slightly reduced at week 22, after withdrawal of FES (0.10ms^{-1} (95% CI: -0.05 to 0.25)) (see Figure 2). There was a clinically meaningful mean difference in the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score of -3.65 points (95% CI: -4.35 to 0.54) at week 18 in favour of the intervention group, which was not sustained at week 22 (mean difference -0.91 points (95% CI: -2.19 to 2.26)).

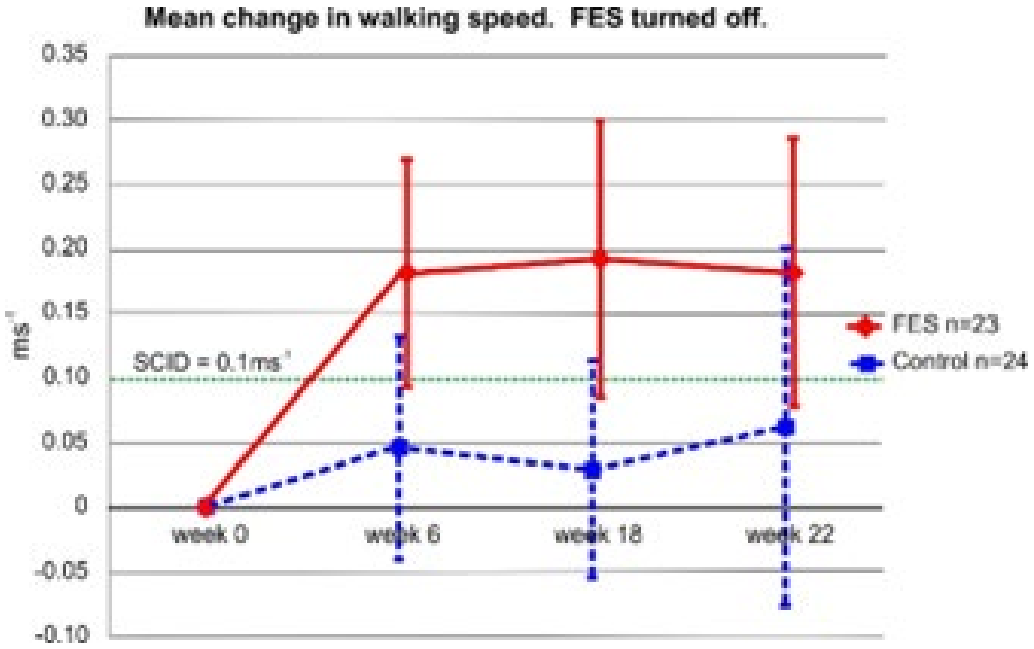

Figure 2: Mean change in walking speed with confidence intervals. SCID = Substantial Clinical Important difference[23]. From the STEPS feasibility study[29].

Twenty-five participants in the FES group completed the "change questionnaire" at week 18. This purpose-designed questionnaire assessed intervention participants' opinion of what aspects of PD had changed since using FES. The most frequently identified factor moderately or considerably improved was walking speed (n=11 participants). The opinion on what was the most important factor was split across nine factors, the most frequently identified being confidence that walks can be completed. Discussion with a group of intervention 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 is an appropriate surrogate measure. Qualitative data from participant interviews suggested increased speed was often associated with an increase in confidence in mobility and a reduced fear of falling, and appeared to have an impact on participation in activities of daily

living, social events and perceived confidence when engaging in these activities. The choice of walking speed as a meaningful primary outcome measure for pwPD for this proposed RCT was further supported through discussion with the Patient Advisory Group (PAG).

In summary, the existing evidence of effectiveness of FES in stroke and MS patients, together with the case series data and the recently completed feasibility RCT of FES in pwPD, provide data supporting proof of concept of the FES intervention, which could help improve an area of unmet need that is identified as being a priority by and for pwPD.

1.7. Recommendations from the STEPS feasibility study

While the study design and intervention were shown to be feasible, in consultation with the Patient Advisory Group (PAG), the following recommendations for protocol adjustments are made:

- The maximum 10m walking speed for inclusion in the study was increased from 0.8 to 1.25ms^{-1}, five months into the feasibility study. This was because many pwPD who were initially screened for the feasibility study were subsequently rejected at the full screening assessment, despite reduced ankle movements, because they walked too fast. Increasing the threshold for inclusion to 1.25ms^{-1} better reflects the cohort of pwPD who have walking problems. This speed also has practical meaning for community mobility, as it is the minimum speed needed to safely use a pelican crossing[48].
- Since starting the STEPS feasibility study, a minimum clinically meaningful difference in walking speed has been established for pwPD of 0.13ms^{-1}. This corresponds to a one level and clinically meaningful change in the Schwab & England Activities of Daily Living Scale[23,49]. This has been selected as the target difference to calculate the sample size for this proposed trial.
- It was found that some participants who had both assessment sessions and FES clinic appointments on the same day found this over-burdensome. To reduce fatigue, clinical FES and assessment sessions should be on different days.
- To avoid short-term carryover effects and to standardise the time between FES use and blinded assessor assessments, FES should not be used on the day of the blinded assessments, before the assessment of outcomes takes place.
- To reduce the possible confounding effect of immediate prior FES use on walking speed measurements recorded without FES, participants in the intervention (FES) group should rest for 10 minutes before the 10m walking speed test is performed by the treating clinician.
- To minimise over-burdening participants, the number of assessments should be reduced to ensure sessions are no longer than 120 minutes long.
- It was observed that there were some differences in the approach to the settings used for the FES devices between treating clinicians. It is recommended that the FES parameters are optimised to ensure comfort and to ensure consistency between centres.
- To evaluate the direct effect of FES on freezing of gait, the Timed-Up-and–Go (TUG) test should be added to the assessments made by the treating clinician. The TUG includes the initiation of walking and turning, two activities particularly affected by freezing.
- It was reported by some participants that they were more active in their daily lives after using FES. It is recommended that a pedometer be used to assess the effect on activity.
- Carers/partners should be involved with application of FES to ensure participants who require assistance can receive help from them. Carers will be encouraged to attend FES clinic appointments so they can learn the application of the device.
- Some participants reported they were more independent while others reported that they needed help from their carer or partner. An assessment of the burden on carers/partners should be included in the qualitative assessments.

2. ASSESSMENT AND MANAGEMENT OF RISK

FES for the correction of dropped foot is a low-risk intervention and there is some considerable experience in its clinical delivery. Since its introduction to the NHS in 1996, over 20,000 people in the UK with stroke, MS, spinal cord injury and other neurological conditions have used FES, with many of these using the device daily. Adherence to FES treatment is estimated to be 86% at one year and 95% of FES users reported that the sensation of FES was acceptable to them, indicating good tolerance of FES[50, 76]. To maximise compliance with the treatment protocol, FES users will be followed up three times in the intervention period. FES users will also be encouraged to contact the FES clinician by phone at any point, if they experience any problems with using FES. The following table summarises the potential risks from the intervention.

Risk	Severity	Incidence	Mitigation	Risk after mitigation
Skin irritation from the electrodes	Minor	10% of patients	- Participants taught skin and electrode care - Only good quality electrodes used - Bi-phasic wave form used, where possible - Intensity kept as low as practical	<2% of patients
Risk of discomfort from stimulation	Minor	Common	- Patients taught the correct use of equipment - Clinicians set levels in acceptable range	Low. Acceptable risk
Poor results achieved due to inexperienced clinicians	Minor - severe	Likely	- Only experienced FES trained clinicians will deliver the intervention - Training will be given by the Chief Investigator.	Low
Falling due to device failure	Minor - severe	Rare	- Equipment checked before issue and at each clinical session - Patient taught correct use of equipment	Very low
Seizure in response to stimulation	Minor - severe	Very rare	- Participants with a history of epilepsy only eligible if they have been seizure free for 3 months or more	Very low
Risk of cardiac event due to stimulation	Severe	Very Rare	- Pacemaker users not accepted on the study	Very low

Spread of cancerous cells due to increase blood flow	Severe	Unknown	- Participants not eligible if they have cancer in the leg that is to be stimulated	Very low
Risk to un-born child	Severe	Unknown	- Participants not eligible if they are pregnant, or planning to become pregnant	Very low

Trial procedures are also considered to be low-risk in terms of potential harm to participants. A detailed risk assessment has been compiled and documented by the CTU and used to inform a monitoring plan, in accordance with CTU standard operating procedures (SOPs). Potential harms caused as a result of participating in this trial will be detected and addressed in accordance with safety reporting work instructions (See Section 13 Safety Monitoring).

3. OBJECTIVES AND OUTCOME MEASURES / ENDPOINTS

3.1. Primary objectives

3.2. To compare change in whole body bradykinesia of people with PD (pwPD) between baseline and 18 weeks post-baseline using FES with usual care versus usual care alone. Secondary objectives

1. To determine if any effects remain four weeks after FES is withdrawn

2. To investigate the effect of FES on other aspects of Parkinsonian gait and living life with PD, to inform the need and design of future research. To achieve this, we will produce first estimates of effect size of FES on secondary outcome measures for:

I. Hypokinesia

II. Akinesia

III. Falls and balance

IV. Activities of daily living

V. Activity

VI. Quality of Life

VII. Cost/utility

VIII. The effect on gait while using FES

3. To determine how pwPD and their carers perceive the usefulness and practical experience of FES use and its therapeutic effect through an embedded qualitative component.

4. To determine the safety of FES in pwPD

5. To investigate potential mechanisms of action of FES in PD, by determining:

I. short-term (up to 6 weeks) changes in inter-limb coordination, anticipatory postural adjustments and limb bradykinesia while stepping and walking.

II. the link between putative mechanisms of action and their relationship to walking speed at 6 and 18 weeks, through causal mediation analysis.

III. changes over time in the strength of muscles directly targeted and not targeted by the intervention.

3.3. Outcome measures

3.3.1. Primary outcome measure

- Change in whole body bradykinesia is defined as the change in 10m walking speed (10WS)[50] recorded using the 10m walking test (10mWT) between baseline and 18 weeks post-baseline, by a blinded assessor.

3.3.2. Blinded secondary outcome measures made by the blinded assessor

Blinded secondary outcome measures are recorded at baseline (week 0) and weeks 2, 6, 18 and 22 post baseline, unless otherwise stated:

- Whole body bradykinesia: 10mWS recorded using the 10mWT.
- Motor symptoms, non-motor symptoms and activities of daily living: Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[52]
- Quality of life: PD summary, mobility and Activities of Daily Living (ADL) indexes derived from the Parkinson's Disease Questionnaire PDQ39[53]
- Akinesia: the 'new' freezing of gait questionnaire (N-FOG)[54]
- Hypokinesia: Stride length, calculated by counting the number of steps taken while performing the 10mWT[45,50]
- Balance: Mini Balance Evaluation Systems Test (miniBESTest, includes Timed Up and Go (TUG))[55]
- Falling and fear of falling: online or paper-based falls diary[24,29], Falls Efficacy Scale International questionnaire (FES-I)[56,57]
- Activity: daily step count averaged over 7 days recorded using a StepWatch[58] at weeks -1 (one week before baseline), 17 & 21.
- Health-related quality of life/utility: EuroQol 5D-5L[59]
- Serious adverse events (SAEs)
- Recording usual care: Levodopa equivalent daily dose (LEDD) and participation in therapeutic activities, such as exercises classes and physiotherapy, as recorded by the participant in the exercise diary.

Blinded assessment of potential mechanisms of action at baseline (week 0) and weeks 2 and 6 post-baseline, unless otherwise stated:

- Inter-limb coordination, assessed using the Phase Coordination Index. This index is derived from the duration and relative phasing of the step duration of each leg, measured using Inertial Measurement Units (IMUs) attached to the feet[40]. Recorded concurrently during the 10mWT.

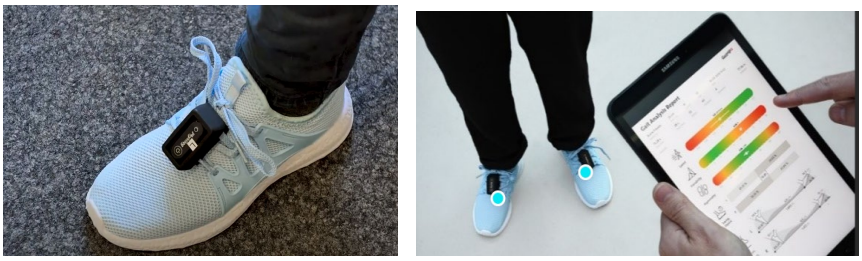

Figure 3: IMU is attached to the participants shoes and round their waist. Sensors are

- Anticipatory postural adjustments (APAs) while stepping onto medially placed targets from a wide based standing position. The motion of the estimate of the centre of mass prior to foot lift

when stepping will provide a direct measure of APAs. This is recorded using IMUs attached to the feet and the lumbar region of the back[41].

- Limb bradykinesia will be assessed via tapping tasks in sitting (concurrently with MDS-UPDRS) and through the maximum velocity of foot motion while walking (concurrently with 10mWS). Foot motion will be assessed via IMU attached to the foot[60].
- Muscle strength of the ankle dorsiflexors and evertors in the targeted and non-targeted limbs, as well as strength in muscles not directly targeted (hip flexors), will be assessed using hand-held dynamometry[61] at weeks 0, 2, 6, 18 and 22 to assess how strength changes over time. Each site will be supplied with the same dynamometer for consistency.

Training and work instructions will be provided to sites on carrying out these tests. Please refer to 'Section 8.4 Blinded baseline assessment visit (Week 0)' and 'Section 8.7 All participants: Blinded assessment visits (Weeks 2, 6, 18 & 22)' for further details on conducting the blinded assessments.

3.3.3. Unblinded secondary outcome measures made by the FES clinician

Unblinded secondary outcome measures recorded at weeks 0-1 (FES set-up clinic) (before FES use for the first time), 2, 6 and 18, unless otherwise stated, in the intervention group only. These assessments will be carried out in the clinical FES sessions and occur on a different day to the blinded assessments:

- The effect on walking will be assessed during the 10mWTs using the following measures:
  - *Time taken (s) to complete the test; used to calculate walking speed.*
  - *Number of steps taken; used to calculate stride length.*
  - *Participant reported Borg Rating of Perceived Exertion (RPE) score (0-10, 0= no exertion, 10= maximal exertion); recorded after each 10mWT*
- The effect of FES on freezing (sudden, short and temporary episodes of an inability to move feet forward) will be assessed using the Timed Up and Go (TUG) test.
- Week 0-1 (FES set-up clinic) assessments will be made without the FES device, before FES use for the first time. The order of these tests are carried out as protocolised:
  - *10mWT*
    - *Walk 1- without FES*
    - *Walk 2- without FES*
  - *TUG – without FES*
- Weeks 2, 6 and 18 assessments will be made both with FES device turned on (orthotic effect) and FES turned off, the order of these tests are carried out as protocolised.
  - *10mWT:*
    - *Walk 1 – without FES,*
    - *Walk 2 – without FES*
    - *Walk 3 – with FES*
    - *Walk 4 – without FES*
  - *TUG*
    - *TUG 1- without FES*
    - *TUG 2- with FES*
- Usability of the FES stimulator will be assessed using the System Usability Scale (SUS)[63] at week 18.
- Participants experience of using the device is assessed with the FES experience questionnaire at week 18.
- Intervention dose will be recorded using the device's internal step counter (steps taken with FES and total time leg is stimulated).
- Device related adverse reactions and SAEs

- Direct intervention costs (clinician contact time and consumables use) will be recorded.

Please refer to ‘Section 8.6 Intervention group only: FES set-up and follow-up visits’ for further details on the FES visits.

3.4. Summary of objectives & outcome measures

Refer to tabulated schedule of events in ‘Section 9 Trial Schedule’ for timings of outcome measures.

Table 1: Summary of objectives and outcome measures

Objectives	Outcome Measures	Timepoint(s)
Primary Objective		
Change in whole-body bradykinesia	Change in walking speed (ms^{-1}) measured using the 10mWT	Week 0, Week 18 Assessor blinded
Secondary Objectives (Blinded Assessor Sessions) *Outcome measures marked with an asterisk (*) are patient reported during the assessment session*		
Time course and carry over of whole-body bradykinesia	Walking speed (ms^{-1}) measured using the 10mWT	Weeks 0, 2, 6 and 22 Assessor blinded
Bradykinesia	MDS-UPDRS Section 3 (task 3.7 instrumented toe tap test)	Weeks 0, 2, 6 Assessor blinded
Hypokinesia	Stride length (m) during 10mWT. Calculated by dividing number of strides taken in 10mWT by 10m.	Weeks 0, 2, 6, 18 and 22 Assessor blinded
Hypokinesia	MDS-UPDRS Section 3	Weeks 0, 2, 6, 18 and 22 Assessor blinded
Akinesia	*The ’new’ freezing of gait questionnaire (N-FOG)[54]	Weeks 0, 2, 6, 18 and 22 Assessor blinded
Falls and balance	*Falls diary[24,29]	Weeks 0, 6, 18 and 22 Assessor blinded
Falls and balance	*Falls Efficacy Scale International questionnaire (FES-I)[56,57]	Weeks 0, 2, 6, 18 and 22 Assessor blinded
Falls and balance	Mini Balance Evaluation Systems Test (miniBESTest, includes TUG)[55]	Weeks 0, 2, 6, 18 and 22 Assessor blinded

Activities of daily living	*MDS-UPDRS Section 1A, 1B and 2	Weeks 0, 2, 6, 18 and 22 Assessor blinded
Activity	Daily step count averaged over 7 days recorded using a StepWatch[58]	Weeks -1 (one week before baseline), 17 & 21 Assessor blinded
Quality of Life	*Parkinson's disease summary, mobility and ADL indexes derived from the PDQ39[53], EQ-5D-5L	Weeks 0, 2, 6, 18 and 22 Assessor blinded
Normal care	*Levodopa equivalent daily dose (LEDD) and participation in therapeutic activities such as exercises classes	Weeks 0, 2, 6, 18 and 22 Assessor blinded
Secondary Mechanistic Objectives (Blinded Assessor Sessions)		
Changes in inter-limb coordination	Assessed using the Phase Coordination Index (PCI). This index is derived from the duration and relative phasing of the step duration of each leg, measured using Inertial Measurement Units (IMUs) attached to the feet[40]concurrently with the 10mWT	Weeks 0, 2, 6 Assessor blinded
Change in anticipatory postural adjustments (APAs)	APAs assessed using IMUs on the feet and lumbar region of the back[41] whilst participant is stepping onto medially placed targets from a wide based standing position. The motion of the estimate of the centre of mass prior to foot lift when stepping, will provide a direct measure of APAs.	Weeks 0, 2, 6 Assessor blinded
Change in limb bradykinesia while stepping and walking	Assessed using IMUs attached to foot[60] concurrently with MDS-UPDRS Section 3 (task 3.7 instrumented toe tap test) and through the maximum velocity of foot motion while walking (concurrently with 10mWT).	Weeks 0, 2, 6 Assessor blinded
Changes over time in the strength of muscles directly targeted and not targeted by the intervention.	Hand-held dynamometry[61] (Nm). Maximum voluntary torque: dorsiflexion, eversion and hip flexion on both FES and non-FES sides.	Weeks 0, 2, 6, 18 and 22 Assessor blinded

Secondary Objectives (Non-blinded FES clinic Sessions) *Outcome measures marked with an asterisk (*) are patient reported during the assessment session*		
Cost/utility	Record of direct clinical contacts and consumables used related to FES provision	Weeks 0-1 (FES set-up), 2, 6, and 18 Non-blinded FES clinician
The effect on gait while using FES bradykinesia	Walking speed with and without FES, 10mWT (ms^{-1})	Weeks 0-1 (without FES only) Weeks 2, 6 and 18 (with and without FES) Non-blinded FES clinician
The effect on gait while using FES Hypokinesia	Step length with and without FES. 10mWT (m)	Weeks 0-1 (without FES only) Weeks 2, 6 and 18 (with and without FES) Non-blinded FES clinician
The effect on gait while using FES Effort of walking	Borg Rating of Perceived Exertion (RPE) score (0-10) while performing the 10mWT, with and without FES	Weeks 0-1 (without FES only) Weeks 2, 6 and 18 (with and without FES) Non-blinded FES clinician
The effect on gait while using FES Akinesia	Timed up and go test with and without FES (s). To be compared with TUG recorded during the minBESTest carried out at the blinded assessment sessions.	Weeks 0-1 (without FES only) Weeks 2, 6 and 18 (with and without FES) Non-blinded FES clinician
Determine how pwPD and their carers perceive the usefulness and practical experience of FES use and its therapeutic effect	FES experience questionnaire	Weeks 18 Non-blinded FES clinician
Intervention compliance and FES usability	Systems Usability Scale (SUS) questionnaire	Week 18 Non-blinded FES clinician
Intervention dose / compliance	Number of steps taken and total stimulation time with FES (value is recorded on the ODFS pace device)	Weeks 2, 6 and 18 Non-blinded FES clinician
Secondary Objectives - qualitative		
Determine how pwPD and their carers perceive the usefulness and practical experience of FES	Qualitative interviews with a subset of participants in FES intervention group, participants who withdrew from the FES intervention group and	Weeks 22 (FES intervention group) Post-withdrawal (FES withdrawal group)

use and its therapeutic effect	partners/carers of those in the FES intervention group.	Week 22 (partners/carers group)
Safety Objectives		
Determine the safety of FES in pwPD	Recording of device related adverse reactions (DARs)	Weeks 0-1, 2, 6 and 18 Non-blinded FES clinician
Determine the safety of FES in pwPD	Recording of serious adverse events (SAEs)	Weeks 0, 2, 6, 18 and 22 Non-blinded FES clinician and blinded assessor

4. TRIAL TREATMENTS

4.1. Intervention arm: FES + usual care

Participants allocated to the treatment arm will attend a set-up appointment to have the FES device fitted to their leg. The session will take approximately 60 minutes in total, including the time taken for the 10mWT and TUG test.

The clinical pathway established for MS and stroke[50] patients will be used, with a set-up session within 1 week from baseline, and clinical (unblinded) sessions at weeks 2, 6 and 18 post-baseline. The intervention is used in addition to usual care.

The CE-marked ODFS Pace is a small, battery-powered, single channel FES device used to correct dropped foot. Electrical stimulation is applied to the common peroneal nerve using skin surface self-adhesive electrodes placed over the head of fibula and the anterior tibialis muscle (see Figure 4).

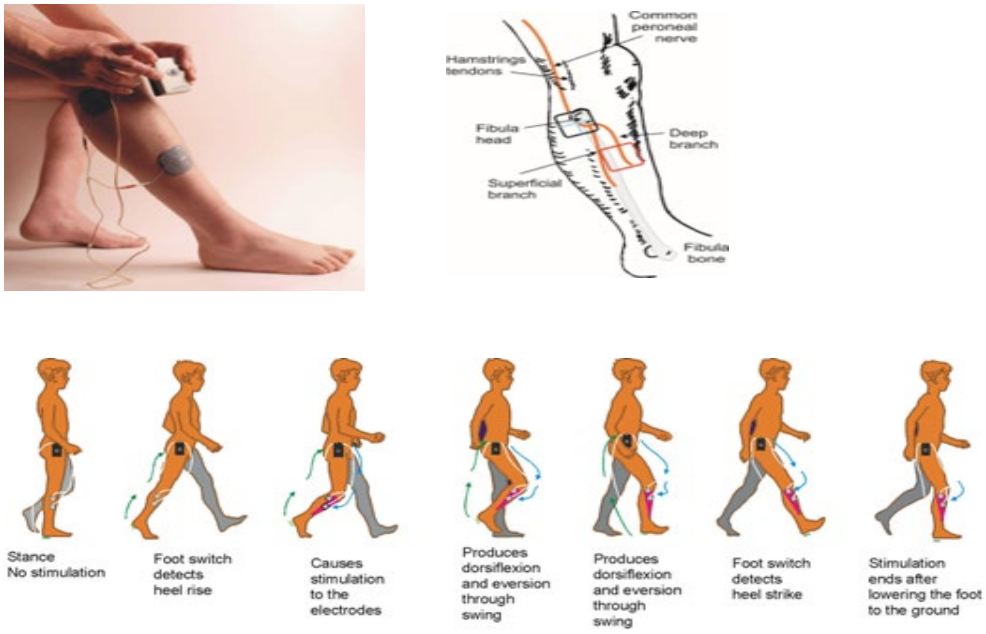

Figure 4. The ODFS® Pace with electrode positions shown relative to the underlying common peroneal nerve. The superficial branch innervates the peroneus longus and brevis. These muscles produce eversion of the ankle. The deep branch innervates the tibialis anterior, extensor digitorum longus and brevis, 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. Stimulation begins when weight is taken from a footswitch placed under the heel and ends when the foot is flat on the ground[29]

Stimulation is timed to the individual's gait cycle using a footswitch in the shoe, causing the foot to lift when taken from the ground. The device will be fitted to the leg that the treating FES clinician identifies as having the greatest deficit in ankle movement and/or greatest Parkinson's symptoms. If it is not

possible to place the device on this side, it is permissible to set up the device on the opposite side. The stimulation intensity will be set at a sufficient level to cause a comfortable muscle contraction, producing dorsiflexion and eversion. The leg the device is fitted on and device settings will be documented on the CRF. The participant and, if appropriate, their carer will be taught how to fit the device, identify the correct movement of the foot and how to adjust the position of the electrodes and stimulation intensity.

Participants will be provided with the stimulators standard User Instruction Manual to take home with them. In addition to the fitted device and User Instruction Manual, participants will also be provided with spare electrodes and a photo of the electrode positions to remind them where they should be placed on the lower leg. They will also be provided with a contact number for the FES clinician and asked to get in touch if they experience any problems using the device or experience side effects, so that assistance can be given.

Potential complications/side effects are listed in the User Instruction Manual and will be explained to the participant. Safety data (device related adverse reactions and SAEs) will be collected retrospectively at each assessment, or in between if the participant contacts the FES clinician to report them. Verbal guidance will be provided on strategies to support their use of the device for the period of the study.

Once the participant is confident with the device and has asked all their questions, they will be provided with a second set-up appointment for the following week (Week 2), where their use of the device will be assessed and any further training provided, as required. Further FES clinical follow-up visits will take place at Weeks 6 and 18 post baseline. All FES clinical sessions will take approximately 60 minutes. After the device has been set-up, intervention participants will be asked to walk every day with the device and use the device whenever they feel it assists their walking. At each FES follow up session, the participant's performance will be recorded using the 10mWT (speed and stride length), Borg RPE score (scale 0-10) after each walk and TUG (s). FES clinicians will also record consumables used and clinician contact time from these sessions. See 'Section 8.6 Intervention group only: FES set-up and follow-up visits' for further details.

4.1.1. Training of FES clinicians delivering the intervention

All FES clinicians delivering the intervention will have previously completed the Odstock Medical FES for the lower limb course; compliance with this will be checked prior to recruitment commencement at sites and clinicians delivering the intervention will be required to sign a training log to confirm they have completed the course. A refresher session will be provided at site initiation and a detailed Work Instruction will be supplied to each site outlining the procedure to ensure that the delivery of the intervention is standardised across sites.

4.1.2. Training of the blinded assessors

Blinded assessors at each site will receive face-to-face training from the Chief Investigator, or appropriately delegated person, on how to carry out all the blinded assessment tests. It is expected that the blinded assessor will have some previous experience carrying out similar tests with this cohort of participants, such as familiarity with the MDS-UPDRS and 10mWT. The suitability of the blinded assessor will be checked by the Chief Investigator during site initiation. The training session will take approximately half a day. During training, a full run through of the blinded assessment session will take place. A training package has been developed to ensure that blinded assessor training is standardised across all sites. Training of the blinded assessors must be documented on the training log and take place before a site can open to recruitment. The Chief Investigator, or appropriate delegate, will countersign the training log to state that the blinded assessor is competent and has completed the training to an acceptable standard. More training can be provided, if required. During

the study, the Chief Investigator, or appropriate delegate, will be available to provide advice to the blinded assessors if they require further guidance. Contact details will be provided to the blinded assessors prior to recruitment commencing.

4.2. Control arm

Participants will receive 'Treatment as Usual at their site. Usual care includes medication designed to modify the amount and action of dopamine in the brain, attendance at medical/PD clinics and/or visits from PD nurses. Data on usual care (all participants) will be captured at each blinded assessment session, which will be scheduled in the same time frames as the intervention group (Weeks 0, 2, 6, 18 and 22).

After substantial consideration and discussions with the PAG, we have chosen not to use a placebo. FES produces movement and has a significant sensory effect. Users are taught how to apply the device and how to produce an effective movement. Low-level sensory stimulation may still have a cueing effect that may assist walking. A credible sham treatment is therefore, in our opinion, not possible for either the participant or the treating clinician.

5. TRIAL / STUDY DESIGN

A multi-centre, two-group, parallel, assessor-blinded, superiority, individually randomised controlled trial comparing FES in addition to usual care to usual care alone. The primary end-point is at week 18. This time point has been used in other studies of FES[15] because it is considered sufficiently long enough for the full effect of FES to become established and for any Hawthorn effect to have passed. FES is then withdrawn from the intervention group participants and further assessments are made at week 22 (four weeks post-intervention withdrawal) to study the potential carryover effect. Please see the participant journey flow chart in Section ix for an overview of the study visit and key timepoints.

5.1. Design considerations for minimising bias

5.1.1. Randomisation:

After providing informed consent and completing screening and baseline assessments, participants will be individually randomised 1:1 to FES with usual care or usual care alone, stratified by recruiting centre to ensure approximately equal numbers of participants in the treatment and usual care only groups at each centre. PenCTU will centrally administer the randomisation using a bespoke, web-based randomisation system. The randomisation sequence, using variable block sizes, will be generated by a statistician independent to the trial team and implemented through a secure web-based system, ensuring allocation concealment.

5.1.2. Blinding:

All outcome measures taken at the blinded assessments will occur without the stimulator being worn and will be made by an assessor blinded to group allocation. Intervention participants will be asked not to use FES on the day of the blinded assessment and reminded that they should not bring the device with them to blinded assessments. Participants will be asked not to discuss their group allocation with the blinded assessor or any other pwPD who are participating in the study. Measures taken while FES is being used will be made by an unblinded treating FES clinician on a separate day, as part of the routine FES clinical visits. Blinding status of the assessor will be checked at the Week 22 visit. The trial statistician will also remain blinded to participant group allocation until the Statistical Analysis Plan is signed off, at which point they will be unblinded.

5.2. Internal pilot for study progression:

An internal pilot will be carried out 12 months after recruitment has commenced to determine whether the trial will progress, where green indicates progression, amber indicates progression with remedial action and red (in any of the three criteria) indicates likely termination of the trial.

Taking the average recruitment rate achieved in the feasibility study of 1.8 participants per site per month, and assuming a slightly slower recruitment rate in the opening months of the study, together with staggered site opening, it is estimated that recruitment of 100 participants after 12 months will put the trial on course to meet the recruitment target of 234 participants after 22 months of recruitment, whilst recruitment of 87 participants after 12 months should be sufficient to meet the recruitment target at the end of the planned 24 months of recruitment. Therefore, the green band is set at ≥100 participants, the amber band is set at 71-99 participants and the red band is set at <71 participants after a 12-month recruitment period. If fewer than 71 participants have been recruited after 12 months, it is unlikely that remedial measures will be sufficient to reach the recruitment target of 234 after 24 months. Number of sites opened and retention rate (defined as completeness of the primary outcome at 18 weeks post-baseline) are also included in the progression criteria and will be assessed 12 months after recruitment commences. Please see Table 2 below for further details on the progression criteria and banding.

Progression criteria after 12 months of recruitment	Green band (progression of trial)	Amber band (progression of trial with remedial action)	Red band (likely termination of trial)
Sites open	7	4-6	<4
Participants recruited	≥100	71-99	<71
Retention rate (defined as completeness of primary outcome at 18 weeks post-baseline)	≥85%	75-84%	<75%

Table 2: Internal pilot: progression criteria after 12 months of recruitment

6. TRIAL / STUDY SETTING

This is a multi-centre randomised controlled trial conducted at 8 secondary care NHS trusts. Confirmed recruiting centres are: Salisbury NHS Foundation Trust (FT), Birmingham Community Healthcare NHS Foundation Trust, Swansea Bay University Health Board (UHB), Leeds Teaching Hospitals NHS Trust, North Cumbria Integrated Care NHS FT, University Hospitals of Derby and Burton NHS FT, Betsi Cadwaladr UHB and East Suffolk and North Essex NHS FT.

All participating sites already offer a FES service to patients who have had a stroke, MS or other upper motoneuron condition and therefore have the infrastructure to support the study. Participating units will be supported by a site Principal Investigator, FES specialist (if not the PI), physiotherapist or clinical scientist and a research nurse.
Additional sites may also be recruited as Participant Identification Centres (PIC).

7. PARTICIPANT ELIGIBILITY CRITERIA

7.1. Inclusion criteria

Patients must satisfy all of the following criteria to be enrolled in the study:

- aged 18 years and above (no upper age limit)
- idiopathic Parkinson's disease
- Hoehn and Yahr stages I to IV
- difficulty in walking due to Parkinson's disease bradykinesia, defined as a measured 10mWS of less than 1.25ms^{-1} (time to complete 10m >8s). Participants asked to "walk briskly but safely".
- able to walk 50m with appropriate walking aids, but without assistance from another person. Appropriate aids include walking sticks, tri or quad sticks, Ankle Foot Orthoses (AFOs) and similar devices.
- able to obtain standing from sitting without the assistance of another person
- able to understand and comply with the treatment and assessment procedures
- able to give informed consent

7.2. Exclusion criteria

Patients who meet any of the following criteria will be excluded from study participation:

- receiving, or scheduled to start, deep brain stimulation, within the next 6 months
- scheduled to start apomorphine, duodopa or produodopa within the next 6 months (those who are currently taking produodopa, duodopa and apomorphine are eligible)
- pyramidal and/or extrapyramidal systems injuries
- untreated or refractory epilepsy with seizures in the last 3 months
- pregnancy or planned 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 conditions that significantly affect walking
- malignancy or dermatological conditions in the leg that would be stimulated
- major cognitive impairment; dementia.
- under treatment for an unresolved deep vein thrombosis in the leg that would be stimulated
- participating in another interventional clinical trial (observational studies are permitted)

8. TRIAL / STUDY CONDUCT

Please refer to the schedule of events table in Section 9 Trial Schedule for a summary of the study visits and outcome measures carried out at each visit.

8.1. Participant identification

There are multiple routes in which potential participants may be identified and recruited onto the study to improve recruitment rates. These routes are detailed in the following sections.

8.1.1. Participant identification and recruitment in clinics

Site Principal Investigators (PI's) will be responsible for promoting the study amongst relevant staff at their hospitals to optimise participant recruitment. Recruitment performance at each site will be closely monitored by the Trial Management Group (TMG).

Participants will be recruited from seven outpatient services. Potential participants will be identified by the local Movement Disorders Teams, at PD clinics and at neurology clinics. It is recommended that site staff review clinic lists in order to identify any potential participants with upcoming appointments to improve participant identification and recruitment. Patient identifiable information will not be used by anyone other than the clinical team. Members of the research team will not require access to identifiable patient data for the purpose of identifying potential participants. Patients identified in clinics that fulfil inclusion/exclusion criteria will be eligible for the study. The clinician will discuss the study with potential participants in clinic at their regular appointment, this may be a face-to-face appointment or virtual/telephone appointment, depending on the site's local arrangements. Time will be given to introduce the study and discuss what it involves, including the nature and objectives of the study and possible risks associated with their participation. Patients will be advised that they have the right to refuse participation, without giving reasons, and that they are free to withdraw at any time, without giving reasons and without prejudicing his/her further treatment. They will also be advised on how their data will be used and signposted to further information about data used for research purposes.

If the patient is interested, they will be provided with a recruitment pack containing a Summary Participant Information Sheet (PIS) and Detailed PIS describing the study and containing contact details of the local STEPS II research team, who they can contact if they have any questions. If the potential participant attends for a face-to-face appointment, the recruitment pack will be handed to them during the visit. If their appointment occurs virtually or over the telephone, the recruitment pack will be emailed or posted to the patient, depending on their preference.

At this stage, participants will be asked if they wish to be contacted by the research team in a few days to discuss the study further, and if so the best time of day to contact them (this call will be carried out by the PI or delegate, following Work Instruction Telephone Pre-screening). Patients who agree will receive a follow-up phone call at least 48 hours after receiving the PIS from a member of the STEPS II research team to discuss the study requirements in more detail. If they do not wish to be contacted, they will be advised to use the reply slip or contact details on the PIS to contact the research team should they wish to participate, but they will not be contacted again about the study unless they are the ones to initiate this.

Details of potential participants who have been identified via this route will be documented in an electronic screening log, hosted on a secure REDcap database, and will include the date the PIS has been provided, whether it was handed to the patient, emailed or posted and whether they wish to be contacted by a researcher. Personally identifiable data and contact information will be recorded on this REDCap electronic screening log database and will be hidden from de-identified trial data. If the participant wishes to be contacted, an automated email will be triggered to the research team once data has been entered into the screening log to remind them to call the patient in 48-hours. If the PIS has been posted to the patient, the automated email will remind the research team to call the participant in 72-hours, to allow time for the PIS to be delivered.

If a potential participant does not wish to be contacted by the research team, and they have not contacted the team themselves using the details on the PIS after 4-weeks, it should be documented on the screening log that they are no longer interested. A reminder email will be sent to the researcher team 4-weeks after the date the PIS has been provided to update the screening log with this information, if no further information has been entered. See Figure 5 for a summary of this route.

8.1.2. Self-referral via STEPS II website

PenCTU is hosting a public facing STEPS II webpage, which contains a lay summary of the study, downloadable Summary PIS and Detailed PIS, lay description of eligibility criteria, details of recruiting sites and an expression of interest form that participants can complete to register their interest in the study. This will provide a route for pwPD to self-refer to the study. The form will ask participants to indicate which site they are interested in, confirm they have downloaded and read the PIS, provide their contact details and date of birth and indicate their preferred days/times to be contacted. Participants will be asked to confirm that they are happy for a member of the local research team to contact them to discuss the study and go through telephone pre-screening (see Section 8.2 Telephone Pre-screening). When the form is submitted, an automated email will be triggered to the research team at the selected site and PenCTU informing them that the participant requires contacting. Research staff should enter the details provided in the email into the screening log. Personally identifiable data and contact information will be recorded on this REDCap electronic screening log and kept hidden from de-identified trial data.

Patients who register their interest through the website will receive a follow-up telephone pre-screening phone call by a member of the STEPS II research team at their chosen site to discuss the

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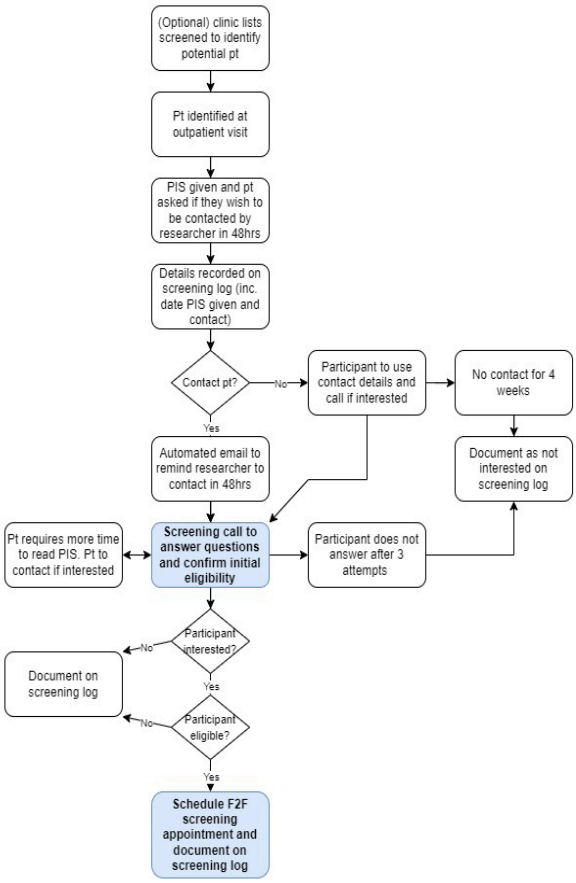

Figure 5. Participant identification via clinics

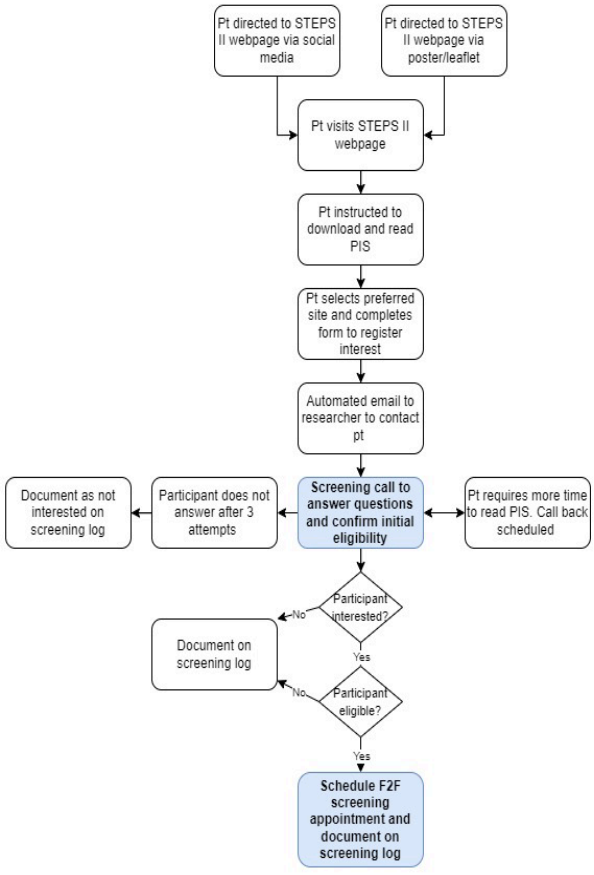

Figure 6. Participant identification via website

8.1.3. Social media promotion

Social media posts and an advert have been developed and will be shared on Salisbury NHS Trust, Peninsula CTU, University of Plymouth, participating sites and Parkinson's Disease Society Twitter, Facebook or LinkedIn accounts to promote the study. The advert/posts will direct viewers to the STEPS II website, where they will be able to self-refer to the study using the route described in

Section 8.1.2.

8.1.4. Posters and leaflets promotion

Leaflets containing a lay summary of the study and key eligibility criteria and a poster will be provided for sites to place in the clinical areas where pwPD attend for their appointments. These will direct pwPD to the STEPS II website, where they will be able to find more information and self-refer using the route described in Section 8.1.2, or prompt them to discuss the study with their clinician, who can recruit the participant via the route described in Section 8.1.1. The poster will also be available in a digital format, and sites will be encouraged to disseminate it via their communication routes, such as newsletters, and share on their social media accounts.

8.1.5. Parkinson's Disease societies & charities

Parkinson's UK has agreed to publicise the study (subject to completion of their research governance procedures). This will occur via their website and social media accounts. Other local Parkinson's Disease societies and charities will also be approached to publicise the study. They will be provided with the poster and leaflet to aid dissemination and direct people to the STEPS II webpage, where they can self-refer using the route described in Section 8.1.2.

8.2. Telephone Pre-screening

This will take approximately 20 minutes. For participants identified in clinic, the research team will receive an automated email after details of a potential participant have been entered into the screening log, including date the PIS was provided and whether the participant wishes to be contacted to discuss the study. If the potential participant has indicated that they do not wish to be contacted, the automated email will instruct the research team not to make further contact. If the potential participant would like to be contacted, the automated email will inform the research team that the participant requires an telephone pre-screening phone call, 48 hours after the PIS has been provided (or 72 hours if the PIS has been posted).

For potential participants who have been identified by self-referral via the website, an automated email will be sent to the relevant research team with their contact details and to inform them that they require a telephone pre-screening call, after they have submitted the online form. Potential participants must indicate that they are happy to be contacted for more information in order to submit the form. The research team must record details from the email onto the electronic screening log to keep a record of potential participants who need to be contacted. Sites are responsible for ensuring this information is maintained and up-to-date.

Participants will be contacted via telephone by one of the STEPS II research team, who is delegated the roles of screening and confirmation of eligibility, as prompted by the automated emails received. Attempt to contact will be made three times, after which a person will be documented as 'not interested' on the screening log, and no further attempts at contact will be made. During this telephone call, participants will be asked if they have read and understood the PIS and encouraged to ask any questions that they have about the study. The researcher should then provide an overview of the study requirements. If the participant requires more time to consider the study, then a further telephone call should be scheduled for a later date.

If they still express an interest in participating, the researcher will go through some initial eligibility screening questions. A combination of discussion with the participant and their physician may be used to confirm eligibility. See 'Work Instruction- Telephone Pre-screening' for further information.

If the participant meets the inclusion/exclusion criteria, as far as can be determined during the phone call, the researcher will then schedule a face-to-face visit for a full screening assessment. The participant should be informed that this assessment will last up to 90 minutes and will involve providing informed consent, re-confirming eligibility criteria (which will require that participant to stand from a seated position and walk 10m unassisted) and provide information on their medication, falls history, social situation and experience with walking. Participant will be informed that they will only be able to proceed with the study if they meet all the eligibility criteria checked at the screening visit. Participants will be instructed to bring a copy of their prescription to the face-to-face screening visit (and any subsequent blinded assessment visits). 'Work Instruction- Telephone Pre-screening' should be followed when carrying out the initial screening call to ensure standardisation across all sites. Information obtained from this call will be logged on the Redcap screening database.

8.3. Informed consent & screening evaluation visit

A total of 90 minutes should be allowed for the face-to-face screening visit. This appointment will consist of receiving informed consent (20 minutes), screening evaluation (55 minutes) and issuing of the StepWatch (15 minutes).

8.3.1. Informed consent

When the participant attends for their face-to-face screening appointment, the researcher must inform the participant that if they do not meet all of the eligibility criteria checked during this appointment, they will not be able to continue with the study. Before any screening tests are carried out, the researcher must first receive informed consent. Approximately 20 minutes should be allowed for this process. Informed consent must be obtained by the site Principal Investigator (PI), or an authorised delegate prior to collecting any study data. Authorised delegates must be suitably trained in the relevant principles of Good Clinical Practice and the requirements of the trial protocol. Training materials will be provided by the coordinating clinical trials unit (PenCTU). Doctors, registered nurses or Allied Health Professionals (band 5 or higher) may be authorised to receive consent for this study. Consent should only be provided after potential participants have had enough time to consider and discuss the study with their clinicians, family or friends. If they agree to take part, formal consent will be taken by the PI or delegated individual. The full inclusion and exclusion criteria will then be assessed.

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes receiving informed consent from participants at their site. They must ensure that any person delegated the responsibility to participate in the informed consent process is duly authorised, trained and competent. If delegation of consent is acceptable, then details should be provided in the site delegation log. This will be monitored centrally by PenCTU.

Informed consent will be received prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating centre.

The participant will be informed they have a right to withdraw from the study, without giving a reason, at any time and without prejudicing their further treatment. Data collected up to the point of withdrawal will still be retained and used in analysis, unless the participant requests that their data is destroyed on the withdrawal form. This data will remain anonymous. Any intention to utilise such data is outlined in the consent literature. Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure that this is carried out in a timely manner.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily, in an environment free from coercion or undue influence. Where a participant can consent

for the trial but later becomes incapacitated, the participant will be withdrawn from the trial as following the trial instructions and procedures will not be possible.

Original versions of completed informed consent forms (ICFs) should be stored in the participant's notes and one copy should be provided to the participant for their records.

8.3.2. Screening evaluation

This will take approximately 55 minutes. At the same clinic appointment, after participants have consented, the screening evaluation will take place to confirm eligibility and collect screening data. A combination of discussion with the participant and use of medical notes may be used to confirm eligibility. Data should be collected in the following order and entered onto the REDCap database. Paper CRFs will be provided if the clinician wishes to record data on these initially and transfer them to the database later:

8.3.2.1. Eligibility confirmation

- Confirmation of the following inclusion criteria (Y/N checklist):
    - Idiopathic PD
    - Confirm participant is >18 years
    - Able to comply with the treatment and assessment procedures, including the ability to start FES treatment within 1 week of baseline appointment (baseline appointment will take place 7 days after the screening visit).
    - Able to give informed consent
- Confirmation of the following exclusion criteria (Y/N checklist):
    - Receiving, or scheduled to start, deep brain stimulation, within the next 6 months
    - Scheduled to start apomorphine, duodopa, or produodopa, within the next 6 months
    - Epilepsy and had a seizure within the last 3 months
    - Pregnant or planning a pregnancy
    - Cardiac pacemaker, or other active medical implanted devices
    - Malignancy, dermatological condition or unresolved deep vein thrombosis in the lower leg
- Confirmation of medical conditions exclusion criteria (Y/N checklist). If the participant has any of the following co-morbidities, they are ineligible:
    - Atypical or secondary parkinsonism, or parkinsonism related to other neurodegenerative diseases
    - Pyramidal or extrapyramidal systems injuries
    - Denervation of common peroneal nerve
    - Neurological condition known to cause dropped foot
    - Severe osteoarticular pathology involving calf bones, knee or tibio-tarsal joints
    - Medical condition that significantly affects walking
- Physical assessment confirmation of eligibility. A 10 metre walking test (10mWT) will be carried out, where the participant will be required to walk 10m, without the assistance of another

person (See 'Work Instruction- 10mWT' supporting document for further details). The following information should be documented from the 10mWT to confirm eligibility:

- Time taken (s) to confirm difficulty walking due to PD bradykinesia (defined as a walking speed <1.25ms^{-1} i.e. takes >8s to walk 10m)
- Able to walk 50m with appropriate walking aids but without the assistance of another person (Y/N)
- Able to stand from sitting without the assistance of another person (Y/N)
- Confirmation that gait is affected by PD (Y/N)
- Modified Hoehn and Yahr Scale stage (I-V). Must be stage I-IV to be eligible.

If potential participant fulfils all the eligibility requirements, the clinician may progress and collect further screening data.

8.3.2.2. Collection of further screening data

- Description of **gait**, as observed by clinician during 10mWT (See 'Work Instruction- 10mWT' supporting document for further detail). Y/N checklist for the following gait characteristics:
  - Reduced dorsiflexion (Y/N)
  - Reduced eversion (Y/N)
  - Freezing (Y/N)
  - Festination (Y/N)
  - Short stride (Y/N)
  - Swing phase compensation (N, R, L)
  - Stance phase compensation (N, R, L)
  - Upper limb reduced swing (N, R, L)
  - Posture affected (N, stooped)
  - Slow walking speed (Y/N)
  - Heel strike (Y/N)
  - Affected side (Right (R), Left (L), R>L, L>R)
  - Lateral lean (N, R, L)

- Collect the following **demographic** information:
  - Sex
  - Ethnicity
  - Employment status (employed/retired due to age/retired due to ill health)
  - Living status (lives alone/lives with partner/lives with family/lives in care home)

- Collect the following **clinical/medical history** information:
  - Date of PD diagnosis (exact date or estimated month/year)

- PD type (mixed, akinetic or tremor-dominant). This should be determined through use clinical observation.
- Current PD medication
- Falls history (participant reported fall rate and injuries due to falls in the last 6 months)
- Comorbidities (heart condition, diabetes, cancer, lower limb joint surgery, other surgery, rheumatoid arthritis, chronic pain and osteoarthritis)

- Collect the following **Activities of Daily Living (ADL) and walking ability** information:
  - Walking aid use (including Beech Band and CUE1 devices*)
  - ADL independence/assistance requirements (determined through discussion with the participant to determine level of support required to carry out ADLs on a 5-point scale from independent in ADLs to completely dependent for ADLs).
  - Assistance requirements with FES device (determined through discussion with the participant to determine whether they would require help putting on the FES device (Y/N))
  - Usual walking distance (m) during “on” and “off” medication periods, as reported by the participant. Defined as the distance that can be walked without taking a rest. This is a participant reported estimate.
  - Participants view on what they consider to be the main problem with their walking is (determined through discussion and using a checklist of common walking problems for pwPD)

  *If the participant uses the Beech Band or CUE1 device, these should be removed when the participant is completing study assessments.
- Ankle proprioceptive sensory discrimination (two-point discrimination to assess participants ability to identify two close points on their ankle, please refer to the Work Instruction Ankle Proprioceptive Discrimination for further information)
- Sensory gradient discrimination test. Participant will stand on two slopes, with support from a frame, with the non-tested foot placed on an adjustable slope. The slope gradient will be adjusted at intervals and the participant must indicate which slope is the most upward facing, until they are unable to discriminate between the two stimuli. See Work Instruction- Sensory Gradient Discrimination Test for detailed instructions on how this test should be carried out. This test will take approximately 10 minutes.

8.3.3. StepWatch issue for baseline

This will take approximately 15 minutes. After the screening evaluation has taken place, at the end of the visit, participants will be issued with a StepWatch to determine the mean steps taken per day over the following 7 days. Participant height should be recorded and required size of leg strap (small, medium or large) will be determined by the clinician. Participants will be provided with a copy of the StepWatch instruction manual and instructed to wear the StepWatch for 7 days, removing it when they have a bath or a shower. Sites should maintain a log of the StepWatch serial number issued to the participant. PenCTU will supply sites with the StepWatches.

A baseline appointment will then be arranged to take place in 7 days. The participant will be asked to return the StepWatch at this visit and informed that they will receive their randomisation allocation via

email at the end of the baseline visit.

8.4. Blinded baseline assessment (Week 0)

All participants will be provided with an appointment for the blinded baseline assessment 7 days after the screening evaluation visit. Study visits should be scheduled at the same time each day. **This must be carried out by the blinded assessor** and 120 minutes should be allowed for this visit. Participants will be asked to return the StepWatch when they attend. The blinded assessor should regularly check in with the participant during this assessment session to see if they require a break.

Assessments in bold and marked with a double asterisk (****example**) are participant reported outcome measures (PROMs) and must be completed by the participant or carer. The blinded assessor should ensure completion of these before moving onto the next test. Baseline assessments should be carried out in the order detailed in the protocol, as this ensures participants have a break from physical assessments by completing the PROMs in between physical tests. Data should be entered into the REDCap database. Paper CRFs will be provided if the clinician wishes to record data on these initially and transfer them to the database later. Please see Table 2 for a summary of the baseline visit assessments:

1. Confirm participant is still eligible and willing to take part (Y/N)
2. ****Record any participation in physiotherapy or exercise classes** (duration and frequency)
3. ****Record reported changes in PD medication from the screening visit**
4. Attach Inertial Measurement Units (IMUs) to participants feet and lumbar region (see ‘Work Instruction- Application of IMUs and PCI’ supporting document for further information). These should remain on the participant until stated otherwise.
5. Carry out the 10mWT (see ‘Work Instruction- 10mWT’ supporting document). Record time taken (s) and number of steps taken, when this is inputted into the REDCap database the speed and stride length will be calculated.
6. During the 10mWT, the IMUs will measure the Phase Coordination Index (PCI) quantification concurrently, as the 10mWT is being carried out, by measuring the duration and relative phasing of the step duration of each leg. This measurement will be downloaded and documented at the end of the session (see ‘Work Instruction- Application of IMUs and PCI measurement’ supporting document for further information).
7. ****MDS-UPDRS Section 1A: Non-motor ADLs**. Blinded assessor should ask the participant these 6 questions relating to complex behaviours (e.g. cognitive impairment and mood) and record their responses.
8. ****MDS-UPDRS Section 1B: Non-motor ADLs.** Participant/carer should complete these 7 questions relating to non-motor experiences of daily living (e.g. sleep, pain, urinary problems, constipation, light-headedness and fatigue).
9. ****MDS-UPDRS Section 2: Motor ADLs.** Participant/carer should complete these 13 questions assessing motor symptoms and signs of PD.
10. Dynamometry to measure active force of dorsiflexion, eversion and hip flexion on right and left sides (see ‘Work Instruction- Dynamometry’ supporting document for further information).
11. ****New Freezing of Gait Questionnaire (N-FOG).** Participant/carer should complete these 9 questions relating to freezing episodes experienced.
12. MDS-UPDRS Section 3: Physical Assessment. Active physical tests directed and assessed by blinded assessor. The attached IMUs will be used to record the speed of movement tap test.
13. ****Falls Efficacy Scale-International (FES-I) questionnaire**. Participant/carer should complete these 16 questions relating to falls episodes experienced.

14. Anticipatory postural adjustment (APA) test. With IMUs attached, participant will be asked to step onto medially placed targets from a wide based standing position. The motion of the estimate of the centre of mass prior to foot lift when stepping will provide a direct measure of APAs. This is measured automatically via the IMUs attached to the feet and the lumbar region of the back. APA data will be downloaded and documented at the end of the session (see 'Work Instruction- APA test' for further information). IMUs should be removed after this test is completed.
15. ****Parkinson's Disease Questionnaire 39 (PDQ-39).** Participant/carer should complete these 39 questions assessing how often pwPD experience difficulties across 8 dimensions of daily living, including relationships, social situations and communication.
16. Balance Evaluation Systems Test (Mini-BESTest). Consists of a series of 14 active physical tests to assess the participant's balance, such as asking the participant to stand on tiptoes, stand on one leg, walk and turn and step over an obstacle. This also includes the Timed Up and Go (TUG) test. These will be directed and assessed by the blinded assessor. See 'Work Instruction- MiniBESTest' supporting document for further information.
17. ****EQ-5D-5L**. Participant/carer should complete these 5 questions and one visual analogue scale (VAS) to provide an indication of the participants health state.
18. Explain and issue the falls and exercise diary. Inform participant they will receive an email containing login details to access the diary upon randomisation. The assessor should instruction informing the participant how to complete the online falls and exercise diary and to complete this daily until the final visit at Week 22. Participants will record any falls on a daily basis. At the end of the week, participants will record any physiotherapy or exercise participation for that week. Participants should be encouraged to complete this online; a paper-based copy will be provided if the participant is unable to complete this online.
19. Retrieve StepWatch and the average daily step count recorded on the device. Please see 'StepWatch User Manual' supporting document for details on how to download data and obtain step count from the StepWatches.

	Assessment/Action	**Blinded assessor measure or PROM**	**Time required (minutes)**
1	Confirm participant is still eligible	Blinded assessor	1
2	Participation in physiotherapy/exercise classes	PROM	2
3	Reported changes in PD medication	PROM	1
4	Attach IMUs to leg and torso	Blinded assessor	1
5	10mWT (time taken, no. steps, PCI)	Blinded assessor	4
6	PCI quantification (concurrent with 10mWT)	Blinded assessor	As above
7	MDS-UPDRS Section 1a: Non-motor ADLs	PROM	3
8	MDS-UPDRS Section 1b: Non-motor ADLs	PROM	5
9	MDS-UPDRS Section 2: Motor ADLs	PROM	7
10	Dynamometry	Blinded assessor	5
11	N-FOG questionnaire	PROM	5
12	MDS-UPDRS Section 3: Physical Assessment	Blinded assessor	14
13	FES-I questionnaire	PROM	5
14	APA test	Blinded assessor	10
15	PDQ-39 questionnaire	PROM	10
16	MiniBESTest	Blinded assessor	15
17	EQ-5D-5L	PROM	2
18	Issue falls and exercise diary	Blinded assessor	2

19	Retrieve StepWatch and step count	Blinded assessor	1

Table 3. Summary of blinded baseline assessments

All baseline data should be entered into the REDCap database according to instructions provided by the PenCTU.

Participation in the study should be recorded in the participants hospital record by documenting a record of the baseline visit and by flagging the hospital record, in accordance with local site policy. The participant's GP is informed (using approved GP letter) and a record of this is made in the participants records, along with a copy of the letter.

8.5. Randomisation procedure

Following completion of the baseline assessments, the participant should be informed that a different, **non-blinded member of the research team** will randomise them later that day and they will receive an automated email confirmation or telephone call once this has been carried out. The local PI or other non-blinded team member, will access the secure, bespoke web-based randomisation system, provided by the PenCTU, to randomise the participant and obtain the allocation group. Please note that it is crucial that randomisation is **not** carried out by the blinded assessor. After successful randomisation, the participant will receive an automated email informing them of their allocation. Non-blinded team members and relevant CTU staff will also receive an email containing this information. In addition to the automated email, a non-blinded member of the site team will telephone the participant to inform them of their allocation and to schedule their next visit.

Participants will be individually randomised 1:1 to FES with usual care or usual care alone, stratified by recruiting centre to ensure approximately equal numbers of participants in the treatment and usual care only groups at each centre. The randomisation sequence, using variable block sizes, will be generated by a statistician independent to the trial team and implemented through the bespoke web-based randomisation service provided by the UKCRC-registered PenCTU, ensuring allocation concealment.

After randomisation, a non-blinded member of the site team should contact the participant to schedule their next study visits. All visits must be scheduled at a similar time of day for participants, to ensure outcome measures are taken at the same time of the day to reduce variation and bias. If allocated to the usual care group, the participant will continue to receive their usual care and be provided with an appointment for their Week 2 blinded assessment visit (see 'Section 8.7 All participants: Blinded assessment visits (Weeks 2, 6, 18 & 22)'). If allocated to the intervention group, the participant will be provided with two appointments to set-up and begin the FES treatment, within 1 and 2 weeks of the baseline appointment (see 'Section 8.6 Intervention group only: FES set-up and follow-up visits'), and a Week 2 blinded assessment visit. They will receive the FES intervention, as described in 'Section 4.1 Intervention arm' FES + usual care', in addition to their usual care.

8.6. Intervention group only: FES set-up and follow-up visits

Participants allocated to the FES intervention group will be provided with dates for the four clinic appointments over the 18 week intervention period, which is usual for this intervention and forms part of the standard FES treatment pathway. Study visits should be scheduled at the same time each day. 'FES set-up visit 1' will be scheduled within 1 week of the baseline appointment (Week 0-1), 'FES set-

up visit 2' will be scheduled at Week 2, FES follow-up visits will be scheduled at Week 6 and Week 18. These appointments will be conducted by an unblinded, experienced FES treating clinician and will be scheduled for the same time of day each visit and occur on a **different day** to the blinded assessments. Several assessments will be conducted at these sessions, as part of the FES treatment pathway, and are described in the following sections. The clinician should check-in with the participant regularly during the session to see if they require a break.

8.6.1. FES set-up visit 1 (Week 0-1)

This will take approximately 60 minutes. At the first appointment, carried out within 1 week of the baseline visit, prior to applying the FES device for the first time, participants will have the following assessments:

- **10mWT (without FES).** Two 10mWTs should be carried out without the FES device. The time taken (s), number of steps taken and Borg RPE score (0-10) for each walk will be documented.
- **Timed Up and Go (TUG) (without FES).** Time to carry out the test (s) and the number of steps taken will be documented.

The clinician will then set-up the device and demonstrate how to use it. Please refer to 'Section 4.1 Intervention arm' FES + usual care' for further details on how set-up should be carried out.

At the end of the session, after the assessments have been carried out, the following information should be recorded on the clinical pathway document and database:

- Device settings, leg applied to and data logs
- Direct intervention costs (record clinician contact time and consumables used)

8.6.2. FES set-up visit 2 (Week 2)

This will take approximately 60 minutes. A second FES appointment will be carried out approximately one week after the first FES set-up appointment, and before the 2-week blinded assessment takes place. Participants will be instructed to attend the visit wearing the device. Participants will attend the clinic to check the set-up of the device and answer any queries relating to using the device. The following assessments will be carried out after the FES clinician has verified and optimised device set-up (refer to 'Section 4.1 Intervention arm' FES + usual care'). The participant may rest for up to 10 minutes between the tests if they are fatigued from the walking completed up to that point of the session. Assessments must be carried out in the following order:

- **10mWT (without FES).** Two 10mWTs should be carried out without the FES device. The time taken (s), number of steps taken and patient reported Borg RPE score (0-10) for each walk will be documented.
- **10mWT (with FES).** One 10mWTs should be carried out with the FES device turned on. The time taken (s) number of steps taken and patient reported Borg RPE score (0-10) will be documented.
- **10mWT (without FES).** One 10mWTs will be carried out with the FES device turned off. The time taken (s) number of steps taken and patient reported Borg RPE (0-10) score will be documented.

All four walks of the 10mWT will be carried out in quick succession, unless the participant requires a rest after each walk. After the 10mWTs, the following assessments and actions should be carried out:

- **Timed Up and Go (TUG) (without FES).** The time to carry out the test (s) and the number of steps taken will be documented.
- **Timed Up and Go (TUG) (with FES).** The time to carry out the test (s) and the number of steps taken will be documented.

- Record any reported device related adverse reactions (See 'Section 13 Safety Monitoring' for further information)
- **Record steps taken and stimulation time from the device, then reset the data logger on the device to zero**

At the end of the session, after the assessments have been carried out, the following information should be recorded on the CRF and database:

- Device settings and data logs
- Direct intervention costs (record clinician contact time and consumables used)

8.6.3. FES follow-up visits (Weeks 6 & 18)

Participants will attend clinic for two further FES follow-up visits at Weeks 6 and 18 post-baseline, on different days to the Weeks 6 and 18 blinded assessment visits. Participants will again be instructed to attend the visit wearing the device.

The assessments and data collection described in Section 8.6.2 above will be repeated (FES set-up 2 visit).

In addition at Week 18 the participant will return the FES device and the following participant reported measures should be collected:

- **Systems Usability Scale (SUS)[77] questionnaire** to record usability of the FES device. This consists of 10 questions with 5 response options (Strongly agree to Strongly disagree) that assess frequency of use, ease of use, whether support is required and confidence using the device. SUS score will be calculated and range from 0-100, with 100 being the highest usability score. See 'Systems Usability Scale' supporting document for further information.
- **FES experience questionnaire.** This questionnaire consists of 22 questions with 5 response options that aim to understand participants experience with using the FES. Questions are categorised as follows:
    - Experience of walking when wearing the FES device (Questions 1-5)
    - Experience of falling since using FES (Questions 6-7)
    - Experience of how FES works for you (Questions 8-11)
    - Impact of FES on your everyday activities (Questions 12-13)
    - Experience of using FES (Questions 14-22)

The Week 18 FES visit should take place shortly **after** the Week 18 blinded assessment visit.

8.7. All participants: Blinded assessment visits (Weeks 2, 6, 18 & 22)

All participants will attend for blinded assessment visits at Weeks 2, 6, 18 and 22 post-baseline**.** Study visits should be scheduled at the same time each day. **The assessments must be carried out by the blinded assessor** and will follow a similar format to the baseline assessment visit (Week 0). Approximately 120 minutes should be allowed for the sessions and the blinded assessor should regularly check in with the participant during the sessions to see if they require a break. These will be provided as and when the participant requests them.

If the participant is in the FES intervention group, these visits must be carried out on a different day to the FES clinic visits. Participants will be asked **not to wear the device** on the blinded assessment day and must not bring the device into the clinic. Participant will be advised not to reveal their allocation group to the blinded assessor at the start of the visit. In addition to the assessments described in the

follow section, all participants will be asked to return the StepWatches at the Week 18 and Week 22 visit, please see 'Section 8.8 StepWatch issue and data collection' for further information.

The assessment schedule described in Section 8.4 should be followed for the blinded assessments, with the following differences:

- Participation in exercise and physiotherapy classes is not recorded at the blinded assessments. This is reported by the participant in the weekly exercise diary.
- Attachment of IMUs is only carried out at Weeks 2 and 6.
- Phase coordination index is only measured at Weeks 2 and 6.
- Anticipatory postural adjustment test is only carried out at Weeks 2 and 6.
- If participant opted to use a paper-based falls and exercise diary, these should be retrieved and reissued at the blinded assessments.
- Weeks 18 and 22: participants will be asked to return the StepWatches please see 'Section 8.8 StepWatch issue and data collection' for further information.

Please see Table 4 below for a summary of the blinded assessment visits:

	Assessment/Action	**Blinded assessor measure or PROM**	**Time required (minutes)**	**Notes**
1	Confirm participant is still eligible	Blinded assessor	1	
2	Reported changes in PD medication	PROM	1	
3	Attach IMUs to leg and torso	Blinded assessor	1	Weeks 2 and 6 only
4	10mWT (time taken, no. steps)	Blinded assessor	4	
5	PCI quantification (concurrent with 10mWT)	Blinded assessor	Included in 10mWT time	Weeks 2 and 6 only
6	MDS-UPDRS Section 1a: Non-motor ADLs	PROM	3	
7	MDS-UPDRS Section 1b: Non-motor ADLs	PROM	5	
8	MDS-UPDRS Section 2: Motor ADLs	PROM	7	
9	Dynamometry	Blinded assessor	5	
10	N-FOG questionnaire	PROM	5	
11	MDS-UPDRS Section 3: Physical Assessment	Blinded assessor	14	
12	FES-I questionnaire	PROM	5	
13	APA test	Blinded assessor	10	Weeks 2 and 6 only
14	PDQ-39 questionnaire	PROM	10	
15	MiniBESTest	Blinded assessor	15	
16	EQ-5D-5L	PROM	2	
17	Collect/re-issue falls and exercise diary (if paper-based format is used)	Blinded assessor	2	Weeks 2, 16 and 18 only
18	Retrieve StepWatch and step count	Blinded assessor	1	Week 18 and 22 only

Table 4. Summary of Weeks 2, 6, 18 and 22 blinded assessments

All data will be entered into the eCRFs on the REDCap database, according to instructions provided by the PenCTU.

In addition to the assessments detailed above, at Weeks 18 and 22 StepWatches should be collected from the participant and step count recorded. Please refer to the following section for further details.

If needed, it is permissible to post the questionnaires to the participant the week prior to their assessment to complete at home, to reduce the burden of the assessment session. The participant must bring the questionnaires with them on the day of their assessment so the blinded assessor can check they have been completed correctly. The blinded assessor will be responsible for entering the responses into the database.

Every effort should be made by the blinded assessor to collect all the data. When assessing eligibility, only participants who are able to comply with the study visits and procedures should be recruited. However, it is recognised that there may be occasions where a participant may attend a visit on a day where they are having particular difficulty with their mobility and fatigue. In this instance, the APA stepping task may be omitted first. If this is not sufficient, the miniBESTest may then be omitted. A protocol deviation form should still be completed for any missing data to enable the monitoring of this by PenCTU. The omission of tests should only occur in a minority of cases.

8.8. StepWatch issue and data collection

At Weeks 17 and 21 post-baseline, sites should issue all participants with a StepWatch via post, with instructions that these should be worn in the 7 days prior to the Week 18 and 22 blinded assessment visits and to return the StepWatch at these visits. Sites will be provided with pre-paid packaging envelopes. Sites should maintain the log of the watch serial number issued, date posted and date returned. PenCTU will be providing a device tracking log for sites to document StepWatch delivery and return. Sites will be provided with 4 StepWatches.

8.9. Payment

To encourage adherence to the visit schedule, participants will be informed during the pre-screening call that they will receive a £20 voucher for each completed blinded assessment visit (baseline and Weeks 2, 6, 18 and 22). Participants will receive one voucher at the end of their time on the study, with a maximum value of £100 if all blinded assessment visits are completed, after their Week 22 visit or after withdrawal. Vouchers will be posted to participants directly; the provision of vouchers will be managed by PenCTU.

Additionally, travel expenses can be reimbursed for all clinic visits. Participants should be provided with a travel reimbursement form at the start of the study and submit one claim form at the end to reclaim travel expenses for all study visits. Sites will reimburse participants expenses and reclaim this cost from the Sponsor via quarterly invoices.

8.10. Recording screening, recruitment and retention information

The following shall be recorded:

- The number of possible participants contacted for telephone screening
- The number of participants consented for face-to-face screening
- The number of participants who are suitable and agree to take part in the study
- The number who complete baseline outcome measures
- The number in each group who drop out after group allocation
- The number in each group drop out at each stage of the study

8.11. End of study

Participants will complete their involvement in the study after their week 22 visit has concluded. This will include participants who take part in the optional qualitative component. The trial will end on completion of all data collection. This timepoint is defined as when the final participant has completed their week 22 visit and this data has been entered into the study database.

9. TRIAL SCHEDULE

This section describes the conduct of the trial in chronological order. A participant journey flow chart is illustrated in Section ix: Participant Journey Flow Chart. ***Table 4. Tabulated summary of trial:***

	Screening	Week 0 -1	Baseline (Week 0)	Randomisation	Post-baseline						
TIMEPOINT			**W0**	**W0**	***W1***	***W2***	***W6***	***W17***	***W18***	***W21***	***W22***
ENROLMENT & STEPWATCH ISSUE:											
Informed consent	X										
Eligibility screening	X										
Gait description	X										
Demographics	X										
Clinical/medical history	X										
ADLs and walking ability	X										
Group allocation				X							
StepWatch issue		x						x		x	
INTERVENTION / TREATMENT PERIOD:											
Usual Care				←	—	—	—	—	—	—	→
Intervention					←	—	—	—	→		
BLINDED ASSESSMENT MEASURES:											
Primary outcome measure: 10mWS									x		
Secondary outcome measure assessments (underlined and marked with an asterisk (*example) are PROMS) :											
****Participation on physio/exercise classes***			X			X	X		X		X
****PD medication (LEDD)***			X			X	X		X		X
10mWT (speed and stride length)			X			X	X		X		X
****UPDRS Sections 1a & 1b: non-motor ADLs***			X			X	X		x		X
****UPDRS Section 2: Motor ADLs***			X			X	X		X		X
****N-FOG questionnaire***			X			X	X		X		X
UPDRS Section 3: Physical assessment			X			X	X		X		X
****FES-I questionnaire***			x			x	x		x		x
****PDQ-39 questionnaire***			X			X	X		X		X
MiniBESTest			x			x	x		x		x

*EQ-5D-5L			x			x	x		x		x
*Falls diary			x			x	x		x		x
Step Watch step count			x						x		x
Dynamometry (mechanistic)			x			x	x		x		x
Phase coordination index (mechanistic)			x			x	x				
Anticipatory postural adjustment (mechanistic)			x			X	X				
UNBLINDED SECONDARY OUTCOME ASSESSMENT MEASURES (FES CLINICIAN):											
10mWT without FES					x	x	x		x		
10mWT with FES						x	x		x		
Timed Up and Go (TUG) with FES						x	x		x		
Timed Up and Go (TUG) without FES					x	x	x		x		
Resources used (clinician time and consumables)					x	x	x		x		
*SUS scale									x		
*FES experience questionnaire									x		
SAFETY MONITORING											
Device related adverse events			←						→		
Serious adverse events			←						→		

10. QUALITATIVE COMPONENT

10.1. Background & aims

To understand the experiences and views of individuals with PD using FES and any potential perceived impact or carryover effect of FES, we will carry out an embedded qualitative study. The finding from the qualitative study can be used to contextualise and provide meaning to the quantitative measures, assisting in their interpretation and providing a holistic and patient-centred understanding and insight of both physical and psychosocial factors. Furthermore, feedback from the feasibility study indicated that carers/family members were sometimes required to assist family members using FES equipment and others felt that the improved mobility was important to them. Therefore, to gain a true understanding of how FES is used in the real-world, and the wider implications and potential burden, we will also explore the views of carers and partners of participants who received FES.

10.2. Research questions

- What are the views and experiences of individuals and with Parkinson's using FES within the RCT?
- What are the views and experiences of family members or carers of the individuals with Parkinson's using FES within the RCT?

10.3. Research design

A qualitative study using telephone or online video (i.e., Zoom or Teams) semi-structured interviews with both individuals with PD using FES and their family members or carers. Interviews will take up to 60 minutes. We are also interested in the views of individuals who are randomised to the FES group but discontinue using it. Therefore, there will be three groups of participants:

- **Group 1:** individuals with PD randomised to the FES arm of the RCT who are willing to take part in the embedded qualitative study. These participants will be asked to take part in one semi-structured interview at approximately Week 22 (4 weeks after they have stopped using FES). This will enable data to be collected about how the participant found FES during the 18 week intervention period and any carry over effects. .

- **Group 2:** individuals with PD randomised to the FES arm of the RCT who discontinue using FES, either via partial withdrawal from the intervention only or full withdrawal from the study, and consent to participating in the qualitative study. These participants will be asked to take part in one single interview after they have withdrawn from the study.

- **Group 3:** family members or carers of the individuals in group 1 who are willing to take part in the embedded qualitative study, and the participant in the RCT is happy for them to take part. These participants will be asked to take part in one interview after their family member has come to the end the study (i.e. Week 22).

10.4. Sampling, participants & recruitment

Group 1: individuals with Parkinson's disease taking part in the FES arm of the RCT

For group 1, we aim to recruit a maximum sub-sample of 50 participants from the overall RCT target sample size of 117 (~42%), as this will provide an in-depth range of views and experiences. The only inclusion criterion is anyone within the FES arm of the study willing to take part in the embedded qualitative study. There is an optional criterion on the Informed Consent Form where the participant can indicate whether they would like to be contacted regarding participation in this part of the study.

We will use a combination of convenience and purposive sampling approaches to achieve a range of views and experiences based on diversity in age, gender, level of mobility, time since diagnosis of Parkinson's and the recruitment of participants from all centres within the trial. This will involve starting off with a convenience sampling approach, where all participants taking part in the FES arm of the RCT and consented to being contacted about participating in the optional qualitative component are invited to take part in the embedded qualitative study. A sampling matrix will then be used to keep track of the demographics of the participants being recruited (e.g., in terms of age, gender, mobility, time since diagnosis and trial centres) and purposive sampling will be used to recruit any gaps within the matrix. Those who consented to being contacted will be sent a letter inviting them to participate with a Participant Information Sheet (PIS). This will include contact details for the qualitative research team. If they are interested in taking part, or have any questions about the qualitative study, they will be asked to telephone or email the qualitative research team, after they have had at least 48 hours to consider participation. If the no contact has been received from the participant after 2 weeks, a reminder invite letter will be sent to them. If the reminder letter is not acted upon, no further contact will be made to the participant and they will be documented as not interested. The researcher will then schedule a call to carry out telephone consent. This may also take place during the initial telephone call, if the participant is happy to do so. During this call the participant will be provided with the opportunity to ask any questions about the study, and if they are willing to participate an appropriately delegated researcher will read out each point on the consent form and ask the participant to verbally confirm whether they agree with each statement. If the participant does not answer within three

telephone attempts, it should be documented in the screening log that they are not interested. After consent has been received, a date and time for the interview will be scheduled via the participants preferred method of contact (either telephone or video-conferencing). This may take place on the same phone call that consent was received, if that participant wishes to do so. Otherwise, a more convenient date and time will be arranged.

Group 2: individuals with Parkinson's disease taking part in the FES arm of the RCT but discontinue using FES

All participants across all centres who are randomised to the FES arm of the study and discontinue using FES, either via partial withdrawal from the intervention only or full withdrawal, will be asked if they are happy to take part in the qualitative study on the withdrawal form, so that we can identify factors that led to their decision and explore their experiences of using FES. We will use a convenience sampling approach with a maximum sample of 15 participants. The withdrawal rate from the intervention group is unknown, therefore it is not possible to say with certainty the sample size that will be achieved. Those who consented to being contacted will be sent a letter inviting them to participate with a PIS and recruited via the same method as Group 1, described above. Interviews will be scheduled and take place via the same method as Group 1, as described above.

Group 3: family or carers of the individuals in group 1

Group 3 will involve a maximum of 25 family members or carers of the Group 1 sub-sample of participants taking part in the embedded qualitative study. This will be a convenience sample of participants and identified by asking the Group 1 participants if they are happy for their family members or carers to be approached to take part in the study, during the informed consent telephone call. If they are, they will be provided with a separate PIS specifically for Group 3 to give their family member or carer. This will be sent via post or email and will include contact details of the qualitative research team. If the family member/carer are interested in taking part, or have any questions about the qualitative study, they will be asked to telephone or email the qualitative research team, after they have had at least 48 hours to consider participation. The participant will recruited via the same method as Group 1, described above. Interviews will be scheduled and take place via the same method as Group 1, as described above.

10.5. Data analysis

Using a combination of hand coding and NVivo 11 software (http://www.qsrinternational.com/what-is-nvivo), data will be analysed using reflexive thematic analysis, as this provides a flexible approach for identifying key patterns relating to the experience of using FES. To provide a clear understanding of the views of different groups of participants and at different stages of the study, interviews will be analysed in the three separate groups. Thematic analysis steps will involve:

1) Familiarisation with the data through reading and re-reading in each set of data, generating initial codes
2) Verifying coding across team members until consensus is achieved
3) Group codes to generate themes
4) Reviewing and developing themes using an iterative process of reviewing the raw data
5) Refining and naming the themes
6) Verification of final themes and comparing across participant groups

11. ECONOMIC EVALUATION COMPONENT

There is no formal economic component in the STEPS II trial. However, health-related quality of life will be collected using the EQ-5D-5L. Intervention health resource cost will also be collected. This information will be used to inform future studies.

12. PARTICIPANT WITHDRAWAL

Participants may wish to withdraw from the study at any stage. Any participant who withdraws will be asked to provide a reason but will be made aware that they are under no obligation to provide one, and that their withdrawal from the study shall in no way affect their access to ongoing treatment. Withdrawal from the study, and reason if provided, will be documented in the participants' clinical records reported to the CTU using a specific eCRF. Data collected prior to withdrawal will be included in the analysis, unless the participant specifically requests that this data be destroyed. All participants who withdraw will continue to be treated as per usual care.

Participants withdrawals are categorised as either pre-randomisation withdrawal, discontinuation, full withdrawal or lost to follow-up. If the participant is withdrawn pre-randomisation, they will be replaced with another participant. If the withdrawal occurs post-randomisation, the participant will not be replaced. The participant may opt to discontinue from part of the study, this could include discontinuation from the intervention, follow-up visits or from completing falls/exercise diaries. Sites should discuss with participants to determine the level of withdrawal required and document the reason for withdrawal, if the participant is willing to provide that information.

13. SAFETY MONITORING

Device-related adverse reactions will be collected at participants FES clinic visits, or if a participant contacts the FES clinician in between study visits to report adverse reactions. Serious adverse events (SAEs) will be reported in line with the pathway detailed in the following sections.

13.1. Definitions

An **Adverse Event (AE)** is any unfavourable sign, symptom, or disease in a participant, regardless of severity and regardless of cause.

A **Device-related Adverse Reaction (DAR)** is an adverse event which is considered to have been definitely, probably or possibly caused by either the trial intervention or the trial procedures.

A **Serious** Adverse Event (SAE) or **Serious** Device-related Adverse Reaction (SDAR):

- results in death
- is life-threatening*
- requires inpatient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability/incapacity
- is a significant or important medical event

*The term "life-threatening" in this context refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospital admissions for elective procedures **will not be reported as SAEs. All unplanned hospital admissions will be reported as SAEs, regardless of duration of hospital stay. This includes visits to ED departments.

A **Suspected Unexpected Serious Device-Related Adverse Reaction (SUSDAR)** is an event which:

- is serious, as defined above, **and**
- is considered to have been definitely, probably or possibly caused by either the trial intervention or the trial procedures, **and**
- is deemed 'unexpected' i.e. the reaction is one which has not been foreseen by the Chief Investigator.

Guidance on assessing events against these definitions is described later in this section. Operational definitions for (S)AEs

13.2. Detecting and recording reportable adverse events

Detailed instructions for the recording and reporting of serious adverse events will be provided to investigator sites by PenCTU in the form of a Work Instruction. The primary means of detecting serious adverse events will be the interactions between the research team member(s) and the trial participant at each of the data collection timepoints. At each visit or telephone call, participants will be asked to describe any adverse events they have experienced.

Any events meeting the criteria for seriousness (defined in Section 13.1) must be recorded by the research team member in the participant's health record and on the relevant Safety Reporting eCRF. SAEs are subject to expedited reporting so must be processed in a timely manner.

13.3. Assessing causality of (serious) adverse events

For serious adverse events, the PI (or authorised delegate) will assess the causal relationship between the SAE and trial participation. For participants in the intervention group, the PI will record their opinion on whether the SAE was caused by using the FES device, and whether the SAE was caused by any trial procedures. For participants in the control group, the PI will record their opinion on whether the SAE was caused by any trial procedures. Causal relationship will be recorded in the participant's health record and in the eCRF. SAEs caused by the intervention or trial procedures in the opinion of the PI will be regarded as serious device-related adverse reactions (SDARs).

13.4. Reporting Serious Adverse Events and Serious Adverse Reactions

All SAEs and SDARs must be reported to PenCTU within 24 hours of the research staff becoming aware of the event, according to instructions provided by PenCTU. For each SAE/SDAR the following information will be collected:

• full details in medical terms and case description
• event duration (start and end dates, if applicable)
• action taken
• outcome
• seriousness criteria
• causal relationship

PenCTU will immediately notify the CI of any reported SAEs / SDARs and the CI will record a second assessment of causal relationship. The CI may upgrade the causality assessment (e.g. from not related to related) but may not downgrade the assessment (e.g. related to not related). Where a causal relationship is suggested, the CI will record an assessment of expectedness. Expectedness will be judged on a case-by-case basis. An event deemed to be unexpected will be regarded as a SUDSAR and will be subject to expedited onward reporting as described in Section 13.5 and will be followed up until the event has resolved or an outcome has been reached.

13.5. Onward reporting of SAEs / SDARs / SUDSARs

Onward safety reporting activities and responsibilities are summarised in Table 5.

Table 5: Onward safety reporting activities and responsibilities

Event	Reported by	Reported to	Reported when	Reported how
SUDSARs	PenCTU	Sponsor	Within* 24 hours	Email to tumi.kaminskas1@nhs.net
SUDSARs	PenCTU	REC† & DMC‡	Within* 7 or 15 days¶	Using non-CTIMP safety report form (available on HRA website), by email
All SAEs/SDARs	PenCTU	Sponsor & DMC	Quarterly	Line listing, by email
Overall safety concerns	PenCTU	REC	Annually	Using annual progress report form (available on HRA website), by email

**of the CI becoming aware of the event*
†*REC - Research Ethics Committee*
‡*DMC – Data Monitoring Committee*
¶*7 days for fatal or life-threatening events. 15 days for others*

13.6. Coding of adverse events

PenCTU will maintain a register of all recorded serious adverse events. Events entered into the eCRF will be coded by designated members of PenCTU staff using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 23.1. Events will be coded at two levels - the ‘preferred term’ (PT) and ‘System organ class’ (SOC). The same version of the MedDRA dictionary will be used throughout the trial.

13.7. Safety oversight

The Trial Management Group (TMG) will discuss any SUDSARs and any emerging safety concerns at monthly TMG meetings. Line listings of SAEs/SDARs, produced by PenCTU, will be reviewed 6-7 monthly by the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC), or sooner if there are participant safety concerns, in accordance with the details set out in the agreed DMC and TSC Charters.

14. STATISTICS AND DATA ANALYSIS

14.1. Target sample size and justification

All participants will be randomised on a 1:1 basis to receive usual care (control arm) or FES in addition to usual care (experimental arm). The required sample size is based on data from the feasibility RCT, where the between-group mean difference in change in walking speed was estimated as 0.14ms^{-1} with a 95% confidence interval (CI) of (0.03 to 0.26).

Assuming a mean difference from baseline of 0.13ms^{-1} between the two arms, and a standard deviation (SD) of 0.28ms^{-1}, a total of 198 participants will be required to give the study 90% power to detect this difference at 18 weeks, with a two-sided significance level of 5%. In order to account for participants who are randomised but do not reach the primary endpoint, a 15% loss to follow-up rate has been added, which increases the required sample size to 234 participants. See Appendix 1 for power scenarios based on the planned recruitment target.

14.2. Planned recruitment rate

The recruitment target is 234 participants over a 24-month recruitment period. Participants will be recruited from eight centres that routinely see pwPD in outpatient clinics. The average recruitment rate achieved in the feasibility study was 1.8 participants per site per month and, assuming a slightly slower rate in the opening months of the study together with staggered site opening, we estimate that recruitment of 100 participants after 12 months will put the trial on course to meet the recruitment target of 234 participants over 22 months of recruitment.

14.3. Statistical analysis plan

A detailed statistical analysis plan (SAP) will be drafted by the trial statisticians and approved by an independent statistician prior to database lock. The study will be reported following the relevant Consolidated Standards Of Reporting Trials (CONSORT) guidelines. The statistical significance level for hypothesis tests will be two-sided at the 5% level and between-group estimates will be presented with two-sided 95% confidence/credible intervals, for both primary and secondary outcomes. Primary analyses for the primary and secondary outcomes will be adjusted for recruitment site (stratification factor) and where relevant the baseline measure of the outcome under consideration. For completeness, simple unadjusted analyses will also be presented. No adjustments for multiple analyses will be made as the trial has a clearly specified primary outcome. Model assumptions will be visually checked and bootstrapping implemented as required e.g. to handle substantial deviations from normality.

14.3.1. Participant analysis populations

The primary analysis population will include all participants, as randomised, for whom the primary outcome, change in walking speed between baseline and week 18, can be derived. Secondary analyses of the primary outcome will consider adherence with allocated treatment, i.e., based on participants who meet a minimum threshold of adherence with their allocated trial treatment (in particular usage of FES); full details will be included in the SAP.

The safety outcomes will be considered on an as treated basis.

14.3.2. Summary of baseline data and flow of patients

Baseline characteristics of participants will be summarised descriptively and used to assess for any marked baseline differences in demographics or outcome measures between the two allocated groups. Loss to follow-up after randomisation will be reported separately for each group, summarised visually via a CONSORT flow diagram. Baseline characteristics will be subjectively examined to assess for potential differences between participants who withdraw, discontinue FES, and those who complete the trial.

14.3.3. Primary analysis of the primary outcome

The primary analysis of the primary outcome measure will compare the change in walking speed between allocated groups using a mixed effects repeated measures model, facilitating inclusion of participants who provide at least one post-baseline walking speed, which is a valid and unbiased approach when these data are missing at random (MAR) or missing completely at random (MCAR). The changes between baseline and each of the four follow- up time points (2, 6, 18 and 22 weeks) will be modelled on allocated group, time point and the interaction between allocated group and time point, with adjustment for baseline walking speed, recruitment site (stratification factor) and ankle proprioceptive sensory discrimination. The primary analysis will estimate the between-group difference (and confidence interval) at the primary endpoint of 18 weeks from this longitudinal model. Intercurrent events related to adherence to treatment (i.e. discontinuation/withdrawal) will be handled using the treatment policy strategy. Participant data collected prior to death will be included in the analyses. Therefore, primary analyses will be programmed and undertaken following the intention-to-treat principle.

14.3.4. Sensitivity and secondary analyses of the primary outcome

A simple, unadjusted estimate of the between-group difference, and corresponding 95% confidence interval, will be calculated based on a two-sample t-test approach.

The potential carryover effect will also be investigated by comparing the between-group difference in the change in 10m walking speed at week 18 and week 22, from the primary analysis model.

Pre-specified sensitivity analyses will be undertaken to assess the robustness of the primary analysis results, specifically the MAR assumption. To explore the impact of this assumption and impact of the missing data, a “best-worst” and “worst-best” case sensitivity analysis will be utilised.

An adaptive trimmed-means approach, which is valid when data are missing not at random (MNAR)67, may also be undertaken as a secondary analysis. This approach targets a different estimand to that of the primary analysis, by using a composite strategy to handle the intercurrent event of participants leaving the study early, therefore discontinuing allocated treatment.

In another secondary analysis of the primary outcome, a different estimand will be targeted by employing a principle stratum strategy to handle the intercurrent event of intervention non-compliance, thus assessing the effect of the FES intervention on walking speed amongst a subpopulation of compliers. Specifically, a complier-average causal effect (CACE) analysis using two-stage least squares instrumental variable methods will be undertaken to provide an unbiased estimate of the efficacy of FES, based on participants who meet a minimum threshold of adherence with their allocated trial treatment.

Further sensitivity/secondary analyses of the primary outcome will be discussed and agreed with the trial management group and oversight committees and pre-specified in the SAP, including any exploratory sub-group analyses.

14.3.5. Secondary outcome analysis

Continuous secondary outcomes will be descriptively summarised and analysed following a similar approach for the primary outcome (I) using simple two-sample t-test approach to calculate the unadjusted between-group difference and confidence interval and (ii) using mixed effects repeated measures models. The changes between baseline and each of the four follow- up time points (2, 6, 18 and 22 weeks) will be modelled on allocated group, time point and the interaction between allocated group and time point, with adjustment for baseline, recruitment site (stratification factor) and ankle proprioceptive sensory discrimination.

Binary secondary outcomes, including the proportions of participants with an increase in walking speed of at least 0.13ms^{-1}, will be analysed using logistic regression models, with adjustment for recruiting site.

Safety outcomes will be descriptively summarised.

14.3.6. Mediational analysis

In order to address the postulated mechanistic hypotheses, a structural equation modelling approach will be adopted. Specifically, path analyses, with adjustments in line with the main analyses as outlined above, will be undertaken to assess the extent to which variability in foot movement (limb bradykinesia), strength, inter-limb co-ordination and anticipatory postural adjustment at weeks 2 and 6 act as mechanisms for changing walking speed at weeks 6 and 18, respectively.

14.4. Interim analysis and criteria for the premature termination of the trial

There is no planned formal, comparative interim analysis for this trial. The DMC will review accruing data by allocated group during the trial delivery period, including the primary outcome and safety outcomes.

There is a planned blinded review of the assumption of the SD used in the sample size calculation. This will happen at the same time at which the recruitment and retention progression criteria are assessed, after the first 12 months of participant recruitment (please see ‘Section 5.2 Internal Pilot for study progression’ for further details). At this time, the observed SD of the change in walking speed between baseline and week 18 will be calculated by the trial statisticians, pooled across all participants with available data. The observed SD (and corresponding confidence interval) will be compared with the assumed 0.28ms^{-1} used in the sample size calculation and reviewed by the trial oversight committees, Sponsor and funder. If the observed SD is larger than expected, implications on the required sample size will be discussed, taking into account other factors such as the emerging retention rate at the primary end point and rates of completeness of the primary outcome, and remedial action will be considered if deemed necessary.

14.5. Procedure(s) to account for missing or spurious data

Reasons for being unable to collect data during an assessment will be recorded on the electronic case report form (eCRF), where appropriate. eCRFs will be assessed for missing data by the CTU and sites will be regularly chased for missing data. The CTU will maintain a record of site compliance with eCRF completion. If data completion is poor, a monitoring visit may be scheduled (See Section 16.4 Trial Monitoring).

The eCRFs will include mandatory fields, which must be filled in before the eCRF can be saved to reduce the risk of missing data. Where questions may need to be left blank, options such as ‘Not applicable’ or ‘Prefer not to say’ will be available, to differentiate these from missing data. Validations

will be written in to the REDCap database, to raise queries with particular data field, such as flagging if the date of a visit does not correspond to the correct timepoint. Periodic reminders will be sent out to participants to complete questionnaires and falls diaries, if they have selected to complete these electronically.

PenCTU data manager will write a series of R scripts to perform the following data tasks to aid data completeness, including checking overall completeness by field of all CRFs, checking all visits have been recorded in a logical order and checking SAE forms have been completed within the timeframe stipulated in Section 13 Safety Monitoring. The scripts will be run on a regular basis and any concerns will be raised individually with sites.

To reduce the risk of missing data for PROMs, participants will complete these during their blinded assessment visits, in between physical assessments. The assessor will check for missing data as each PROM is completed.

14.6. Other statistical considerations.

Any changes made to the SAP will be documented, including details of when the change was made (e.g. prior to data export) and whether the statisticians were blinded to allocated group at the time of the change.

15. DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate Data Management Plan (DMP).

The main study database will be developed by PenCTU, using the commercial electronic data capture system REDCap. The system uses validation and verification features to monitor study data quality and completeness.

15.1. Data collection tools and source document identification

A bespoke web-based application and REDCap database, developed by PenCTU, will be used for data management and recording participant data. Source data will include participants' medical records (e.g. for certain eligibility criteria and medical history), participant-completed documents (e.g. informed consent forms, falls and exercise diaries), worksheets provided by PenCTU and eCRFs. In the context of clinical care, investigator site staff must ensure that details of a patient's participation in the trial are recorded in the participant's health record. As a minimum, the participant's health record should be updated to include:

- Consent and eligibility for study
- Dates of all study visits and follow ups
- Device related adverse events
- Completion or discontinuation of study

Source data should be accurate, legible, contemporaneous, original, attributable, complete, consistent and available on request. The CTU will verify source data and source documents as stipulated in the study monitoring plan (see Section 16.4 Trial Monitoring). Study data will be recorded on eCRFs.

Participant questionnaires will be completed on eCRFs and participants will receive reminder emails to complete these. Paper-based options will be available on request and entered onto the eCRFs by site staff.

The investigator should keep a record of all participating patients and all original signed informed consent forms.

15.2. Data handling and record keeping

All eCRF data is stored in PenCTU's REDCap Community production infrastructure, hosted by AIMES on MS Azure datacentres located in the European Union. AIMES are NHS DSP Toolkit compliant and hold ISO27001 and Cyber Essentials Plus certifications. Microsoft Azure datacentres are Service Organization Control (SOC) type 1 and type 2 compliant. Data will be stored on hardware dedicated to PenCTU's instance of REDCap Community. All electronic data are backed up and stored with a full audit trail.

15.3. Access to Data

Direct access to investigator site records will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections,- in line with participant consent.

15.4. Archiving

Following completion of trial data analysis, the Sponsor will be responsible for archiving the study data and Trial Master File in a secure location for at least five years after the end of the trial. PenCTU will prepare the Trial Master File for archiving in accordance with the requirements of the Sponsor's SOP. PenCTU will prepare a copy of the final dataset for archiving according to the requirements of the CTU's SOP.

Principal Investigators at sites will be responsible for archiving Investigator Site Files and trial data generated at the site according to local policy. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical records containing source data or other trial related information should be labelled, physically or electronically, so as to ensure retention until the Sponsor gives authorisation to destroy. e.g. "Keep until dd/mm/yyyy" (where the date given is five years after the last participant's final visit).

16. OVERSIGHT, MONITORING, AUDIT & INSPECTION

16.1. Trial Management Group

A Trial Management Group (TMG) comprising the CI, co-applicants, trial statisticians, PPI representatives, CTU staff and Sponsor representatives will meet monthly throughout the trial to review overall trial progress, protocol compliance and data quality and completeness, identifying and addressing any issues with trial conduct as they arise.

16.2. Trial Steering Committee

A Trial Steering Committee (TSC) comprising an independent chairperson, independent clinician, independent statistician, two PPI representatives and designated members of the TMG will meet six monthly throughout the trial to provide overall supervision of a trial on behalf of the Sponsor and funder and to ensure that the trial is conducted in accordance with the protocol and governance guidelines. The full composition, role and function of the TSC will be described in a separate charter. TSC meetings will be guided by feedback from the DMC and TMG in advance of TSC meetings. The TSC will be responsible for reviewing DMC recommendations to decide whether to continue or

terminate the trial and whether amendments or changes to study conduct are required.

16.3. Data Monitoring Committee

A Data Monitoring Committee (DMC) comprising an independent chairperson, independent statistician and one independent clinician will meet approximately six monthly throughout the trial and be responsible for reviewing trial data to safeguard the interests of trial participants, assess safety and efficacy of the intervention, review external evidence with an impact on risk/benefit balance and for monitoring overall conduct of the clinical trial. The DMC will provide recommendations about stopping, modifying or continuing the trial to the TSC. DMC meetings will be held prior to TSC meetings, the DMC will be advisory to the TSC.

16.4. Trial monitoring

In accordance with CTU standard operating procedures for risk assessment and monitoring, a specific trial monitoring plan will be generated by the CTU, based on the CTU's risk assessment, with input from the TMG. The monitoring plan will be signed off by the CI and Sponsor before implementation.

CTU will perform ongoing central monitoring, outputs from which will be discussed by the TMG. Central monitoring will include close supervision of participant recruitment rates, attrition rates, data completeness (missing data), data quality (using range and consistency checks), protocol non-compliance, calendar checks (to identify deviations from participants' visit schedules), consent process checks (through collection of completed de-identified consent forms) and appropriateness of delegated duties at investigator sites (through collection of site delegation logs). Central monitoring will be used to identify areas of potential poor performance at individual investigator sites. Poor performance at sites may trigger on-site monitoring visits (subject to any COVID-restrictions), hosted by the investigator site PI and relevant members of the PI's team. On-site monitoring (if applicable) will be conducted by CTU staff according to established CTU standard operating procedures.

17. PUBLIC AND PATIENT INVOLVEMENT

In a survey of 1000 people with Parkinson's disease (pwPD) by Parkinson's UK, balance and falls were identified as the number one un-met research need [2]. This research project builds upon our experience of conducting three observational studies and feasibility RCT in pwPD [24,28,29,30]. We invited participants from the previous studies to form a Patient Advisory Group (PAG) that was led by Sheila Nell of the local Parkinson's UK Society group. The PAG have helped us to identify and refine the research question and study cohort, namely targeting the intervention at slower walkers. The group members were enthusiastic about the study and made further suggestions, which led to modification of the protocol, as it was thought to be too demanding for some pwPD. Feedback relating to practical difficulties dealing with FES equipment, has led to refinement in the usability aspects intervention. The PAG provided feedback on aspects of mobility that were affected by PD, in particular falls and balance and the positive effect experienced after using FES. This included the therapeutic effect, meaning that FES did not need to be used every day to experience improved mobility. A detailed balance assessment (mini BESTest) was added to the protocol. The PAG reviewed all participant documentation prior to submission to ethics. Improved procedures for performing the qualitative interviews were also suggested and were incorporated into the study. The protocol was tested in the feasibility study. The PAG met regularly throughout the study, providing input to a substantial amendment submission and discussed the study findings prior to submission of the final report.

The PAG was reformed from Participants of the feasibility for preparation of this application. The group reviewed and discussed the findings of the first study and reviewed the proposal for the new study. The group were asked if the study's results matched their experience of using FES. They agreed that they did. The choice of primary outcome measure was discussed, and it was agreed that speed was an important factor in walking; in particular being able to keep up with family and friends enabled better interaction. Several group members reported that they had experienced a therapeutic effect for walking speed and that this was an important effect of the intervention. One member reported that they had had difficulty using the FES equipment and it was agreed that improved support was needed for some FES users. The group felt that the amended protocol had reduce the burden from the assessment sessions due to the reduction in the number of assessments required. They supported the addition of the Timed-Up-and-Go test for assessing the effect of FES on freezing and agreed this was potentially an important treatment effect. The addition of the StepWatch activity monitor was also supported. Plans to include assessment of mechanism were discussed and approved. The addition of an upper limb assessment to assess whole body bradykinesia was welcomed. Plans were discussed to aid recruitment to the study including activities to publicise the trial by presenting the study to local Parkinson UK groups, including co-presentation with members of the PAG, a method that will also be used for dissemination of the results.

We will extend our current Patient Advisory Group (PAG) to at least ten members and we will review the membership each year. A larger PAG and the use of video conferencing will allow us to increase diversity by inviting members from a wider and more diverse area, removing the need to travel. Members will receive IT support. Given the progressive nature of the PD and the length of study, this provides the opportunity to give members the option to stepdown from the group. We will manage the contribution of the PAG through both a PPI lead and a PPI Co-ordinator. Sheila Nell, who has led the PPI in STEPS I, has stepped down and her role will now be taken by Richard Wood-Pen. We thank Sheila for her contribution. Richard, who is a retired project manager, was a participant in the STEPS feasibility study and has been part of the PAG that has contributed to the design of this study. Richard is a co-applicant and will be a member of the steering committee and advise on the overall conduct of the study. To reduce the administration burden and workload for the PPI lead, the PPI Co-ordinator (Maggie Donovan-Hall) will support the PPI lead by organising meetings, capturing PPI feedback, organise payments and monitor PPI impact.

Our Patient Advisory Group (PAG) will provide us with important patient perspectives on all aspects of the project. 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. PPI activities being incorporated at all stages of the study and will include:

1. Design of the research: The PAG will continue to advise the team to improve the design of the trial in terms of the successful participant recruitment methods, data collection processes, and intervention details.
2. Management of the research: The PAG will advise on recruitment strategies. They will also identify relevant questions to be included in the topic guide for the semi-structured interviews.
3. Developing participant information resources: The patient information sheets, consent forms, interview topic guide and any other patient documentation will be designed in partnership with the PAG.
4. Involvement in decision making process: PPI lead will be a member of the steering committee and directly report pack to the PAG.
5. The importance of continuous PAG communication: The PPI co-ordinator will stay in touch with the PPI lead and PAG through a short PPI newsletter that will be circulated on a quarterly basis.
6. Contributing to the reporting of the study report: Our results will be discussed with the PAG and their relevance and importance to pwPD. Interpretation of the interview findings will also be guided by the PAG.

7. Dissemination of research findings: We will work with the PD Society to publicise our results in a plain English format, providing articles and presentations. Members of the PAG will be invited to co-present the findings, ensuring that their view and perspective is represented.

The PPI Co-ordinator will be responsible for assessing and evaluating the PPI. This will be carried out by keeping a 'PPI Impact Log' that will capture:

1) The topics discussed with the PAG
2) What suggestions were made by the PAG
3) What changes resulted from the suggestion
4) The feedback given to the PAG of these changes
5) The PAGs reflections on the impact of these changes

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1. Research Ethics Committee (REC) review

The CI will obtain approval from the UK Health Research Authority (HRA) and Research Ethics Committee (REC) for the trial protocol, informed consent forms and other study documentation (e.g. Patient Information Sheet, GP letters). The Chief Investigator will ensure that this study is conducted in conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion. If required, amendments will be reviewed and accepted by the HRA and/or NHS R&D departments before they are implemented in practice at sites.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will be responsible for producing annual reports and will notify the REC at the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

This study was reviewed by Yorkshire & The Humber- Sheffield Research Ethics Committee.

18.2. Peer review

The study was funded by NIHR through open competition after independent external peer review was conducted.

18.3. Regulatory Compliance

The trial will not commence until a favourable REC opinion and HRA approval has been obtained. Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. For any amendment to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to

confirm their support for the study as amended.

18.4. Protocol compliance

Non-compliance with protocol will be captured on specific non-compliance report forms according to instructions provided by PenCTU and in accordance with PenCTU standard operating procedures. Protocol non-compliance will be reviewed periodically by the Trial Management Group as part of central monitoring (see 'Section 16 Oversight, Monitoring, audit and inspection'), with the aim of identifying and addressing recurrent episodes of non-compliance. Each reported non-compliance is reviewed by the PenCTU trial manager. PenCTU staff must immediately inform the PenCTU QA Manager if they believe that a serious breach has occurred (see below). Where the trial manager and/or PenCTU QA Manger believes that a non-compliance might constitute a serious breach, the trial manager should ensure that a completed non-compliance report form is provided to the Sponsor immediately.

18.5. Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(1.a) the safety, rights or physical or mental integrity of the participants of the trial; or

(1.b) the scientific value of the trial

Where a non-compliance meets the above criteria, PenCTU will immediately notify the CI and Sponsor. The Sponsor will email a serious breach report to the REC and to HRA (using the breaches.nres@nhs.net email address) within seven days of becoming aware of the event.

18.6. Data protection and patient confidentiality

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR) 2016.The trial Sponsor is the Data Controller for the trial data. PenCTU is a data processor, centrally managing trial data generated at investigator sites. The University of Plymouth is the data custodian since data are stored on databases managed by the University of Plymouth.

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening. Investigator site staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information in accordance with ethics approval.

Any paper-based data collection tools (e.g. worksheets and questionnaires) for capturing source data will remain at investigator sites. Investigator site staff will enter participant data into purposed designed data capture systems. Access to the system for all users (including PenCTU staff) is via a secure password-protected web-interface. Each participant will be allocated a unique system-generated study number. Participants will be identified in all study-related documentation by their study number and initials. Data collected and analysed during the study will be pseudonymised by the use of this unique identifier. A record of trial participants' names and contact details, hospital numbers and assigned trial numbers will be stored securely in a locked room at the trial site and is the responsibility of the site PI.

In order to facilitate central coordination of the study and contact between participants and qualitative researchers, participants' contact details will be entered into the data capture system by investigator site staff (after consent). Only limited staff at PenCTU will have access to these details and these details will not be made available in any form to any persons unless needed for study conduct.

Datasets prepared for transmission to statisticians (for analysis), co-applicants or Sponsor will be pseudonymised and will not contain any direct identifiers or participant contact details.

Audio data from qualitative interviews and session delivery audio and video recording of facilitators will be recorded either via Microsoft Teams or Zoom or using an encrypted digital audio recorder. Data collected using both Microsoft Teams and encrypted digital recorders will be stored on Microsoft SharePoint on the University's secure server using the participant's unique study number. All data will be deleted from digital recorders as soon as it is securely transferred. Audio recordings and transcribed data will only be accessible to the 'designated members of the qualitative evaluation team.

Transcription of audio recordings of interviews or sessions will only be carried out by members of the research team or professional services with confidentiality agreements in place.

18.7. Financial and other competing interests

The Chief Investigator, PIs at each site and TSC/DMC committee members will sign a declaration form to disclose any financial or other competing interests including, but not limited to:
• any ownership interests that may be related to products, services or interventions considered for use in the trial or that may be significantly affected by the trial
• commercial ties including, but not restricted to, any pharmaceutical, behaviour modification, and/or technology company
• any non-commercial potential conflicts e.g. professional collaborations the may impact on academic promotion.

Declaration forms will be filed in the Trial Master File (TMF).

18.8. Indemnity

This is an NHS-Sponsored research study. If an individual suffers negligent harm because of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an ex-gratia payment may be considered in the event of a claim.

18.9. Amendments

The Sponsor may make a non-substantial amendment at any time during a trial. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor must submit a valid notice of amendment to the REC for consideration. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amended documents will be allocated a new sequential version number. Once approved by REC, this version will supersede any previous versions.

18.10. Post trial care

Participants in the intervention group will return the FES device at their 18 week FES follow-up visit. The FES equipment is loaned to sites for the purpose of the study and must be returned to Salisbury NHS Trust after the study has concluded. Should participants wish to continue using FES after their

final visit, they will be advised to speak to their FES clinician or GP to explore any local options that may be available to them. Participants will be informed prior to agreeing to participate, and reminded at their final visit, that the FES device is not currently part of the standard care or NICE recommended for pwPD, and therefore may not be available to them on the NHS after their time on the study has concluded.

18.11. Access to the final trial dataset

During the study, the PenCTU data team will have access to the trial dataset, including identifiable participant data. Other members of the CTU and the wider study team will have restricted access to pseudo-anonymised study data. Access to the dataset will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits and inspections. Access will be overseen by the CTU data manager and trial manager. Access to the final dataset will be provided to the trial statisticians for analysis.

After the trial has been reported, the anonymised individual participant data that underlie the results will be available on request from the CI and Sponsor, along with supplementary files as required (e.g. data dictionaries, blank data collection forms, analysis code, etc.). Data will be shared with (or access to the data will be provided to) requestors whose proposed use of the data has been approved by the CI and Sponsor, under an appropriate data sharing agreement. It will not be possible to identify participants personally from any information shared.

19. DISSEMINATION POLICY

19.1. Dissemination policy

The data arising from the trial will be owned by the Sponsor. On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared. This report will be submitted to the Trial Sponsor and Funder and will be publicly available. Participating investigators will not have rights to publish any of the trial data without the permission of the CI and Sponsor.

The trial will be reported in a manuscript that will be submitted to a peer-reviewed medical journal as open access. The trial will be reported in accordance with relevant Consort Guidelines. All publications arising from this trial will acknowledge the Funder and a copy of all manuscripts will be provided to the Funder for review at the time of submission to a journal. However, the Funder does not have the right to revise any submission prior to publication. The trial protocol will also be submitted for open access publication to a peer-reviewed journal. A lay summary of the trial results will be produced and published on the PenCTU website, trial participants will receive a notification via email (if provided) or post when available. An anonymised participant level dataset will be produced and held within PenCTU.

19.2. Authorship eligibility guidelines and any intended use of professional writers

Authorship of all manuscripts and papers relating to this trial will be determined according to the International Committee of Medical Journal Editors criteria. All members of the TMG who have contributed to trial design, management, analysis and interpretation will be granted authorship of the Final Trial Report. The CI will retain lead author status on the Final Trial Report. There is no intention to use professional writers.

19.3. Authorship eligibility guidelines and any intended use of professional writers

In addition to a lay summary of the trial results, regular updates will be made available on the STEPS II website and / or emailed (posted if no email address available) to trial participants who have

provided consent. Communication will take the form of short updates (4 monthly intervals until publication) and newsletters (yearly intervals until publication) and will contain content around (but not limited to) timelines, milestones reached, recruitment and site updates, information and / or support relating to Parkinson's Disease, study assessments and the intervention.

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21. APPENDICES

Appendix 1: Power (based on two-sided test at 5% significance level) for detecting varying effect sizes based on recruiting 234 participants

	Target Difference in Change in Walking Speed[1]	SD of Change in Walking Speed[1]	Equivalent Detectable Standardised Effect Size	Power if 80% retention to 18 weeks (186 participants followed-up)	Power if 85% retention to 18 weeks (198 participants followed-up)	Power if 90% retention to 18 weeks (210 participants followed-up)
Base case	**0.13**	**0.28**	0.464	88%	**90%**	92%
Fix SD, vary detectable target difference	0.09	0.28	0.321	59%	61%	64%
	0.11	0.28	0.393	76%	79%	81%
	0.15	0.28	0.536	95%	96%	97%
	0.17	0.28	0.607	98%	99%	99%
Fix target difference, vary SD	0.13	0.37	0.351	66%	69%	72%
	0.13	0.33	0.394	76%	79%	81%
	0.13	0.29	0.448	86%	88%	90%
	0.13	0.26	0.500	92%	94%	95%

[1] change in walking speed between baseline and 18 weeks