STATISTICAL ANALYSIS PLAN

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

Funding Body: NIHR Research for Patient Benefit (PB-PG-1014-35012)

IRAS and HRA Number: 16/SW/0041

Sponsor: Salisbury NHS Foundation Trust

Chief Investigator: Prof Paul Taylor, Salisbury NHS Foundation Trust

Current stage of SAP: First Draft

Statistical Analysis Plan Final Sign-Off:

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BUCRU sign-off			
Chief Investigator	Paul Taylor		

Amendments:

Amendment Number	Date	Sign-off

1. Study summary

World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ISRCTN17609599
Date of registration in primary registry	5th April 2017
Secondary identifying numbers	RfPB: PB-PG-1014-35012 IRAS project ID: 192222 REC reference: 16/SW/0041
Source(s) of monetary or material support	Research for Patient Benefit (RfPB) funding stream of the National Institute for Health Research (NIHR)
Sponsor	Salisbury Health Care NHS Trust Dr Steff Scot Tel: 01722 336262 Ex 2027 E-mail: stef.scott@salisbury.nhs.uk
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Public title	STEPS
Scientific title	The Effectiveness of Peroneal Nerve Functional Electrical **ST**imulation (F***E***S) for the Reduction of Bradykinesia in **P**arkinson's Disease: A Pragmatic Feasibility **S**tudy for a Single Blinded Randomised Control Trial (STEPS).
Countries of recruitment	UK
Health condition(s) or problem(s) studied	Bradykinesia in Parkinson's Disease
Intervention(s)	Functional Electrical Stimulation delivered to the common peroneal nerve Normal care (no intervention)
Key inclusion and exclusion criteria	• Inclusion criteria: • aged 18 years and above idiopathic Parkinson's disease

Data category	Information
	• Hoehn and Yahr stages I to IV • difficulty with gait (includes any deficit in dorsiflexion or eversion, bradykinesia, festination, akinesia or • hypokinesia) • able to walk 10m with appropriate walking aids but without assistance from another person • medically stable • able to understand and comply with assessment procedures • able to give informed consent Exclusion criteria: • able to walk 10m in less than 12.5s (walking speed >0.8ms-1) indicating non limited functional walking • other treatment than standard drug therapy (FES, deep brain stimulation, duodopa, apomorphine) • atypical or secondary parkinsonism or parkinsonism related to other neurodegenerative diseases • dropped foot due to any neurological condition other than Parkinson's Disease • untreated or refractory epilepsy • pregnancy • cardiac pacemaker, or other active medical implanted devices • denervation of the common peroneal nerve • malignancy or dermatological conditions in the area of the electrodes • major cognitive impairment; dementia.
Study type	A Pragmatic Feasibility Study for a Single Blinded Randomised Control Trial
Date of first enrolment	Planned for April 2016
Target sample size	68
Recruitment status	Closed
Primary outcome(s)	• Patient identification, recruitment, willingness to be randomised and loss-to-follow rates
Key secondary outcomes	• Participant views on what would constitute a meaningful outcome measure. • Participants views on the recruitment information and process

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

2. Aims and objectives:

Aims and objectives

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

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

This will be assessed by examining the effect on:

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

Before a full RCT can be undertaken there are matters that must be addressed. We therefore propose a feasibility study to determine the following objectives:

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

3. Overall design and analysis:

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

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

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

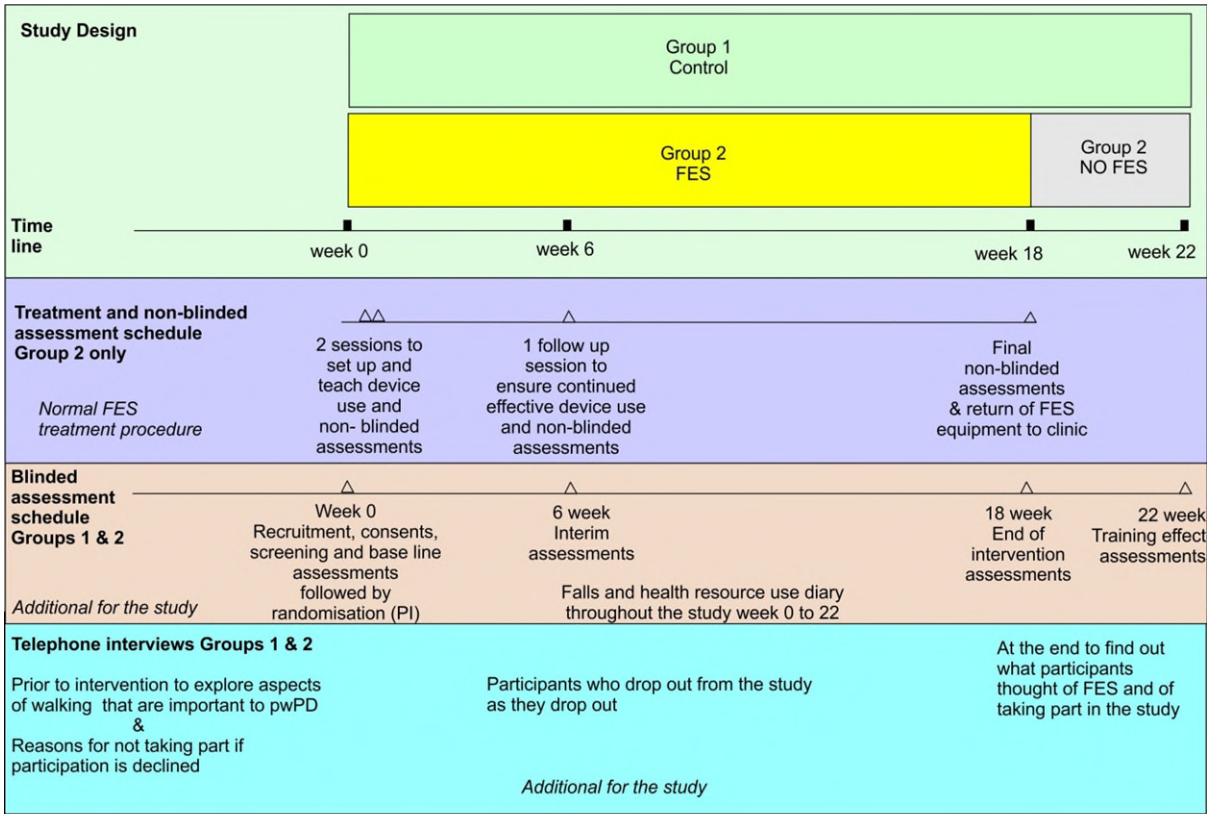


Figure 2. Trial design.

4. Participant recruitment:

4.1 Summary of sample size considerations:

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

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

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

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

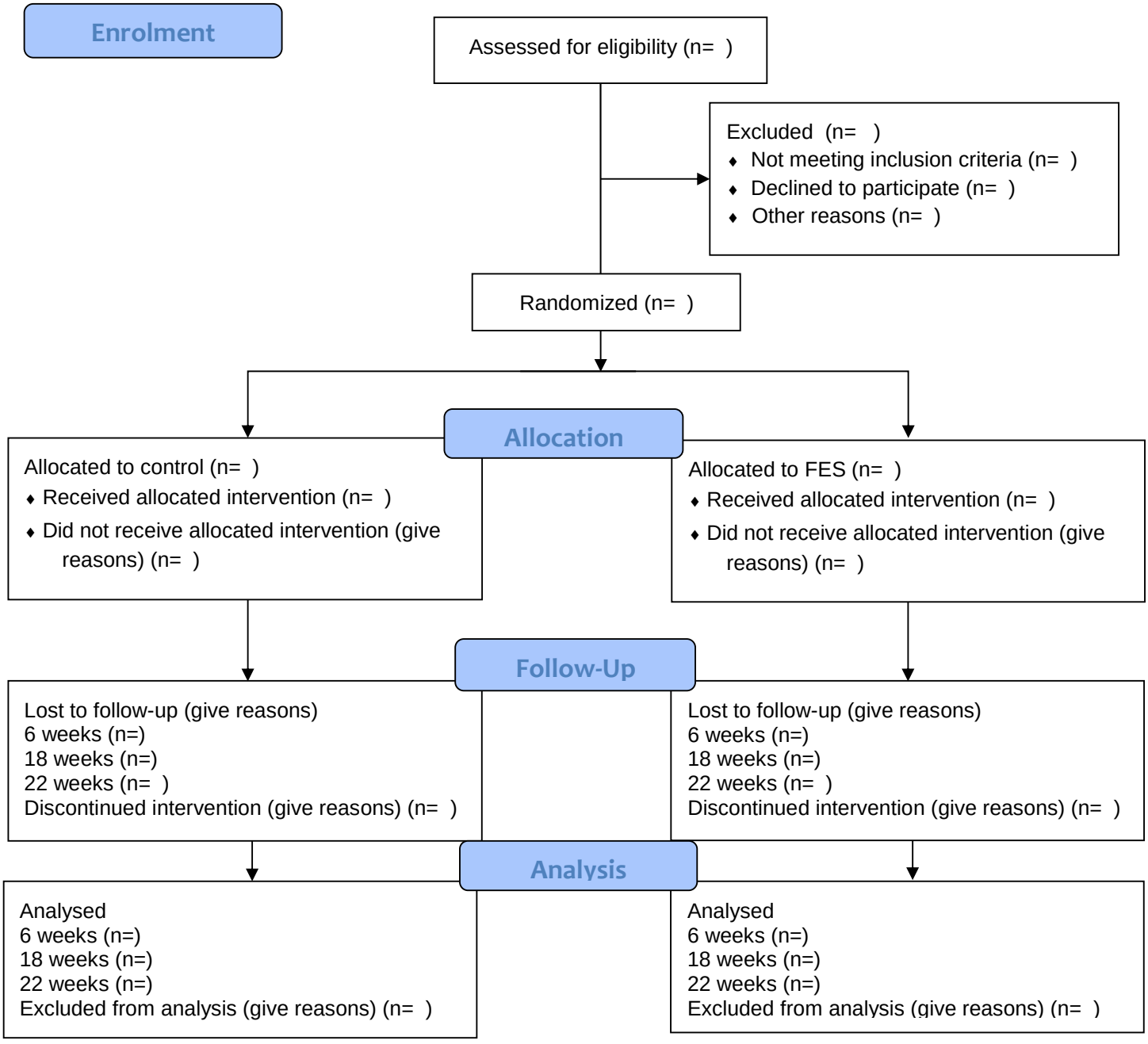
4. A within-subject correlation I for outcome variable circa 0.7 with 90% confidence interval *+/- 10%. (*Using a conservative estimate of R of 0.7, based on an observed R of 0.85 in observational studies on the same patient population. Since the time frame for the proposed full RCT will be longer than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

Sample size calculations from NCSS PASS v.11

4.2 CONSORT flow chart:

A CONSORT flow chart will be produced showing the flow of recruitment into the RCT (numbers available, approached, eligible, randomised, along with reasons if not approached or not eligible) and through the study (numbers with outcome data, reasons for withdrawing etc.).

Figure 2: CONSORT Flow Diagram



5. Trial data collected:

Variable	Purpose	Source	Level of measurement	Recoding	Analysis assumptions
Stratification variables					
Study site	Stratification variable and covariate in main analyses	Screening	Nominal	Salisbury London	
Participant descriptives at baseline					
Date of baseline visit	Baseline characteristic	Baseline Assessment of 10mWT	Date		
Date of Birth	Baseline characteristic	Study entry form	Date		
Age	Baseline characteristic		Scale	Calculated from DoB and date of baseline visit	Normal distribution
Gender	Baseline characteristic	Study entry form	Nominal	Male Female	
Source of participant	Baseline characteristic	Study entry form	Nominal	Hospital GP PD Soc. web page Word of mouth Movement disorder nurse Other	
Date at diagnosis	Baseline characteristic	Study entry form	Date	Age at diagnosis calculated from data at diagnosis and date of birth	Normal distribution
Medical history	Baseline characteristic	Study entry form	Text	Medical history text to be coded	
Medications	Baseline characteristic	Study entry form and Baseline Assessment of 10mWT	Nominal	Baseline medications at baseline derived from list of medications to be identified and coded from study entry and baseline	
Receiving physiotherapy	Baseline characteristic	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal		
Attending exercise class	Baseline characteristic	Baseline Assessment	Nominal		

or group		of 10mWT, and assessments at week 6, 18, 22			
10m walking speed m/s (attempt 2)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Ratio		Normal distribution
10m walking cadence steps/min (attempt 2)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Ratio		Normal distribution
10m walking – freeze number (attempt 2)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Count		
10m walking festination (attempt 2)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Count		
Walking aid during test	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	None Stick 2 sticks Frame Verbal cue Visual cue Other	
Walking description	Baseline characteristic	Study entry form	Nominal	Multiple responses allowed: Reduced dorsiflexion Reduced eversion Freezing Festination Short strides Slow walking	
Heel strikes	Baseline characteristic	Study entry form	Nominal	No Yes	
Affected side	Baseline characteristic	Study entry form	Nominal	R L R>L L>R	

				R=L	
Walking distance at best	Baseline characteristic	Study entry form	Nominal	0m 10m 50m 100m 500m 1000m 5000m More	
Walking distance at worst	Baseline characteristic	Study entry form	Nominal	0m 10m 50m 100m 500m 1000m 5000m More	
Assistive devices for walking	Baseline characteristic	Study entry form	Nominal	Multiple responses possible: Stick 2 sticks Frame (no wheels) Frame (wheels) Wheelchair Mobility scooter Audio queuing Visual queuing Ankle foot orthosis	
Participant view of main walking problem	Baseline characteristic	Study entry form		List of problems to be identified and coded	
Leg circumference at head of fibula – Left leg mm	Baseline characteristic	Study entry form			
Leg circumference at head of fibula – right leg mm	Baseline characteristic	Study entry form			
Modified Hoehn and Yahr scale	Baseline characteristic	Study entry form, and assessments at 0, 6, 18 and 22 weeks (part of MDS-UPDRS)	Nominal	Unilateral only Unilateral and axial Bilateral – no balance impairment Mild bilateral – pull test recovery Mild to moderate Severe disability Unable to walk	
Other medical conditions	Baseline characteristic	Study entry form	Nominal	No Yes	
Current living	Baseline	Health	Nominal	Alone	

situation	characteristic	Economic Assessment at week 0		At home with immediate family Friend/ relative's home Residential care Other	
Current occupation	Baseline characteristic	Health Economic Assessment at week 0	Nominal	Paid work – FT Paid work – PT Unpaid work – FT Unpaid work – PT Retired Home keeper Unable to work – PD Unable to work – other reason Not working – other reason	
Fall in past 6 weeks resulting in injury or medical attentions	Baseline characteristic	Health Economic Assessment at week 0	Count	No Yes – once Yes – 2 or 3 times Yes – 4 to 6 times Yes - 7 to 10 times Yes – more than 10 times	
Fall in past 6 weeks resulting in injury or medical attentions	Baseline characteristic	Health Economic Assessment at week 6,	Count		
Fall in past 12 weeks resulting in injury or medical attentions	Baseline characteristic	Health Economic Assessment at week 18	Count		
Fall in past 4 weeks resulting in injury or medical attentions	Baseline characteristic	Health Economic Assessment at week 22	Count		
Total falls over 22 weeks			Count	Derived by adding data on falls collected at 6, 18 and 22 weeks. Participant excluded if any data missing	
Plantarfexion – passive ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments	Continuous		Normally distributed

		at week 6, 18, 22			
Plantarfexion – passive ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Dorsifexion – passive ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Dorsiflexion – passive ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Eversion – passive ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Eversion – passive ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Inversion – passive ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Inversion – passive ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Plantarfexion – active ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT,	Continuous		Normally distributed

		and assessments at week 6, 18, 22			
Plantarfexion – active ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Dorsifexion – active ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Dorsiflexion – active ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Eversion – active ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Eversion – active ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Inversion – active ROM (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Inversion – active ROM (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Continuous		Normally distributed
Plantarfexion –	Assessment at	Baseline	Nominal	No contraction	Normally

MRC (Right ankle)	week 0, 6, 18, 22	Assessment of 10mWT, and assessments at week 6, 18, 22		Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	distributed?
Plantarfexion – MRC (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	No contraction Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	Normally distributed?
Dorsifexion – MRC (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	No contraction Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	Normally distributed?
Dorsiflexion – MRC (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	No contraction Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	Normally distributed?
Eversion – MRC (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	No contraction Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	Normally distributed?

Eversion – MRC (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	No contraction Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	Normally distributed?
Inversion – MRC (Right ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	No contraction Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	Normally distributed?
Inversion – MRC (Left ankle)	Assessment at week 0, 6, 18, 22	Baseline Assessment of 10mWT, and assessments at week 6, 18, 22	Nominal	No contraction Flicker or trace Active (no gravity) Active (gravity) Active (gravity & slight resistance) Active (gravity & moderate resistance) Active (gravity & strong resistance) Normal power	Normally distributed?
PDQ39 - mobility	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item1, item2, item3, item4, item5, item6, item7, item8, item9, item10)/40)*100 10 items coded 0-4. Summed score transformed to 0-100 score (higher scores indicate worse mobility)	
PDQ-39 – activities of daily living	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item11, item12, item13, item14, item15, item16)/24)*100 6 items coded 0-4. Summed score transformed to 0-100	

				score (higher scores indicate worse ADL)	
PDQ-39 – emotional well-being	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item17, item18, item19, item20, item21, item22)/24)*100 6 items coded 0-4. Summed score transformed to 0-100 score (higher scores indicate worse emotional wellbeing)	
PDQ-39 - stigma	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item23, item24, item25, item26)/16)*100 4 items coded 0-4. Summed score transformed to 0-100 score (higher scores indicate worse stigma)	
PDQ-39 – social support	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item27, item28, item29)/12)*100 3 items coded 0-4. Summed score transformed to 0-100 score (higher scores indicate worse social support)	
PDQ-39 – cognitions	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item30, item31, item32, item33)/16)*100 4 items coded 0-4. Summed score transformed to 0-100 score (higher scores indicate worse cognitions)	
PDQ-39 - communication	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item34, item35, item36)/12)*100	

				3 items coded 0-4. Summed score transformed to 0-100 score (higher scores indicate worse communications)	
PDQ-39 - Bodily discomfort	Outcome measure	Assessment at week 0, 6, 18, 22	Interval	(SUM(item37, item38, item39)/12)*100 3 items coded 0-4. Summed score transformed to 0-100 score (higher scores indicate worse bodily discomfort)	
PDQ-39 – PDSI overall score	Outcome measure		Interval	SUM(mobility, ADL, emotional, stigma, support, cognitions, communications, discomfort)/8 Calculated from 8 dimensions above to give 0-100 score with high scores indicating worse outcome	
MDS-UPDRS – Non-motor aspects of daily living		Assessment at week 0, 6, 18, 22		13 items coded 0 (normal) to 4 (severe), first 6 scored by a rater and next 7 scored by patient. SUM(item1.1, item1.2, item1.3, item1.4, item1.5, item1.6, item1.7, item1.8, item1.9, item1.10, item1.11, item1.12, item1.13) Potential range is 0 to 52 with high scores indicating greater severity	
MDS-UPDRS – Motor aspects of daily living		Assessment at week 0, 6, 18, 22		13 items scored by the patient coded 0 (normal) to 4 (severe). SUM(item2.1,	

				item2,2, item2.3, item2.4, item2.5, item2.6, item2.7, item2.8, item2.9, item2.10, item2.11 item2.12, item2.13) Potential range is 0 to 52 with high scores indicating greater severity	
MDS-UPDRS – Motor examination		Assessment at week 0, 6, 18, 22		33 items coded 0 (normal) to 4 (severe). Scored by rater. SUM(item3.1, item3.2, item3.3nec, item3.3rue, item3.3lue, item3.3rle, item3.3lle, item3.4r, item3.4l, item3.5r, item3.5l, item3.6r, item3.6l, item3.7r, item3.7l, item3.8r, item3.8l, item3.9, item3.10, item3.11, item3.12, item3.13, item3.14, item3.15r, item3.15l, item3.16r, item3.16l, item3.17rue, item3.17lue, item3.17rle, item3.17lle, item3.17jaw, item3.18) Potential range is 0 to 132 with high scores indicating greater severity	
MDS-UPDRS – Motor complications		Assessment at week 0, 6, 18, 22		6 items coded 0 (normal) to 4 (severe). Scored by rater with patient input. SUM(item4.1, item4.2, item4.3, item4.4, item4.5, item4.6) Potential range is 0 to 24 with high scores indicating greater severity	
MDS-UPDRS		Assessment		Total score not	

– Summed total		at week 0, 6, 18, 22		recommended (Goetz et al 2008)	
Medication and MDS-UPDRS during motor examination		Assessment at week 0, 6, 18 and 22		No medication Medication – off Medication - on	
Dyskinesia and impact on MDS-UPDRS motor examination		Assessment at week 0, 6, 18 and 22		No dyskinesia Dyskinesia – did interfere with ratings Dyskinesia – did not interfere with ratings	

N-FOG (New Freezing of Gait questionnaire)		Assessment at week 0, 6, 18 and 22		9 items in scale.
				Item1 coded 0 (no freezing) or 1. Items 2-9 only scored if item1=1.
				Item4 only coded if item3>=1.
				Item6 only coded if item5>=1.
				
				If (item3 eq 0) item4=0
				If (item5 eq 0) item6=0
				If item1 eq 0) total=0
				If item1 eq 1) total=sum(item2, item3, item4, item5, item6, item7, item8, item9)
				
				Total score between 0 and 28 with higher scores indicating greater freezing	

FES-I (Falls Efficacy Scale-International))		Assessment at week 0, 6, 18 and 22		16 items each coded 1 to 4. Total score has a range of 16 to 64 with higher scores indicating greater concern. Sum(item1, item2, item3, item4, item5, item6, item7, item8, item9, item10, item11, item12, item13, item14, item15, item16)	
Frequency of conducting activities listed				16 items coded 0 (not applicable), 1 (regularly), 2	

in FES-I				(sometimes), 3 (occasionally), 4 (never)	
Distance able to walk without rest				Not able to walk 5m 20m 100m 200m 300m 500m 1km More than 1km	
Frequency of leaving own home				More than once per day Once per day 5-6 days a week 3-4 days a week 1-2 days a week Once every 2 weeks Once a month Less than once per month Never	
Mini BESTest (Balance Evaluation Systems Test)		Assessment at week 0		14 tests scored 0 (normal), 1 (moderate impairment) or 2 (severe impairment). Total score 0 to 28 with high scores being worse. Item3=MIN(Item3L, Item3R) Item6=MIN(Item6L, Item6R) Total=SUM(Item1, Item2, Item3, Item4, Item5, Item6, Item7, Item8, Item9, Item10, Item11, Item12, Item13, Item14)	
EQ-5D-5L		Assessment at week 0			
EQ-5D-5L derived index	Used to derive QALYs at 22 weeks			Singe index of health mapped from 3L value set using Van Hout algorithm as per NICE statement Van Hout B, Janssen M, Feng Y et al. (2012) Interim	

				scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health, 15: 708-15. Potential values up to 1 with high scores indicating better health	
Health today	Secondary outcome weeks 0, 6, 18, 22			Visual analogue scale ranging from 0 = worst health can imagine to 100 = best health can imagine	
Stride length while performing 10m WT					
Number of falls	Falls diary	0 to 6 7 to 18 19 to 22		(a) Number of falls (b) Proportion falling	
Walk speed device turned on		Week 1,6 18			
Health resource questionnaire		Assessment at week 0			
Serious Adverse event		CI		No Yes	
Blinded		Questionnaire 22 weeks		No Yes	
Allocation guess		Questionnaire 22 weeks		Control Treatment	

6. Missing data:

Outcome data will be sought for all randomised participants even if they weren't given or didn't use the FES. No imputation methods will be used for the main analysis (though see section on sensitivity analysis). We will assume that the missing data mechanism is "Missing Completely at Random" (MCAR).

7. Interim analysis:

No interim analyses are planned.

8. Blinding:

The statistical analysis will be conducted by the trial statistician/ data analyst blind to treatment arm. The results of the statistical analysis will be presented to the rest of the trial team blinded to treatment arm. Once the interpretation of the results has been agreed within the trial team then the treatment arms will be un-blinded to the whole trial team by PenCTU.

9. Main analysis of outcomes:

Participants will be analysed in the group they were randomised to, and (with the consent of participants) we will attempt to collect complete data on everyone and use those data in the analyses.

Baseline descriptive data on demographics will be presented overall and for both groups separately. This will help with (a) assessment of external validity of the trial, and (b) to see whether the 2 groups were comparable at baseline (no significance tests will be conducted).

9.1 Primary outcome

The primary outcome is the …….

Multiple regression including study site as a “fixed effect” factor will be used to compare mean …….. groups.

Study site is a design (stratification) variable and so included in the statistical model.

9.2 Secondary outcomes

The profiles from the patients’ answers to the EQ-5D-5L will be weighted using the EuroQol’s published United kingdom value set to produce a composite, utility based quality of life score. Quality Adjusted Life Years will then be created from the ?? time point utility scores assuming a linear change between the time points and using the area under the curve approach (see economic evaluation).

Multiple regression will be used to investigate differences between the two groups in the other continuous outcomes measured at six weeks post-baseline (e.g……..), 18 weeks post baseline (eg ……..), 22 weeks and 26 weeks (e.g. …….). …….. will be

investigated using logistic regression (binomial or multinomial depending on the number of categories), again taking study site into account.

9.3 Other outcomes

Adherence to FES will be analysed using …….

9.4 Sub-group analyses

9.5 Additional analyses:

10. Safety and Adverse events

11. Other variables:

Health Economics Analysis Plan

Templates for tables of results

Table 1: Descriptive statistics

	Control (n=??)	FES (n=??)
Site n (%) Salisbury London		
Age mean (SD)		
Gender n (%) Male Female		
Age at diagnosis (years) Mean (SD)		
Modified Hoehn and Yahr Scale score		
Current Living situation		
Current occupation		

	Weeks after randomisation			
	0 weeks	**6 weeks**	**18 weeks**	**22 weeks**
Primary outcome				
10m walking speed m/s (attempt 2)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)	-			
Overall baseline SD (90% CI)		-	-	-
Secondary Outcome				
MDS-UPDRS – Non-motor aspects of daily living (higher scores indicate greater severity)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
MDS-UPDRS – Motor aspects of daily living (higher scores indicate greater severity)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
MDS-UPDRS – Motor examination ((higher scores indicate greater severity)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90%				

CI)				
MDS-UPDRS – Motor complications (higher scores indicate greater severity)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ39 – mobility (higher scores indicate worse mobility)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 – activities of daily living (higher scores indicate worse ADL)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 – emotional well-being (higher scores indicate worse emotional wellbeing)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 – stigma (higher				

scores indicate worse stigma)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 – social support (higher scores indicate worse social support)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 – cognitions (higher scores indicate worse cognitions)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 – communication (higher scores indicate worse communications)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 - Bodily discomfort (higher scores indicate worse bodily discomfort)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between				

groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
PDQ-39 – Summary Index (high scores indicating poorer health)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
EQ-5D-5L index values (higher values indicating better health)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
EQ-5D-5L VAS (higher scores indicate better health)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
N-FOG (New Freezing of Gait questionnaire) (higher scores indicating greater freezing)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				

Stride length (10/number of steps)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
FES-I (Falls Efficacy Scale-International)) (higher scores indicate greater concern about falling)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				
Mini BESTest (Balance Evaluation Systems Test) (higher scores indicate greater impairment)				
Group 1 (mean (SD))				
Group 2 (mean (SD))				
Mean difference between groups adjusted for baseline (95% CI)				
Overall baseline SD (90% CI)				

Table Falls data

Falls	**Falls in 6 weeks prior to baseline**	**Falls in 22 weeks post randomisation**
Group 1 (median(IQR))		
Group 2 (median(IQR))		
Difference between groups adjusted for baseline (95% CI)		
Overall baseline SD (90% CI)		

Table 2: Baseline outcome measures

	Control (n=??)	FES (n=??)
EQ-5D-5L derived index mean (SD). Potential range -0.281 to 1, lower scores indicate worse health		
EQ-5D Health Today mean (SD. Potential range 0-100, lower scores indicate worse health		

Table 3: Primary and secondary outcome measure at 6 weeks

		6 week follow-up
Primary		
Secondary		
EQ-5D-5L derived index Potential range -0.281 to 1, lower scores indicate worse health	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	
EQ-5D Health Today Potential range 0-100, lower scores indicate worse health	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	

Table 4: Secondary outcome measures at 18 weeks

		4 week follow-up
Secondary		
Dorseflexion angle in degrees	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	
Plantarflexion angle in degrees	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	
Ankle inversion angle in degrees	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	
Ankle eversion angle in degrees	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	
Use of walking aids	Plaster (n(%) using aids) Support boot (n(%) using aids) Adjusted odds ratio (95% CI) p-value	

EQ-5D-5L derived index Potential range -0.281 to 1, lower scores indicate worse health	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	
EQ-5D Health Today Potential range 0-100, lower scores indicate worse health	Control (mean(SD)) FES (mean(SD)) Adjusted mean difference (95% CI) p-value Standardised effect size	

Table 5: Secondary outcome measures at 18 weeks

		18 week follow-up
Secondary		

Table 6: Serious adverse events

		10 week follow-up
Any serious adverse event	Control (n(%)) FES (n(%)) Adjusted odds ratio (95% CI) p-value	 - -

Table 7: Adherence to exercise

		10 week follow-up
Adherence		