University of Southampton

University Hospital Southampton NHS
NHS Foundation Trust

PDSAFE
Fall Prevention in Parkinson's Disease

PROTOCOL

A randomised controlled trial of the effectiveness and cost-effectiveness of PDSAFE to prevent falls among people with Parkinson's disease

PDSAFE Main RCT

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
A&E	Accident & Emergency
AE	Adverse Event
AR	Adverse Reaction
CES	Carer Experience Scale
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSI	Carer Strain Index
CTU	Clinical Trials Unit
DeNDRoN	Dementias and Neurodegenerative Diseases Research Network
DMEC	Data Monitoring and Ethics Committee
DVD	Digital Video Disc
EQ-5D	European Quality of Life-5 Dimensions
EU	European Union
FES-I	Falls Efficacy Scale – International
FRR	Falls Rate Ratio
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
GETuP	Group Exercise Trial for Parkinson's disease
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IRAS	Integrated Research Application System
MMSE	Mini Mental State Examination
Mini-BESTest	Mini Balance Evaluation Systems Test
MoCA	Montreal Cognitive Assessment
MREC	Multicentre Research Ethics Committee
NFoG	New Freezing of Gait Questionnaire
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
OCTRU	Oxford Clinical Trials Research Unit
PASE	Physical Activities Scale for the Elderly
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire
PI	Principal Investigator
PwPD	Person/People with Parkinson's disease

Abbreviation	Explanation
ProFANE	Prevention of Falls Network Earth
QALY	Quality Adjusted Life Year
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SS-180	Standing Start 180^{o} Turn Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale

1. INTRODUCTION

1.1 Background

Approximately 100-180 per 100,000 of the population in the UK suffer from Parkinson's disease (PD); a common progressive neurological condition[1]. People with PD (PwPD) are twice as likely to experience falls as a healthy elderly population. Falls are defined as an event that results in a person coming to rest on the ground or other lower level, not as a result of a major intrinsic event or overwhelming hazard[2]. A near fall is an occasion on which an individual felt they were going to fall but did not and managed to save themselves[3]. Repeat-falls are a risk factor for further falls[4] and carry devastating consequences such as fractures, immobility and fear of falling leading to dependency and social isolation. The aetiology of falls in PD is determined by both physical and cognitive deficits, especially when loading both systems. Fear of falling has been shown to produce a significant negative effect on quality of life through the restriction of activities resulting in a predisposition to secondary reductions in muscle strength and cardiovascular fitness[5].

In the UK only a small percentage (28%) of PwPD reportedly gains access to physiotherapy[6]. Preventing a cycle of inactivity and injurious falls is a priority for health care workers but research into the benefits of disease specific exercises and strategies with a focus on safe mobility is limited. Reduced balance control and falls do not respond to medication[7] but there is evidence that physiotherapy can be beneficial[8-10]. Previous researchers have evaluated balance training, muscle strengthening and movement coordination and found beneficial effects on balance control, near-falls and quality of life (QoL) among PwPD but inconclusive findings with respect to fall rate[11,12]. Participation in intensive and relevant physical practice and cognitive strategies which address the disease-specific problems (such as bradykinesia, freezing of gait, abnormal axial posture and poorly coordinated stability) as well as utilising guidelines to enhance adherence are likely to reduce the number of injurious falls and possibly reduce health costs.

In older people without PD, exercise programmes specifically targeting balance have been shown to be effective in preventing falls. A body of research has grown from a few large trials that demonstrate regular exercise is needed to maintain physical functioning and reduce the risk of falling; the key exercise component comprises balance and muscle-strength training followed by flexibility and endurance training[13]. The recommendations are for high intensity interventions that address risk factors rather than multifactorial interventions. In contrast only a small number of inconclusive trials have focused specifically on PwPD. Most PwPD will develop reduced balance as the disease progresses. Other disease specific problems that affect balance and together lead to fall events are bradykinesia, freezing, dyskinesia, narrow base and stooped posture, lack of axial rotation and shuffling gait. A shuffling pattern of walking with increased flexion of the hips and spine is characteristic of PD with loss of plantar flexion at the ankle, reduced forces and loss of heel strike during gait. These disease specific movement problems need to be addressed in a falls prevention programme along with features found to be important for those in the general elderly healthy population. Findings from the Exsart trial by Ashburn (142 participants) demonstrated a trend towards reduction of fall events and injurious falls with a positive effect of exercise on near-fall and quality of life[8]. A similar

sized trial (GETuP) comparing a group exercises, strength and balance training, with PwPD reported a non-significant 32% reduction in fall rate compared with usual care[9]. Exercises, cueing and strategies for improving function and movements are the main approaches to physical intervention by physiotherapists with aims to enhance activity levels, facilitate movement initiation, increase functional ability and improve safety. Evidence of effectiveness is strongest for gait re-education and activities of daily living with positive effects of rhythmical cueing on stepping and turning influencing in particular the initiation of movement and quality of pattern. Research findings support the use of external rhythmical cues to enhance motor relearning[10] and action observation strategies using a DVD has a positive effect on the walking ability of people who suffer from freezing of gait[14].

Exercise and motor training can improve the performance of balance related activities amongst this population and our previous work suggests that such activities are likely to reduce the risk of sustaining near-falls but it is still unclear whether having actual falls can be modified by an exercise-based intervention[8]. Adherence to fall prevention strategies among the general elderly population is only moderate to poor. Limited research has been carried out to evaluate strategies to enhance uptake and engagement[15]. In our proposed new trial the provision of a personalised DVD promoting exercise, cueing and functional activity, incorporates the PRoFaNE[16] (www.profane.eu.org) recommendations and provides a unique opportunity to evaluate a new mode of enhancing adherence. Falls among those over 70 years of age account for more than 50% of hospital admissions for accidental injury and may be costing the NHS in England up to 4.6 million per day[17]. While there are a number of studies looking at the economic cost of falls in the elderly[18-20], there are no known cost-effectiveness analyses in this population with this type of intervention to date.

1.2 Hypothesis

PDSAFE is a novel personalised exercise and strategy intervention based on the latest published research evidence and our extensive experience of managing the movement and stability problems of PwPD. We propose that those people with Parkinson's disease who follow the novel intervention will fall less than those who do not and that the programme is cost-effectiveness.

2. TRIAL DESIGN

2.1 Trial Summary

This is a multi-centre, single-blinded, randomised, controlled trial for PwPD to compare (i) PDSAFE (a novel personalised treatment based on the latest published research evidence and our extensive experience of managing the movement and stability problems of PwPD) and routine care with (ii) provision of a Parkinson's information DVD and routine care with a fall education booklet provided at the end of the trial. The trial aims to recruit 600 PwPD.

Figure 1 shows how PwPD progress through the trial; the various stages are addressed in subsequent sections of this document. At the screening visit participants will be asked whether they would also be willing to take part in an additional qualitative study if they are randomised into the intervention arm of the trial. A subgroup of participants from the intervention arm of the trial will be selected from those that have indicated a willingness to take part in the qualitative study (see Section 3.2). Also at the screening visit participants will be asked whether they have a carer (Figure 2). In the event that the carer is present the researcher will ask whether they would be interested in taking part in a trial component looking at carers' quality of life. An information sheet will be provided along with an invitation letter, response slip, and pre-paid Freepost envelope. If the carer is not present, the PwPD will be asked to pass on an envelope containing the aforementioned items.

2.2 Primary Aim

The primary aim of this trial is to determine the effectiveness and cost effectiveness of a novel personalised exercise and strategy intervention (PDSAFE) as a supplement to usual healthcare management in PwPD.

2.3 Research Questions

Secondary objectives of the trial are to answer the following questions:

1. Do fallers with PD who undertake PDSAFE with usual care fall less than those who do not undertake the treatment programme during months 0-6 after randomisation?
2. Do fallers with PD who undertake PDSAFE with usual care fall less than those who do not undertake the treatment programme during months 6-12 after randomisation?
3. Is the PDSAFE intervention cost-effective, compared to usual care for PwPD, from an NHS perspective?
4. Do fallers with PD who undertake PDSAFE have better balance, mobility and quality of life than those who do not?
5. What are the personal insights of those who participate in the intervention?

Figure 1 Trial flow diagram for people with Parkinson's disease in the PDSAFE trial

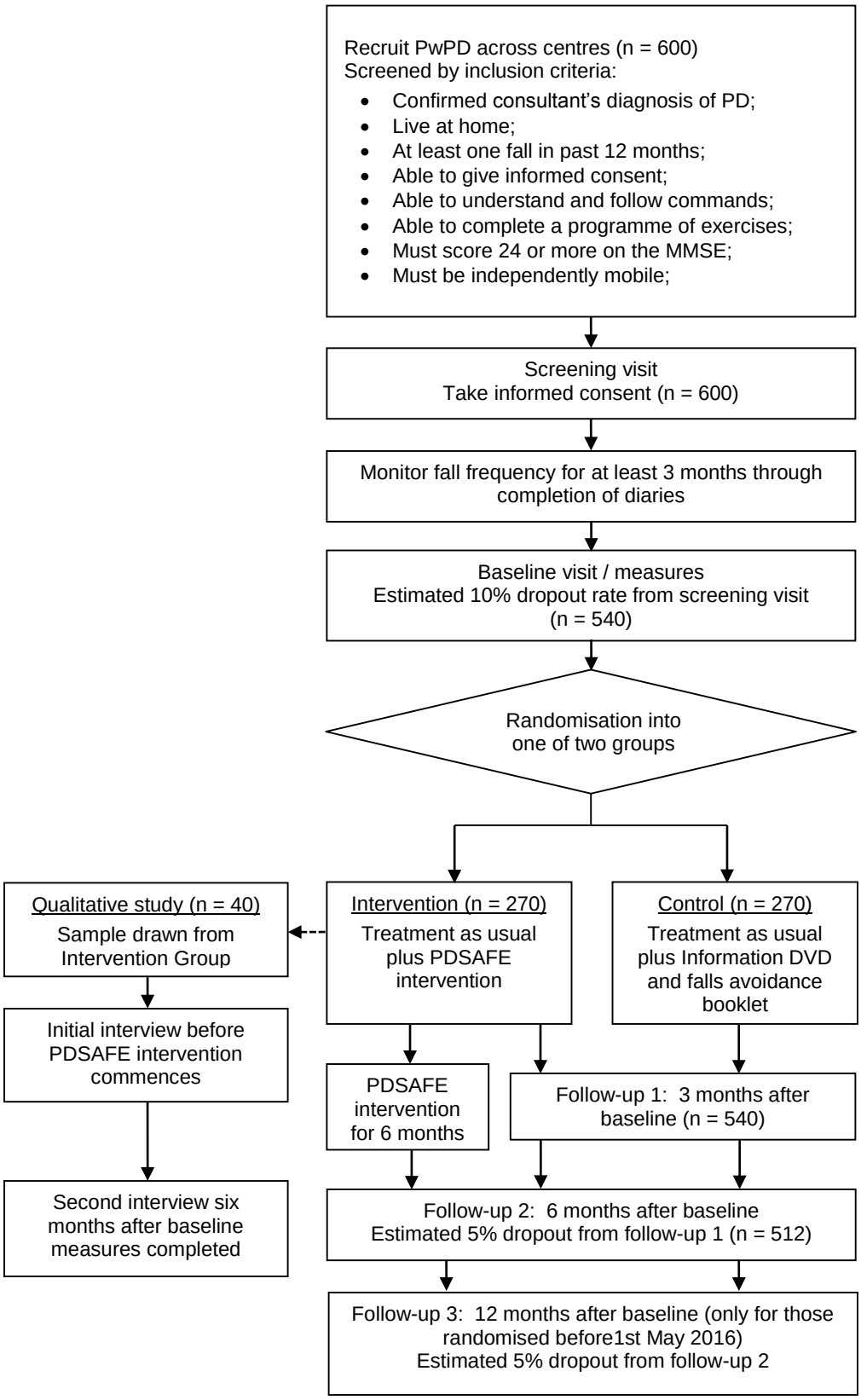
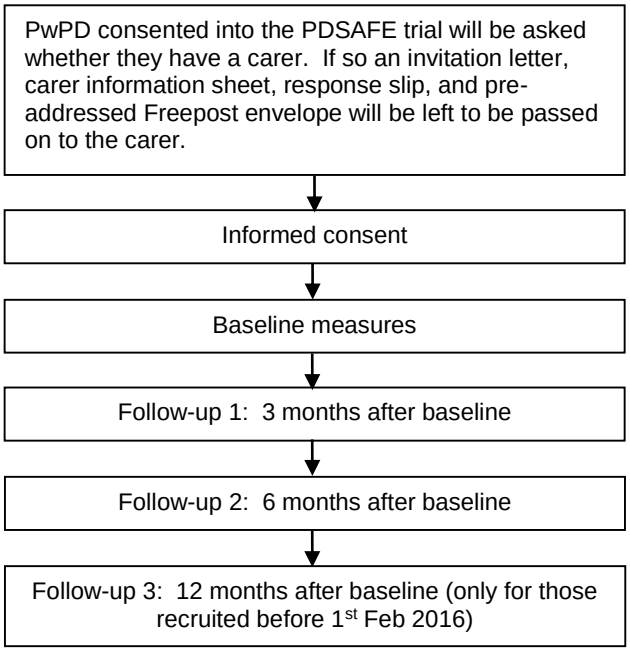


Figure 2 Trial flow diagram for carers of participants with Parkinson's disease in the PDSAFE trial



2.4 Outcome Measures

The primary outcome is the risk of repeat falling between 0-6 months post-randomisation. Analyses will control for falls in the three month period prior to recruitment and disease severity. Falls data will be collected through self-completed diaries[3]. Outcome measures are summarised in Table 1.

Secondary outcomes include repeat falling between 6-12 months, rates of falling between 0-6 months, and between 6-12 months post randomisation, fracture rate, near-falls and assessments of balance, activity levels, mobility and quality of life. Pre-stated subgroup comparisons will be carried out in subgroups with low and high disease severity. Personal insights will be recorded through a qualitative research component. An economic evaluation will also be performed. Our secondary outcomes will include fractures and near-falls (these will be taken from the fall diaries); everyday activity levels will be recorded using the; The Mini-BESTest[21] is a test of balance control; the chair stand test , the UPDRS (Unified Parkinson's Disease Rating Scale - motor section)[22], the New Freezing of Gait (NFoG) test[23] is a questionnaire on freezing of gait (freezing is closely linked to falling); the Parkinson's Disease Questionnaire (PDQ-39)[24] is a quality of life measure designed specifically for PwPD and the short generic quality of life measure European Quality of Life -5 Dimensions (EQ-5D)[25] will be included for economic evaluation, The Geriatric Depression Scale (GDS) 15 question version)[26] and the International version of the Falls Efficacy Scale (FES-I)[27], PASE (Physical Activity Scale for the Elderly) [28]. The measure of hand grip [29]) will be included as sub-study in one research centre only). The Carer Experience Scale (CES) and the Caregiver Strain Index (CSI) will be administered to carers at baseline and follow-up time points to capture some broader effects of the intervention [31, 32].

Table 1: Summary table of screening instruments and outcome measures

Screening Measures	Source	Time points
Montreal Cognitive Assessment (MoCA)	Assessor	
Retrospective recall of falls over previous 12 months		
Mini-Mental State Examination (MMSE)		
Hoehn & Yahr Scale		
Demographics and Medical History		
Primary Measure		
Fall events 0-6 months (falls)	Monthly self-report diaries	Completed from screening visit to end of participation in trial (maximum of 15 months).
Secondary Measures		
Fall events 0-6 months (near-falls and fractures)	Monthly self-report diaries	Completed from screening visit to end of participation in trial (maximum of 15 months).
Fall events 6-12 months (falls, near-falls and fractures)	Monthly self-report diaries	Completed from screening visit to end of participation in trial (maximum of 15 months).
Mini-BESTest		
Timed Chair Stand Test		
Hand grip (sub-study in one area only)		
Unified Parkinson's Disease Rating Scale (UPDRS) (motor assessment section only)		
Medication Use		
Geriatric Depression Scale (GDS) - 15 question version	Self-report	
Fall Efficacy Scale International (FES-I)		
New Freezing of Gait – questionnaire		
PDQ39 – questionnaire		
Physical Activity Scale for the Elderly (PASE)		
Health Professionals and Exercise		
Economic Measures (PwPD)		
Health and social care resource use sheet	Assessor	Completed at baseline and at each follow-up assessment (3, 6 and 12 months).
EuroQol EQ-5D	Self-report	
Economic Measures (Carer)		
Carer Demographics and Caring Role	Self-report	Completed at baseline and at each follow-up assessment (3, 6 and 12 months).
Carer Experience Scale (CES)	Self-report	
Carer Strain Index (CSI)	Self-report	

2.5 Primary Outcome Data Collection

Fall events (falls and near-falls) will be recorded using monthly self-completed diaries which have been used successfully in other studies[16]. Diaries will be delivered to participants by assessors when visiting to conduct screening, baseline, and follow-up assessments. Assessors will instruct participants as to how the diaries should be completed before leaving them. Where appropriate, assessors will phone participants to remind them to complete their diaries. Participants will be asked to return diaries by post each month in the FREEPOST envelope provided.

2.6 Power and Sample Size

Primary outcome: risk of repeat falling between 0-6 months

In the EXSART trial the control group risk of repeat falling in a 6 month period was 68% and that in the exercise group was 56%. We anticipate risks to be lower in PDSAFE since EXSART was restricted to people falling twice or more in the previous year. Assuming the control group risk between 0-6 months to be 63% reduced to 50% in the intervention group leads to the requirement for 228 participants per group with data for analysis 456 in total. Allowing for 5% to drop out between randomisation and 6 months leads to the requirement for 480 participants to be randomised. Further allowing for 10% to drop out between agreeing to the 3 months pre-randomisation falls collection and randomisation, leads to the requirement to recruit 534 participants to the pre-randomisation falls collection period. We aim to recruit 600 to the pre-randomisation falls collection period. Power calculation scenarios are summarised in Table 5 (Appendix).

Secondary outcomes: risk of repeat falling between 6-12months, and fall rates between 0-6 and 6-12 months

Assuming the same reduction from 63% to 50% also applies during the period 6-12 months post randomisation, and allowing for 10% to drop out between randomisation and 12 months, and 10% to drop out between agreeing to the 3 months pre-randomisation falls collection and randomisation, leads to the requirement of recruiting 564 participants to the pre-randomisation falls collection period.

Power calculations (see Table 5 – Appendix) for rates of falling are based on Tango [33] and relate to the number of falls during a fixed follow-up period analysed using negative binomial regression conditioned on baseline counts: specifically formula 23 in the paper was used assuming equal rates in the baseline and follow-up periods in the control group and a follow-up period of twice the length of the baseline. Anticipating a falls rate ratio (FRR) of 0.8 between 0-6 months post randomisation, that is a 20% reduction in the rate of falling in the intervention group compared to control group, and based on a rate of 2.5 falls in the 3 month baseline period, we require 197 per group at analysis leading to recruiting 488 participants to the pre-randomisation falls collection period.

Other scenarios are considered for the differences in risk of repeat falling, or for the FRR in the Table 5 (Appendix) and generally lead to recruiting numbers below 600 to the pre-

randomisation falls collection period. All the calculations aim for 80% power in 5% two-sided tests between the intervention and control groups.

2.7 Eligibility Criteria

Participants are eligible to be included in the trial if they meet the following criteria:

1. Have a confirmed Consultant's diagnosis of Parkinson's disease.
2. Live at home.
3. Have experienced at least one fall in the previous 12 months.
4. Able to give informed consent.
5. Able to understand and follow commands.
6. Able to complete a programme of exercises.
7. Score 24 or more on the Mini-Mental State Examination (MMSE).
8. Be willing to participate.

2.8 Exclusion Criteria

Participants will not be eligible to be included in the trial if any of the following apply:

1. People who live in nursing homes.
2. Those who are not independently mobile, i.e. in need of assistance to walk inside, or rated the highest (most severe) on the Hoehn & Yahr [34] disease severity scale.

2.9 Recruitment and Informed Consent

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We have identified several research centres across England representing a range of socioeconomic environments and where health care workers have demonstrated an interest in working with us on the investigation. These include, but are not limited to: Southampton; Portsmouth; Bournemouth, Poole; Exeter, Newcastle, Hampshire, Plymouth and Cornwall.

We have studied the experience of recruiting to a previous randomised controlled trial on falls management [35]. We are confident we will achieve our target sample. Within one of our proposed recruiting areas, West Hampshire, there are approximately 1300 to 1400 PwPD (Romsey/Winchester, Southampton City and New Milton/Totton areas). Our paper [35] on recruitment of PwPD from Dorset reports a 13% recruitment rate though we were only looking for repeat fallers, in contrast to the current proposed trial where we aim to recruit all of those who have experienced one or more falls. We believe we could conservatively expect to recruit somewhere around 15% of those on a clinical list.

Participants will be recruited; through the clinical registers of PD specialists in each of the designated areas, from people known to researchers (lists of people who have indicated willingness to participate in further research studies) and from Parkinson's UK local groups. We will work closely with clinicians, such as Consultants and PD Nurse Specialists, and the first contact with potential participants will be made by a health care professional known to them. Suitable people identified from a specialist register, will receive a letter from their

Consultant asking if they would like to participate in the trial. In addition we will work with clinical trial co-ordinators from the Clinical Research Network (CRN) Parkinson's specialty and approach Parkinson's UK local support groups, as well as community and out-patient services. Throughout the development stage the trial has been discussed with PwPD and with health care workers in the research networks and they have all expressed a willingness to support recruitment.

If patients show interest in taking part in the trial, permission to pass on the patients' contact details to the research team will be sought. The research team will write to the patient to ask whether they would like to take part in the trial, enclosing a Participant Information Sheet, a response slip and Freepost pre-addressed return envelope. Patients wanting further information, or wishing to take part in the trial will be invited to complete and return the response slip in the pre-addressed Freepost envelope. On receipt of a response slip indicating that the patient is interested in the trial, an assessor from the trial research team will phone the patient to answer any questions that may have arisen and check their eligibility (as far as possible) to join the trial. If the patient is eligible and willing to proceed an appointment will be made for the assessor to visit them at home to take consent and complete the trial screening measures. Participants will be asked to sign a consent form before conducting any procedure specifically for the trial. Participants will be given plenty of time (at least 24 hours from telephone contact) to consider whether they wish to take part in the trial. Having given informed consent, the assessor will screen the participant and then will give the participant a set of diaries in which to record falls up to the time of the baseline visit (at least three months). Assessors will instruct participants as to how the diaries should be completed.

Once they have consented to take part in the main trial, participants will be asked whether they would be willing to take part in a qualitative sub-study which will run alongside the main trial. Those expressing an interest will be asked to confirm that their details may be passed to the qualitative researcher. The qualitative researcher will subsequently contact the participant if they are suitable for the qualitative study. Participants will be selected to take part in the qualitative study on the basis of a maximum variety sampling strategy.

Participants will also be asked whether they have a carer. In the event that the carer is present the researcher will ask whether they would be interested in taking part in a sub-study looking at carers' quality of life. An information sheet will be provided along with an invitation letter, response slip, and pre-paid Freepost envelope. If the carer is not present, the PwPD will be asked to pass on an envelope containing the aforementioned items. If the carer indicates that they are interested in taking part, they will be asked to attend the baseline visit for the participant (PwPD) and informed consent will be taken from them at that time.

2.10 Randomisation

Participants will be visited by an assessor three months after their screening visit. The assessor will collect the completed falls diaries and check that the participant is willing and able to proceed to the next stage of the trial. The assessor will then conduct the baseline assessments with the PwPD. After these have been completed the assessor will randomise the participant using an online procedure which ensures that they (the assessor) remain blinded.

The randomisation outcome will be e-mailed to the trial co-ordinating centre via the PDSAFE e-mail address and forwarded to the therapy team. One of the local therapists will inform the participant of the randomisation outcome and advise on the timescale for their first visit which should be within two weeks (maximum of four weeks).

Random allocations will be computer generated, stratified by centre and allocated in blocks with random size of 2, 4, 6 or 8. This will ensure that allocation groups within centres are as evenly distributed as possible, while maintaining a system where allocations are unlikely to be deduced by those needing to remain blinded.

2.11 Pilot Trial

Prior to embarking on the main trial, a small scale external pilot study (PDSAFE Stage 1 Pilot Study) will be conducted in two centres: Southampton and Newcastle. Progress to the main trial will not be stopped by the outcome of the pilot. The pilot study will specifically look at the treatment content and delivery of the PDSAFE intervention. This will confirm the most appropriate way of delivering the intervention. For the purpose of the pilot study, up to ten participants will be recruited in each centre. . A separate protocol has been developed for the PDSAFE Stage 1 Pilot Study and has received ethical approval from National Research Ethics Service (NRES) Committee South Central – Hampshire B.

2.12 Post-randomisation Withdrawals

Participants may withdraw from the trial at any time without prejudice. Should participants withdraw from the trial completely no further data will be collected. They will be asked if we can use the data already collected.

Subjects may be withdrawn from the trial intervention at the discretion of the Chief Investigator and/or Trials Steering Committee due to safety concerns.

2.13 Blinding

Therapists and participants cannot be blind to the intervention they are delivering or receiving. In contrast, assessors who collect data from participants after randomisation can be blinded to group allocation and should not know to which treatment group participants belong. Assessors will not have access to the therapists' treatment lists and randomisation allocations will not be communicated to them.

However, previous experience has shown that participants may occasionally and inadvertently inform assessors of the treatment they are receiving. We aim to reduce this effect by explicit reminders to participants before assessment visits. We shall ask all assessors to record their estimate of which group they think the participant belongs, and their confidence in that prediction. This will enable us to test whether inadvertent loss of blinding leads to bias, and to adjust for any bias detected.

2.14 Methods for Unblinding the Trial

Participants (in the intervention and control groups) and the physiotherapist treating them will be aware of their allocated group in the trial. Only the assessors will be blinded to group allocation.

For planned analyses of data, treatment codes will not be broken until all decisions on the analysis of the data from each individual subject have been made and documented.

2.15 Trial Intervention

All participants in the trial will continue with their usual care as deemed appropriate by health care providers, this will usually comprise attendance at medical clinics, medication, and visits from PD nurse specialists. Participants may attend group activities and join physical movement sessions as part of their usual care, though from experience such sessions are rarely intensive or prolonged. Participants will be asked to record their usual care and encouraged to avoid changing that practice unless specifically requested by a health care worker during the time they are participating in the trial (12 months for those randomised before 1st May 2016; and six months for those randomised after this date).

For participants receiving the PDSAFE intervention, the aim is to develop strategies for safe mobility, independence, reduction of fall risk and development of problem solving through individual treatment sessions with a physiotherapist, the use of personalised visual feedback and printed information and guidance.

A central component of the PDSAFE intervention is an exercise programme to target modifiable risk factors for falls[36]. The active elements of the programme will emphasise progression and comprise: functional muscle strength training of the lower limbs with or without the use of resistance through a weighted vest or belt and balance training which can be progressed through more complex and varied starting positions, postures and repetitions. Strategy training, to improve freezing of gait and performance of complex tasks specific to fall-related activities and circumstances within the home environment will be addressed. In this way we will be using the latest evidence of exercise effect to address fall risk factors. The exercise programme will be personalised to each participant and targeted at specific problems in their own environment by a physiotherapist who will assess and, through clinical reasoning, select exercises and strategies from a menu of activities that will be both printed in a booklet and presented as video vignettes. Individual videos will be made from the vignettes and (in addition) of each participant doing their exercises; the video will be put on a DVD and returned to the participant so that their personal sessions can be followed easily at leisure in their own time at home. An example of how the programme can be delivered is as follows: the first five minutes of the one hour session will focus on warm-up, followed by 30 minutes of strengthening and balance training; the final 25 minutes could be spent strategy training and hazard identification. The physiotherapist will record how much time is spent on the different tasks which will be personalised to the individual. It is important to note that not all falls are preventable. The participant will be asked to carry out the exercises three times per week.

(i) Strengthening: functional strengthening of the lower limbs targeted to increase strength in quadriceps and calf muscles. Exercises will include eccentric muscle activity and vary speed of contraction.
(ii) Balance and co-ordination: Balance exercise and dynamic movement including stepping and reaction time in all directions and during more complex tasks.
(iii) Freezing of gait: cognitive techniques using a variety of approaches, including attention strategies to address specific freezing difficulties in the context in which they occur.

The strategy training will comprise 25 minutes of analysis of activities that provoke freezing, instability and falls specific to the individual context and task in which they occur. The aim is to promote behaviour modification and learning and to increase confidence and stability specific to problems identified. To develop learning and problem solving skills the exercise programme will be accompanied by an education pack and DVD which includes the following: identification of areas around the house that provoke freezing (freezing hot spots), and increase feelings of instability and falls risk. Thus a context and task specific evaluation of falls risk will be undertaken and a map of the house will be drawn up to identify specific problematic areas and strategies identified to address the problems. Video will be taken of the participant engaged in activities with and without cognitive strategies and address task specific freezing of gait and instability. Repeat videos will be used for feedback about changes in performance and areas to focus on for future practice. Participants will be asked to practice the strategies to reduce freezing and falls risk on a daily basis and to integrate these into task performance where possible. Participants receiving the PDSAFE intervention will be asked to comply with an agreement to exercise. Past experience has shown this to improve compliance with rehabilitation interventions.

The intervention will take place over a 6 month period with a further 6 month follow-up. A total of up to 12 sessions of therapy each lasting for one hour (35 minutes exercise, 25 minutes developing strategies to improve movement behaviour and prevent falls) will be delivered. The total duration of the intervention is 6 months. Therapy will be delivered intensely at first and faded over time to maximise motivation and behavioural change.

The following would be an example a typical delivery plan. During the first two to three weeks the therapist would develop the personalised exercise programme and teach this. The programme would be videoed for the person to watch at their convenience. In addition during this time the therapist would work with the participant to identify context specific freezing and falls areas of the house. They would develop and teach problem solving including for example, the use of different cueing strategies. During the following visits performance would be monitored and adjusted to ensure continued progress. Video feedback would take place to encourage learning and problem solving. Two examples of possible schedules are shown in Table 2 but flexibility will be retained for personalising the intervention and intermittent checks may be made by phone call.

Table 2: Two examples of schedules of physiotherapist visits

Week	Number of physiotherapist visits for participants receiving the PDSAFE intervention	
	Example 1	**Example 2**
1	2	2
2	2	2
3	1	2
4	1	1
5	1	
6	1	1
7	1	
8	1	1
Subtotal	**10**	**9**
Follow-up visits:		
End of month 3	1	1
End of month 4		1
End of month 5	1	1
Total number of visits	**12**	**12**

2.16 Control / Intervention

Participants in the control group will continue to receive their usual care as described in the first paragraph of 2.15. In addition they will be given a DVD containing information about Parkinson's disease. They will be visited by a physiotherapist after randomisation and at the end of the trial after their final -follow-up assessments have been completed, at which time they will receive guidance on physical activities and strategies for balance and safety according to their profile of fall events and a booklet about fall prevention.

2.17 Compliance / Contamination

We will encourage participants to maintain the usual care they are receiving at the point of entering the trial throughout the trial. It is also possible that participants in either of the groups could receive physiotherapy as part of their usual care. However, from experience this is unlikely to be of the same intensity as that provided through the PDSAFE intervention and therefore any additional effects of the PDSAFE intervention will still be detected. Records of the exercise sessions will be kept by the therapist and participants. Health and social care resource use data will be collected and these should indicate any other treatments received by participants. Participants in both groups will be asked not to significantly change any existing pattern of activity during the trial.

2.18 Concomitant Illness and Medication

Information on any existing medical and/or surgical conditions will be taken and recorded at the consent visit.

Details of medications being taken by the participant will be recorded at the baseline and follow-up assessment visits.

3. METHODS AND ASSESSMENTS

3.1 Schedule of Delivery of Intervention and Data Collection

PwPD randomised before 1st May 2016 will be involved with this trial over a period of 15 months; those randomised after this date will be involved for only nine months. Carers who participate will be involved over a period the same period as their associated PwPD. Table 3 shows the assessment points for the trial.

Screening: Potential participants will be visited at home and after consent will be assessed for cognitive impairment using the MoCA [37] and the MMSE [38], and severity of disease using Hoehn & Yahr [34]. They will be asked to retrospectively recall any fall events during the previous 12 months using a standardised questionnaire[3]. Those who have fallen at least once will be eligible. Individuals who don't meet the eligibility criteria will not be able to continue in the trial.

Pre-randomisation fall rate: Participants will be asked to prospectively record fall events using a monthly diary sheet divided into days for three months between recruitment and randomisation. These findings will be used for comparison with post-intervention fall frequency. A further advantage of this period is that it will enable participants to become familiar with the falls diary procedure. We anticipate it will improve the quality of the fall data in the main trial and identify those who are unable to follow the process.

Table 3: Assessment points for PDSAFE

Visit number	**1**		**2**	**3**	**4**	**5**
Visit	**Screening Visit**	**Pre-randomisation Fall Rate**	**Baseline and Randomisation**	**3 Month Follow-up**	**6 Month Follow-up**	**12 Month Follow-up**
Informed consent	✓					
Medical history	✓					
Screening measures	✓					
Falls diary (with associated resource use questions)		✓	✓	✓	✓	✓
Outcome measures (see Table 1)			✓	✓	✓	✓

Visit number	1		2	3	4	5
Visit	**Screening Visit**	**Pre-randomisation Fall Rate**	**Baseline and Randomisation**	**3 Month Follow-up**	**6 Month Follow-up**	**12 Month Follow-up**
Qualitative Study			✓		✓	
Economic Analysis			✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓
Carer measures			✓	✓	✓	✓

Baseline only: At baseline, prior to randomisation, a medical history structured to include co-morbidities will be taken including details of medication, living status and current rehabilitation input. Disease severity will be recorded using Hoehn & Yahr [34] and the motor assessment section of the Unified Parkinson's disease Rating Scale (UPDRS 0-180; low = good) [22].

Assessments: After randomisation participants will continue to prospectively record fall events using monthly diary sheets until the end of their time in the trial. Other measurements will be completed at baseline, 3 months after randomisation, 6 months and 12 months. Table 4 shows the acceptable time windows for completion of assessments. The assessment sessions will be arranged at the same time of day in particular mid-medication cycle when movements are most effective, they will be completed at home and last approximately ninety minutes.

Table 4: 'Windows' for follow-up visits for PDSAFE

Visit name	Range for visit	Deadline for visit
Screening	At least 3 months before randomisation	Not applicable
Baseline Assessments and Randomisation	At least 3 months after screening	
3 Month Follow-up (Week 13)	12-15 weeks after randomisation	18 weeks after randomisation
6 Month Follow-up (Week 26)	25-29 weeks after randomisation	32 weeks after randomisation
12 Month Follow-up (Week 52)	50-55 weeks after randomisation	60 weeks after randomisation

3.2 Qualitative Study

Aims and Design

A supplementary longitudinal qualitative study will be conducted alongside the main trial. This is the first time within the UK that such a design has been employed within the context of a falls prevention trial with PwPD to our knowledge. This qualitative component aims to explore the impact of PD on daily life and experiences of the intervention by addressing the following research questions:

a) What are the daily challenges experienced by PwPD who fall?
b) What are the expectations of PwPD who fall about the intervention and how do these change over the course of the trial?
c) What are the views of people with PD who fall about facilitators and barriers to participating in the intervention?
d) What do PwPD who fall value/not value about participating in the intervention?
e) Why did PwPD think they fell: what were the causes?

The qualitative study will draw on following principles of grounded theory [39, 40].

- Gathering rich, in-depth data through 'intensive interviewing'.
- Conducting detailed analysis which becomes increasingly theoretical.
- Writing reflective memoranda to assist with data interpretation.
- Developing interpretative theory which conceptualises the experience of participating in our intervention for fall prevention.

Methods

In contrast to a purposive sample more usually employed within grounded theory research, this study will use a maximum variety sampling strategy [41] addressing gender, age, level of impairment, location and history of falls. This will enable preparation and planning ahead of data collection, as the time frame imposed by the trial is likely to be challenging. Interviews will be audio recorded and transcribed to facilitate analysis and the following strategies will be used to ensure that the study is conducted rigorously, and data analysis carried out systematically [42].

- The researcher will write memos throughout the analysis to facilitate reflexivity.
- A research diary will be written which will both promote reflexivity and provide an audit trail of the development of theory.

A sample of forty people from the intervention group, 10 from each recruiting area, will be invited to participate in this sub-study. Semi-structured interviews [43, 44] will be carried out in participants' homes in order to address the research questions identified above (with appropriate lone worker research policies implemented). The interview guide will be designed with help from service users with PD, carers and health professionals who work with PwPD. The interview guide will be piloted and refined with older PwPD, prior to start of data collection.

Two interviews will be carried out with each of forty participants (10 from each area) randomised to the intervention arm of the trial. The first interview will be conducted after consent is received, but prior to the start of the intervention, and the second at six months,

following completion of the intervention. Subject to ethics approval, strenuous efforts will be made to follow up and interview those from the sample who subsequently drop out of the trial, acknowledging that they have particularly useful and under-researched perspectives about participation in home-based rehabilitation.

3.3 Carer Quality of Life Study

As part of the health economics component of the trial, an opportunistic sample of carers of PwPD participating in the trial will be recruited. The aim is to measure the broader effects of the intervention to the carer. As having a carer is not a pre-requisite for PwPD being recruited into the trial, it is likely that some PwPD in the trial may not have a suitable carer. Where one is available they will be invited to join the trial: if there is more than one, the main carer, as identified by the PwPD, will be approached. After consenting to join the trial, carers will be asked to complete two brief quality of life questionnaires, the CES[31] and the CSI[32] (taking no more than 10 minutes). Carers will be asked to complete the same quality of life questionnaires at each follow-up visit.

4. ADVERSE EVENT MANAGEMENT

4.1 Adverse Events (AEs)

The most common Adverse Events likely to occur with PwPD relate to falls, which are being recorded (in falls diaries) as part of the trial. Only SAEs will be collected.

4.2 Serious Adverse Events (SAEs)

The reporting of Serious Adverse Events (SAEs) will follow the guidance outlined by the National Research Ethics Service (NRES) for research other than Clinical Trial of Investigational Medicinal Products. An SAE will be defined as untoward occurrence which fulfils one or more of the following criteria:

i. Results in death;
ii. Is immediately life threatening;
iii. Requires in-patient hospitalisation or prolongation of existing in-patient hospitalisation;
iv. Results in persistent or significant disability or incapacity;
v. Is otherwise considered medically significant by the investigator.

Incidents of hospitalisation and disability, falls, or incapacity attributable to a participant's Parkinson's disease will not be recorded, as these would be expected among this patient population. Similarly, any hospitalisation that was planned prior to randomisation or cannot be attributed to the trial intervention will not be recorded as an SAE. Trial centres will use a standardised safety reporting form to inform the trial co-ordinator of serious adverse events within twenty-four hours of becoming aware of them (initial report). SAEs which may be linked to trial procedures will be recorded as Suspected Unexpected Serious Adverse Reactions (SUSARs). Other adverse events which may be linked to trial procedures, but not deemed to be serious, will be recorded as Adverse Reactions (ARs). The causality of SAEs

(i.e. relationship to trial treatment) will be assessed by the Investigator(s) on the SAE form. All SAEs, SUSARs and ARs will be reviewed by Dr Helen Roberts, Consultant in Elderly Care, to determine whether the SAE is *related* and *unexpected* as defined by the NRES guidance.

4.3 Reporting SAEs

All SAEs that occur between the assessor screening visit and the final assessor visit will be reported. SAEs will be reported using a standardised SAE form. The Principal Investigator in each centre must provide an initial report of any SAE to the trial co-ordinating centre within 24 hours of them becoming aware of it. A follow-up report should be sent when additional information is received. The trial co-ordinator will liaise with the Principal Investigator in each area to compile all the necessary information. The trial co-ordinating centre is responsible for reporting SAEs, where appropriate, to the sponsor, ethics committee and DMEC chair within required timelines.

4.4 End of Trial

The end of the trial will be defined as when the final follow-up visit (either at six or twelve months depending on date of randomisation) has been completed. The trial will be stopped prematurely if:

- Mandated by the Ethics Committee;
- Following recommendations from the Trial Steering Committee (TSC);
- Funding for the trial ceases.

The Research Ethics Committee (REC) will be notified in writing if the trial has been concluded or terminated early.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act.

Participants will be identified using a unique trial number only. Personal identifying information will be stored within each trial centre for the purpose of getting in touch with participants throughout their participation in the trial. Anonymised trial data will be stored on the secure, password protected, central servers of the University of Southampton with access restricted to members of the research team (assessors, therapists, and trial coordinator). Handling of personal data will be clearly documented in the Participant Information Sheet. The Participant Information Sheet will remind participants that the trial research team may, in certain circumstances, be under a statutory obligation to break confidentiality to report issues which may jeopardise the participant's safety, or the safety of another person.

5.1 Data Collection and Management

The Case Report Forms (CRFs) will be designed by the trial team in conjunction with the chief investigator and statistician.

Assessors based in each research centre will collect data from participants in their respective areas. Data will be collected using paper questionnaires and entered into the trial database using a secure internet based system. Paper questionnaires will be identifiable by a participant identity number and will be kept in a locked cabinet, in a locked room, at each centre until archiving at the end of the trial.

Data will be entered centrally by the trial administrator, and/or the trial co-ordinator. Photocopies of CRFs from Exeter may need to be sent to Southampton to facilitate data entry for that centre. A courier service that enables tracking will be used.

The trial coordinator, with the assistance of the programming team at OCTRU, will check the dataset for spurious/missing items and approach the assessors as necessary to correct the information held.

5.2 Database

The database will be set up by the programming team at OCTRU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer, statistician and trial co-ordinator.

5.3 Data Storage

Trial electronic data will be stored by University of Southampton in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

5.4 Archiving

Trial documentation and data will be archived for at least 10 years after completion of the trial.

6. STATISTICAL ANALYSIS

6.1 Main Analysis

The main analysis will be based on intention to treat in that participants will be analysed according to the group to which they were allocated irrespective of the extent of intervention received. The primary outcome risk of repeat falling over the 6 month period after randomisation will be compared between intervention and control groups using a logistic regression model including repeat falling or not during the pre-randomisation falls collection period, Hoehn and Yahr [34] score, and centre as covariates.

Repeat falling during 6-12 months and other binary secondary outcomes will be examined using similar logistic regression models to the primary outcome. The rates of falling over 0-6 months and over 6-12 months will be examined in a negative binomial model including baseline rate of falling over the 3 month pre-randomisation falls collection period, Hoehn and Yahr [34] score, and centre as covariates, fitted using either the nbreg or xtpoisson regression commands Stata [45] to be finalised at a blind review of the data. In the model the effect of intervention is summarised as a falls rate ratio (FRR) (intervention/control) with ratios below 1.00 indicative of lower rates in the intervention group. All participants in the main trial will have been asked to complete the baseline three months falls collection, and the length of follow-up time over which falls events are collected between 0-6 months and 6-12 months post randomisation will be included as exposure times in the regression. Rates of falling and near-falls in each of the three month periods between the pre-randomisation period and 12 months in the intervention and control groups will be displayed graphically. Other secondary outcomes will be examined in mixed normal models for repeated measurements at 3, 6 and 12 months controlling for centre, Hoehn and Yahr [34] score, and baseline value, including participants with incomplete follow-up information in the analysis.

Sensitivity analyses will be conducted to examine the impact of missing data due to causes other than death, using worst-case and other single imputation on conclusions. Since only participants successfully completing the initial three months falls diary collection period will be entered into the main trial, we hope that loss of diary information will be minimised.

Data on compliance with the intervention will be examined and any SAEs, SUSARs, or ARs listed by intervention group. No formal interim analyses are planned. A statistical analysis plan will be developed.

6.2 Planned Sub-group Analysis

The planned analysis of the primary outcome will be performed within the subgroups of participants with Hoehn & Yahr [34] scores of 1-3 and 4. The planned analysis of the primary outcome will be also performed within the subgroups of participants with UPDRS scores of 26 and under (less severe) and 27 and over (more severe). The comparison of the intervention effect between Hoehn & Yahr [34] groups 1-3 and 4 will be tested as an interaction. The comparison of the intervention effect between UPDRS groups 26 and under (less severe) and 27 and over (more severe) will also be tested as an interaction. We will examine the effect of the intervention separately in each centre.

6.3 Economic Analysis

Resource use data will be collected via a tick box resource sheet (sent out with the monthly falls diaries) to identify the cost of falls (and the cost savings of falls averted) to health and social services. Information on hospital admissions, length of stay, type of fracture, GP appointments, physiotherapy, occupational therapy, ambulance call outs and A&E attendances as well as drug costs (maximum daily dose for all drugs) and residential home admissions will be identified and measured. By collecting such costs, the cost savings arising from reducing the number of falls and related injuries will be estimated. The cost of implementing the

PDSAFE intervention will be identified and measured so that if the programme were to be 'rolled out' to larger numbers, estimates of the costs would be available. Relevant costs will include: therapist time spent delivering the intervention; costs for training therapists; DVD costs; time spent on telephone feedback.

Readily available unit costs will be attached to all items of resource use and a mean cost per patient estimated. With residential care homes costing in excess of £800- £1,000 per week for some disabled patients, any delay in admission arising from preventing falls will result in substantial cost savings. Falling and fear of falling can also severely reduce the quality of life of individuals with PD. Hence, in line with recent recommendations from the National Institute for Health and Care Excellence (NICE) the economic evaluation will also include the generic quality of life instrument, the EuroQol EQ-5D [25,46,47] so as to measure Quality Adjusted Life Years (QALYs) gained/lost [25,46,47]. In a bid to capture the broader effects of caring for a PwPD who fall, carers will be asked to complete a carer quality of life measure the CES [31] and the CSI[32] at each assessment point. The incremental cost and the incremental benefits (effectiveness and utility) will be reported within an incremental cost-effectiveness ratio (ICER) format where appropriate. Since falls are the primary clinical outcome of the trial, the economic evaluation will estimate the incremental cost-per-fall averted, as well as the incremental cost per QALY gained.

6.4 Qualitative Analysis

Data analysis will comprise the following stages [46]:

- Initial coding (detailed, line-by-line coding sticking close to data).
- Focused coding (i.e. using most significant earlier codes to categorise large amounts of data).
- Axial coding (organises coding into super- and subordinate categories, and provides coherent analytic framework);
- Theoretical coding (support coherence and accessibility of analysis, and how analysis contributes to theory building).

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Ethical Conduct of the Trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements.

Answering questions from questionnaires can sometimes cause distress. As we are testing the feasibility of a number of different questionnaires it might be possible that participants feel tired or fatigued. We will inform all participants that they do not have to answer any question that they do not wish to answer and that we can stop at any point. We will ensure adequate rest times are given in between assessments and check with participants whether they are feeling tired and stop immediately if necessary. Assessment times should take no longer than

90 minutes in total. To minimise potential distress questions and questionnaires validated for use among people with PD will be included and selected, based on the best available evidence.

It is possible that taking part in assessments or performing balance and walking tasks can cause instability. To minimise the risk of falling, a researcher will be standing close by to ensure participants' safety at all times. All participants will be informed that they do not have to perform any tests or assessments they do not feel comfortable with and assessments will be stopped if participants show signs of fatigue.

The protocol, final version of the Participant Information Sheet and Informed Consent Form and all written information given to trial participants will have been approved (given a favourable opinion) in writing by a Research Ethics Committee (REC).

7.2 Sponsor

The research will be sponsored by the University Hospital Southampton NHS Foundation Trust. Ethical and governance approval will be sought from Multicentre Research Ethics Committee (MREC) via the Integrated Research Application System (IRAS) for all recruiting areas. We will work with local Research and Development (R&D) departments to ensure the research is conducted in the appropriate manner.

7.3 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

Indemnity insurance for any harm caused to participants by the design of the research protocol will be provided by the sponsor.

7.4 Trial Timetable and Milestones

See Figure 3 for trial timetable, milestones and recruitment targets.

7.5 Administration

The trial will be co-ordinated by the trial coordinator () with support from the chief investigator (Professor Ann Ashburn). The trial coordinator will be responsible for the day-to-day co-ordination and the local assessors and treating therapists will be responsible for the clinical aspects in their relevant trial centre. The trial coordinator will also be responsible for staff recruitment, training and support. All members of staff at the University of Southampton are linked to the appraisal system and have access to academic training. The treatment team, Professor Ann Ashburn, Professor Lynn Rochester, Professor Alice Nieuwboer, and Drs Vicki Goodwin and Emma Stack, have developed the treatment programme for the PDSAFE intervention.

Professor Ann Ashburn will lead the team and work closely with the trial coordinator and assessors from each of the centres. Day to day trial procedures of each of the stages of the research will be managed at regular meetings with the researchers. For those unable to attend meetings in Southampton in person, Skype and teleconferencing will be used to ensure regular communication across all areas.

Figure 3 Gantt chart for years 2 to 4 of the PDSAFE trial

Time plan Year 2-4	2014								2015												2016												2017								
	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S
	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53
Main Trial																																									
i) Recruitment*																																									
ii) Treatment																																									
iii) Assessments																																									
iv) Statistical input																																									
v) Health economics																																									
Qualitative Study																																									
ii) Interviews and analysis																																									
iii) Complete analysis and write																																									
Analysis & write up of total trial																																									
i) Primary and secondary																																									
ii) Final report and draft papers																																									

Trial management will focus on pre-set targets, regular review and internal and external assessment. The chief investigator and trial coordinator will meet weekly and the Trial Management Group (TMG) (comprising applicants, trial co-ordinator, and members of OCTRU) will communicate on a regular basis. TMG meetings will be every two months initially, though this will be adjusted as appropriate over time. Independent trial steering and data monitoring committees will be convened according to HTA guidelines to ensure high quality conduct of the trial.

Members of the research team are experts in their field and actively involved in rehabilitation trials. Co-investigators/grant holders for the trial are:

Dr Claire Ballinger (Senior Qualitative Health Researcher, University of Southampton).

Dr Victoria Goodwin (Senior Research Fellow at the University of Exeter).

Professor Sallie Lamb (Professor of Rehabilitation at University of Warwick; Professor of Trauma Rehabilitation at the University of Oxford, Director of Oxford Clinical Trials Research Unit.

Dr Emma McIntosh (Reader in Health Economics and Health Technology Assessment at the University of Glasgow).

Professor Alice Nieuwboer (Professor of Physiotherapy at the University of Leuven, Belgium).

Dr Ruth Pickering (Senior Lecturer in Medical Statistics at the University of Southampton).

Dr Helen Roberts (Senior Lecturer and Honorary Consultant in Geriatric Medicine at the University of Southampton).

Professor Lynn Rochester (Professor of Human Movement Science at Newcastle University).

Professor Ashburn's leadership will ensure the smooth running and successful completion of the proposed trial. Ashburn is a member of the NIHR South Central RfPB Board; she led a previous trial of fall prevention in PD and has worked with Ballinger gaining considerable experience in recruitment, use of falls diaries, delivery of interventions and the circumstances surrounding fall events. Ballinger has expertise in qualitative research methodologies and is a member of the European PD Taskforce. Pickering has been a Medical Statistician on a number of rehabilitation trials and has a particular interest in trials of PD and falls. Nieuwboer and Rochester are extremely experienced researchers in the field of PD rehabilitation bringing expertise in the analysis and management of the movement disorders; they were Principal Investigator (PI) and Co-investigator on the EU funded Rescue Trial on cueing in PD. Roberts is the Director of South Coast DeNDRoN and Geriatrician with a speciality in the medical management of people with PD. Goodwin has experience of recruiting to and conducting RCT trials; she completed a three year study of PD fallers for her PhD. McIntosh is an experienced economist; she developed the economic evaluation for PDMed and PDSurg and will bring valuable knowledge to PDSAFE. Lamb is an NIHR Senior Investigator with considerable knowledge of organising trials of complex interventions. The Oxford Clinical Trials

Research Unit will provide advice on regulation, quality assurance, trial conduct, and provide a database for data management.

7.6 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced rehabilitation researchers with experience in running clinical trials and Parkinson's disease as well as 'lay' representatives. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need, but not less than once a year. Routine business will be conducted by email, post or teleconferencing.

The Trial Steering Committee, throughout the trial will take responsibility for:

- Major decisions such as a need to substantially change the protocol for any reason.
- Monitoring and supervising the progress of the trial.
- Reviewing relevant information from other sources.
- Considering recommendations from the DMEC.
- Informing and advising on all aspects of the trial.
- Closing the trial prematurely if necessary.

7.7 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed comprising two clinicians with experience in undertaking clinical trials / caring for subject with Parkinson's disease and a statistician. All members are independent of the trial. Meetings will be held at regular intervals determined by need, but not less than once a year. Routine business will be conducted by email, post or teleconferencing.

The DMEC can recommend premature closure of the trial and can unblind the data if required. The DMEC, throughout the trial, will take responsibility for:

- Monitoring data and making recommendations to the TSC as to whether there are any ethical or safety reasons why the trial should not continue.
- Monitoring patient safety data (SAEs).
- Providing advice to the chief investigator, TSC, funder, or sponsor, as appropriate.

7.8 Essential Documentation

A Trial Master file will be set up and held securely at the co-ordinating centre in Southampton.

8. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

The trial will be carried out in accordance with the Good Clinical Practice Guidelines and in line with the Standard Operating Procedures (SOPs) of OCTRU.

OCTRU is a fully registered Clinical Trials Unit and has a comprehensive set of SOPs for the management of clinical trials and best practice will be employed throughout to ensure the project is managed to the highest possible standard. OCTRU will have a monitoring role in the trial to ensure adherence to good practice and to its SOPs. OCTRU's Head of Quality and Regulatory Affairs will be available to guide the project in all aspects of quality management and regulatory issues.

In order to check the quality of assessments being performed on all participants and the delivery of physiotherapy, advice and information, an additional member of the PDSAFE team may join the assessor and/or physiotherapist on an occasional visit. This will only apply to a very small number of participants.

9. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to the trial collaborators. The main report will be drafted by members of the Trial Management Group, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

All publications will be subject to the forthcoming PDSAFE publication protocol, which will explicitly stipulate the requirements for authorship of publications.

Findings will be disseminated to academic audiences through publications in academic journals and presentations at academic conferences. Dissemination to practitioners will focus on articles in practitioner-orientated publications and presentations at practitioner-orientated conferences. Dissemination to people affected by Parkinson's disease (service users and carers) and voluntary workers will be achieved using printed and web-based materials through organisations and networks such as Parkinson's UK and DeNDRoN.

10. FINANCIAL SUPPORT

The trial is funded by the NIHR Health Technology Assessment Programme.

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12. APPENDIX

12.1 Power Calculation Table

Table 5: Power calculations for primary and secondary falling outcomes

			NUMBERS REQUIRED IN ANALYSIS		NUMBERS NEEDED AT:	
			per group	total	RECRUIT-MENT[a]	RANDOM-ISATION[b]
Risk of Repeat falling **EXSART risks of repeat falling 0-6 months: control group=68%, intervention group=56%**						
0-6 months (5% loss to follow-up)	**Control**	**Intervention**				
13% difference	63%	50%	228	456	534	480
15% difference	70%	55%	163	326	382	344
15% difference	60%	45%	173	346	408	366
6-12 months (10% loss to follow-up)	**Control**	**Intervention**				
13% difference	63%	50%	228	456	564	508
15% difference	70%	55%	163	326	404	364
15% difference	60%	45%	173	346	430	386
Fall Rates **EXSART: Falls Rate Ratio (FRR) over 6 months follow-up=0.833, with the control group rate of falls over 3 months of follow-up=3**						
FRR 0-6 months (5% loss to follow-up)	**Baseline rate /3 months**					
0.75	3		100	200	236	212
0.8	3		164	328	386	346
0.75	2.5		120	240	278	254
0.8	2.5		197	394	464	416
0.75	2		150	300	352	316
0.8	2		246	492	576	518
FRR 6-12 months (10% loss to follow-up)						
0.75	3		100	200	250	224
0.8	3		164	328	408	366
0.75	2.5		120	240	298	268
0.8	2.5		197	394	488	438
0.75	2		150	300	372	334
0.8	2		246	492	610	548

a - Numbers needed at recruitment allow for 10% of those agreeing to enter the pre-randomisation falls collection period not to participate in the main trial, and a further loss of 5% of falls information by 6 months, and 10% by 12 months. This is conservative in the case of the falls rate models, since participants dropping out during a period will contribute some exposure time to the analysis.
b - Numbers needed at randomisation allow for 5% loss of falls information by 6 months and 10% by 12 months.