UNIVERSITY OF Southampton

University Hospital Southampton NHS
NHS Foundation Trust

PD SAFE
Fall Prevention in Parkinson's Disease

STATISTICAL ANALYSIS PLAN

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

PDSAFE Main RCT

Version 1 – 15 May 2017

Based on version 6 of protocol

	Name	Title/Role	Signature	Date
Author	RUTH PICKERING	MEDICAL STATISTICIAN	Ruth Pickering	24th May 2017
Reviewer	ANN ASHBURN	CHIEF INVESTIGATOR	A Ashburn	24May2017
Reviewer	KIM SEYMOUR	TRIAL MANAGER	K Seymour	24May2017

Oxford Clinical Trials Research Unit (OCTRU)

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1. INTRODUCTION

This document details the proposed presentation and analysis for the main paper reporting results from the NIHR HTA Multicentre Randomised Controlled Trial of the PDSafe programme to prevent falls in people with Parkinson's. The results reported in the paper should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal paper is submitted for publication. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial.

Key personnel

Trial statistician(s):
RUTH PICKERING
Primary Care and Population Sciences (MP 805)
South Academic Block
Southampton General Hospital
SOUTHAMPTON, SO16 6YD
Tel: 023 8120 6565
Email: rmp@soton.ac.uk

Chief Investigator (s):
Professor Ann Ashburn
Faculty of Health Sciences,
University of Southampton
MailPoint 886 Southampton General Hospital
Tel. 023 8120 6469
Fax. 023 8120 4340
Email. ann@soton.ac.uk

Trial Manager:
Dr Kim Chivers Seymour
Faculty of Health Sciences
University of Southampton
Level E, Centre Block
Mail point 886
Southampton General Hospital
SO16 6YD
Tel: 023 8120 4943
Email: kimchivers.seymour@soton.ac.uk

Data Manager:
Dr Kim Chivers Seymour
Contact details as above

DSMC Members:
Prof Carl Clarke - Chair
Professor of Clinical Neurology & Honorary Consultant Neurologist
Department of Neurology
City Hospital, Sandwell and West Birmingham Hospitals NHS Trust
Dudley Road
Birmingham, B18 7QH
Email: carlclarke@nhs.net
Tel: 0121 507 4073

Dr Rebecca Walwyn
Principal Statistician
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research, University of Leeds
Leeds, LS2 9JT
Email: R.E.A.Walwyn@leeds.ac.uk
Tel: 0113 343 5485

Prof Sarah Tyson
Professor of Rehabilitation
Stroke & Vascular Research Centre School of Nursing, Midwifery & Social Work, Jean McFarlane Building, University of Manchester, Oxford Rd, Manchester M13 9PL
Email: sarah.tyson@manchester.ac.uk
Tel: 0161 306 7781

TSC Members:
Prof Pip Logan - Independent Expert
Professor of Rehabilitation Research
School of Medicine, University of Nottingham
Email: Pip.Logan@nottingham.ac.uk
Tel: 0115 8230235

Professor Helen Dawes – Independent Expert
Elizabeth Casson Trust Chair
The Movement Science Group
Faculty of Health and Life Sciences
Oxford Brookes University
Email: hdawes@brookes.ac.uk

Mr John Wood – Patient representative
Email: Johndwood11@btinternet.com

2. CHANGES FROM PREVIOUS VERSION OF SAP

This is the first approved version of this SAP.

3. BACKGROUND INFORMATION

The intervention examined here is a personalised exercise programme along with strategy training intervention including a personalised DVD based on latest research evidence, to prevent falling in people with Parkinson's Disease (PwPD).

Objectives

The main objective is to reduce falling in PwPD: we propose that PwPD following the PDSafe programme will fall less than those who do not. Prior to, but more importantly, during the course of the trial, consistent evidence (e.g. Canning et al. 2015) has emerged that interventions are more effective in people with mild to moderate disease, rather than severe classifications. For example, a recent meta-analysis of individualized home-based exercise program RCTs for older people, aiming to reduce falls and improve physical performance, showed no significant effect of intervention on falls rate. However, when the more severe group was removed this result was significant (Hill et al. 2015). Hence, our pre-specified analyses, particularly those related to disease severity, are likely to assume importance in the interpretation of the trial. Therefore as well as examining the difference in the pooled sample (i.e. all participants regardless of severity), we will complete a pre-specified analysis relating to disease severity, and will accept treatment effect in the group excluding extreme severity as evidence of effectiveness.

Study Design

This is a multi-centre, single-blinded, randomised, controlled trial for PwPD to compare the PDSafe programme against control. PwPD will be recruited to a pre-randomisation 3 month fall collection period during which they will document any falls using a falls diary. At the end of this period, participants, still willing, will be individually randomised to receive the PDSafe programme or not. Both groups will continue to complete falls diaries for the year following randomisation. The PDSafe intervention is a 6 month programme, and the primary endpoint is at 6 months, approximately coinciding with the end of the intervention. All trial procedures will take place in participants' homes. There will be home follow-up assessments at 3 month, 6 months (primary) and one year.

Date of start of recruitment:	01/JUL/2014
Date of expected end of recruitment:	30/SEP/2016
Date expected final randomisation :	30/NOV/2016
Date expected end follow-up:	30/APR/2017
Date expected analysis:	30/JUN/2017 (Primary, 6 month analysis)
Target number of subjects:	600 to pre-randomisation 3 months falls collection period
Participating Centres:	Southampton, Portsmouth, Bournemouth and Poole, Exeter, Hampshire, Newcastle, Plymouth, Cornwall

Eligibility

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.

Treatment Interventions

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 during their 12 months on the trial and encouraged to avoid changing that practice unless specifically requested by a health care worker.

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. The intervention is described in detail in the Trial Specific Instructions 9 – PDSAFE Intervention.

Adherence with allocated treatment will be described.

Sample Size

Primary outcome: risk of repeat falling between 0-6 months
In the EXSART trial (Ashburn et al. 2007) 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 be lost to follow-up 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 calculations for various scenarios are summarised in Appendix 2

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 be lost to follow-up 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 (Appendix 2) for rates of falling are based on the calculations of Tango (2009) and relate to the number of falls during a fixed follow-up period analysed using negative binomial regression conditioned on baseline counts: specifically using formula 23 in the paper and 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 participants per group at analysis leading to recruiting 488 participants to the pre-randomisation falls collection period.

All the calculations are based on 80% power and 5% two-sided tests, but the target numbers have been inflated to give a "buffer" allowing for the possibility that some of the assumptions are not met.

Strategies for achieving adequate recruitment

The trial team have considerable experience of recruiting PwPD to trials. We will monitor early recruitment carefully and take steps to correct below target recruitment if it occurs.

Randomisation

Random allocation will be computer generated by R M Pickering and submitted to the OCTRU for web-based implementation. It will be 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.

Hypotheses and Definition of Primary and Secondary Outcomes

The primary outcome is the proportion of participants with repeat (≥2) falls in the period 0-6 months following randomisation.

Secondary outcomes include the proportion of participants with repeat (≥2) falls in the period 6-12 months randomisation. Rate of falling in the periods 0-6 months and 6-12 months are also key secondary outcomes.

Outcomes Assessment Schedule

Screening Measures	Source	Time points	Anticipated intervention effect
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			
Proportion with ≥2 falls during the period 0-6 months post randomisation (falls)	Monthly self-report diaries	Completed from screening visit to end of participation in trial (maximum of 15 months).	Fewer falls
Secondary Measures			
Fall events 0-6 months (fractures and near-falls)	Monthly self-report diaries	Completed from screening visit to end of participation in trial (maximum of 15 months).	Fewer falls and near falls
Fall events 6-12 months (falls, fractures and near falls)	Monthly self-report diaries	Completed from screening visit to end of participation in trial (maximum of 15 months).	Fewer falls and near falls
Mini-BESTest	Assessor		
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		Decreased depression
Fall Efficacy Scale International (FES-I)			Increased self efficacy
New Freezing of Gait - questionnaire			
PDQ39 - questionnaire			
Physical Activity Scale for the Elderly (PASE)			Increased physical activity
Economic Measures (PwPD)			
Health and social care resource use sheet (with associated home diary to aid recall)	Self-report	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		

Data Management Responsibility

Data is managed by the main trial team at Southampton.

4. QUALITY CONTROL AND DATA VALIDATION

1. Paper CRFS will be received from Portsmouth, Southampton, Hampshire and Bournemouth & Poole; scanned copies will be received from Exeter, Cornwall, Newcastle and Plymouth. Upon receipt these will be date stamped (on every page) by the trial office and logged as received on the Open Clinica – TMS and trial-specific CRF database. Paper CRFs will also be scanned and saved on the TMF as PDFs.
2. Data forms are checked for completeness and legibility; if issues are identified the CRFS will be returned to the relevant assessors using the 'Date Query Form' as required.
3. CRFs will then be filed in the "awaiting data entry" filing cabinet.
4. Single data entry into the trial database using a secure internet based system, Open Clinica, will be done manually by the trial admin team based in Southampton. Several automated checks are set up for the data entry screens and validation programs with in Open Clinica, e.g. the MMSe scores are auto-calculated and the participant cannot be registered unless they have met the minimum score of 24.
5. Once data entered, each CRF is date stamped again and filed in the participant folder in the locked trial filing cabinets. The trial-specific monitoring database is updated.
6. Checks of data entry accuracy will be carried out quarterly; another member of the trial team auditing approximately 5% of data entered by each individual. If errors are found, a further 5% will be checked and a report will be generated for presentation to the Trial Manager and CI to take further action.
7. If the OCTRU website is down then data entry will have to be delayed until is restored.

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).

5. DATA SAFETY MONITORING COMMITTEE AND INTERIM ANALYSES

A DMEC has been set up and will meet comprising two clinicians with experience in undertaking clinical trials and/or caring for subject with Parkinson's disease and a statistician. Meetings are held at regular intervals determined by need, but not less than once a year; other routine business is conducted by email, post or teleconferencing.

Throughout the trial, the DMEC 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.

6. DESCRIPTIVE ANALYSES

Representativeness of Study Sample and Patient Throughput

We will document the numbers of potential trial participants identified and recruitment outcome (recruited to pre-randomisation 3 months falls collection period, ineligibility, or refusal). The flow of participants through each stage of the trial: recruitment to 3 months pre-randomisation falls collection period; randomisation; 6 months assessment; and 12 months assessment, will be summarised in the form of a flow

diagram (as suggested by CONSORT (Schulz et al. 2010). We will also document numbers returning falls collection diaries in the 3 months prior to randomisation, the periods 0-6 and 6-12 months post randomisation, and also the 3 month periods 0-3, 3-6, 6-9 and 9-12 months post randomisation. Deviations from planned intervention and assessment will be described by study group, together with any reasons available. We will describe the distribution of times each assessment took place (with respect to randomisation), and document the proportion of assessments falling within the planned times frames for these assessments.

The number of ineligible patients randomised, if any, will be reported, with reasons ineligible. However we do not anticipate this to be a problem as eligibility will be assessed prior to the 3 months falls collection period, but any errors at this stage are likely to be uncovered before randomisation.

Baseline Comparability of Randomised Groups

Participants randomised to the PDSafe intervention and control groups will be described separately with respect to centre, age, time since PD diagnosis, number of retrospectively reported falls in the year prior to the 3 months falls collection period, number of prospectively reported falls in the 3 months falls collection period, Hoehn and Yahr stage, UPDRS motor exam, living status, PD related rehabilitation, any orthopaedic, cardiac or mental health condition, L-DOPA equivalent dose, and dopamine agonists.

Numbers (with percentages) for binary and categorical variables, and mean (or median), standard deviation, and minimum to maximum for continuous variables will be presented. There will be no tests of statistical significance, or confidence intervals presented, for differences between randomised groups on any baseline variable. If descriptive statistics indicate a substantial difference between groups, secondary analyses additionally controlling for such baselines characteristics will be conducted to support the pre-stated primary analyses.

Comparison of Losses to Follow-up

The numbers (with percentages) of losses to follow-up (non-completion of assessment and withdrawal from the trial) over the primary six months and entire 12 months post randomisation follow-up period of the trial will be reported and compared between the intervention and control groups. The amount of completed falls diary time will be reported for each trial arm. Hospitalisation and deaths (and their causes) will be reported separately.

Description of Available Outcome Data

The patterns of availability of all outcome variables from baseline to end of follow-up, will be summarised for the two groups with differentiation of fully, or partially completed, ratings from those completely missing, or with sketchy detail. Where instruments give instructions for dealing with missing item responses these will be followed. Where specific instruction is not given, pro-rata estimation of total and subscale scores will be employed with rating scales and subscales that contain eight or more items when at least 75% of item responses are available. Totals obtained from the completed items, will be increased according to the percentage of items (or total score obtainable from completed items where unequally weighted) completed. The proportions of cases without all items completed will be reported for each treatment group.

Outcomes that are assessed at visits that are not carried until beyond the deadline for the assessments shown in the table below will be treated as missing.

Table: '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	40 weeks after randomisation
12 Month Follow-up (Week 52)	50-55 weeks after randomisation	60 weeks after randomisation

The visit "windows" and deadlines shown in the table do not apply to the primary outcome of repeat falling and secondary outcome of the rate of falling because these are taken from the falls diaries. Rates of falling data can be calculated within a time period if some of the diaries for the period are not returned. Sensitivity analyses are planned for the primary outcome of repeat falling to take account of participants who drop out before the end of the period in question and are thus excluded from the primary analyses of repeat falling status. We will report diary return rates as the distribution of number of diaries returned within 3 month periods (prior to randomisation, and within the four 3 month periods of follow-up).

Description of Adherence with Intervention

Numbers receiving each component of the PDSafe intervention will be documented.

7. BLINDING

Blinding will be achieved by having separate researchers in each centre responsible for recruiting participants, contacting the randomisation service, and making all assessments. OCTRU will pass on allocation to treating therapists who will be unaware of baseline and subsequent trial assessments. In particular treating therapists will be unaware of falls reported by participants in their falls diaries. Researchers taking trial assessments will be blind to group allocation.

The number (and percentage) of any unblinding of assessors will be documented in relation to each assessment. We will examine the number of assessments where the assessor considered that they were aware of the allocated intervention, and also whether they were correct.

8. DATA MANAGEMENT PLAN

Data is managed by the main trial team at Southampton.

Validation of primary analysis

The primary outcome analysis will be carried out by the trial statistician as described in section 10. It will be repeated and verified by Dr RM Pickering.

9. PATIENT GROUPS FOR ANALYSIS

The main analysis will be based on intention to treat (ITT) in that participants will be analysed according to the group to which they were allocated irrespective of the extent of intervention received. In the event of us failing to find a statistically significant effect, we will perform per protocol analyses restricted to groups receiving their allocated treatment (and maybe restricted to groups receiving the intervention to different extents).

The primary analysis of the proportion of participants' repeat falling in the period 0-6 months following randomisation will be restricted to participants who do not withdraw from the trial before 6 months of follow-up, Where participants have not returned diaries for the complete 6 months, they will be classified as a repeat faller if they have recorded two or more falls in their returned diaries, telephone checks on falling will be checked to see if they report two or more falls, if these further checks indicate non-repeat falling they will be coded as a non-repeat faller. Similarly the analysis of the secondary outcome, repeat falling during the period 6-12 months, will be restricted to participants who have not withdrawn before 12 months, and will be based firstly on returned diaries, and if some diaries are missing, telephone checks on falling will be reviewed to see if repeat falls are reported.

The secondary analyses of fall rates in 0-6 months and 6-12 months automatically take account of varying periods of follow-up (amongst those who start falls diaries at the beginning of the period in question).

Safety: any adverse events that we become aware of in participants who are randomised in the trial will be included in our safety monitoring. Events in participants in the 3 months pre-randomisation falls collection period will also be monitored.

We will compare outcome between those participating in the qualitative interviews or not, within those allocated to the PDSafe programme.

10. ANALYSES TO ADDRESS PRIMARY AIMS

The primary outcome repeat falling during the 6 months period after randomisation, will be compared between intervention and control groups using a logistic regression model including falling during the pre-randomisation falls collection period, disease severity (using the UPDRS motor exam or the Hoehn and Yahr score; chosen at a blind review of the data), centre, age and gender as covariates. The definition of the baseline falling covariate will be decided at blind review of the data prior to analysis, a possible definition being the log of the number of falls during the 3 months pre-randomisation falls collection period (replaced by 0.5 if there are zero baseline falls). Choices over definition of covariates taking place at blind review will be based on analysis from a dataset not including the group allocation variable, and will define covariates so that they have most explanatory power.

Blind Review of the Data

Prior to the primary analysis the dataset will be reviewed excluding the allocation variable.

Adjustment of P values for Multiple Testing

There is only one primary outcome: the proportion of participants repeat falling in the period 0-6 months, thus no adjustment for multiplicity is required.

Missing Data

The primary analysis of the proportion of participants with repeat falling in the period 0-6 months following randomisation will be restricted to participants who have not withdrawn from the trial before 6 months. Where participants have not completed all diaries we will establish repeat falling status firstly from those diaries that were returned, for those not reporting repeat falling in available diaries we will review records of telephone checks of falling, and if repeat falls were not mentioned will code the participant as a non-repeat

faller. This will be carried out at the time of blind reviewing (dataset without the allocation variable). Similarly the analysis of the secondary outcome repeat falling in the period 6-12 months will be restricted to participants who haven't withdrawn from the trial within the period, and where there are missing diaries a similar process to above will be followed with repeat fall status firstly taken from available diaries.

The secondary analyses of fall rates in 0-6 month period, and the 6-12 month period, automatically take account of varying periods of follow-up (amongst those who return at least one diary during the period in question) and these analyses will not be restricted to participants who don't withdraw within a follow-up period.

Published guidance on scoring (total and sub-) of other outcomes will be followed. Where no guidance is available we will increase scores based on totals pro-rata to take account of any missing items, as long as at least 75% of items are recorded. Totals obtained from the completed items, will be increased according to the percentage of items (or total score obtainable from completed items where unequally weighted) completed.

Pre-specified Subgroup Analysis

The planned analysis of the primary outcome will be performed removing the most severe subgroup of participants according to UPDRS at baseline (with scores of 59 and over) (Martinez-Martin et al, 2015). During the course of the trial further studies reported that treatment effect was greatest in this subgroup and we now believe this to be of similar importance to the treatment comparison from the sample of all participants as a whole. We also plan a second set of subgroup analyses relating to severity as defined by the Hoehn & Yahr (1-3 less severe, and 4 more severe). Other subgroup analyses are planned according to MOCA values (26 and above, and 25 and under) at baseline; and with subgroups coded as freezers or not at baseline. A comparison of the intervention effect between each of the Hoehn & Yahr, MOCA and freezing subgroups, as defined above. Formal tests of interaction of the treatment effect differing across subgroups, will be performed. We will also examine the effect of the intervention separately in each centre.

Treatment by Centre Interaction

The PDSafe programme is proscriptive and includes a DVD personalised for each participant but produced from a standard set of exercises. The intervention will be delivered by therapists employed within the trial and educated to deliver the intervention in a standardised way. Thus we are not expecting major differences across centres, however consistency of effect will be assessed across the four centres by informal examination of the within centre effects. There will be limited capacity to investigate these formally due to within centre sample sizes. Similar trials show little or no therapist effect and the trial is not powered to include random therapist effects.

Sensitivity Analysis

We will perform sensitivity analyses to examine the robustness of the conclusions to assumptions about missing outcome data. The primary conclusions will be based on the ITT analysis. Sensitivity of conclusions to various assumptions about the values taken when data are missing will be examined, and multiple imputation will be carried out.

To address non-adherence with the intervention, analyses will be repeated restricted to participants included in the intervention group receiving at least 7 sessions. A Complier Causal Effect Analysis (CACE) will be carried out to take account of the adherence of participants with the intervention (based on a variety of definitions of adequate adherence with intervention decided at blind review of the data).

These analysis will not be considered the definitive analysis of the PDSafe programme, but will be used to explore robustness of conclusions. In the event that we fail to find a statistically significant effect size the

sensitivity analyses will address the question as to whether there was an effect in some participants but we missed it because of contamination by participants not receiving all (or enough) of the PDSafe programme.

11. ANALYSIS TO ADDRESS SECONDARY AIMS

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, disease severity (UPDRS score and/or Hoehn and Yahr score, depending on the choice for the primary analysis), age, gender, centre and amount of therapy received as covariates, fitted using either the nbreg or xtpoisson regression commands Stata (2009) 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, age, gender, UPDRS scores, Hoehn and Yahr scores, and baseline value, including participants with incomplete follow-up information in the analysis.

12. ADDITIONAL ANALYSES

Any analyses not specified in this SAP will be exploratory in nature.

13. SAFETY ANALYSIS

Hospitalisations "arising from the trial intervention" are reported as SAEs. For this trial, SAE relate to hospitalisation as a result of fall or injury whilst completing the intervention exercises, either with or without the PDSAFE therapist present. Given that the population group for this trial is likely to comprise of mainly elderly participants, this definition of an SAE is being used for PDSAFE to reduce the reporting of SAEs without compromising participant safety.

Incidents of hospitalisation and disability, falls, or incapacity attributable to a participant's Parkinson's disease are instead recorded through follow up assessment (baseline, 3, 6 and 12 months)

SARs 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 (that is the relationship to trial treatment) as assessed by the Investigator(s) will be reported on the SAE form. All SAEs, SUSARs and ARs will be reviewed by Dr Helen Roberts, Consultant in Elderly Care, to check/determine the assessment of whether an SAE is related and unexpected as defined.

Numbers of serious adverse events will be tabulated and included in the tables presented to the DSMC. The main serious adverse side effect of the PDSafe programme might be falling and consequent fractures – PwPD being encouraged to move more and thus fall more. However this is the primary outcome of the trial, we anticipate that with the level of follow-up included within the PDSafe programme that we will be able to get participants moving more without falling and in fact reduce the rate of falling. Serious adverse events will be reviewed by the DMEC.

Safety summaries will be reported in the final statistical report. It is not anticipated that there will be sufficient serious adverse events to warrant statistical testing.

14. REFERENCES

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15. APPENDIX 1: GLOSSARY OF ABBREVIATIONS

CI	Chief Investigator
DSMC	Data and Safety Monitoring Committee
PwPD	People with Parkinson's Disease
SAP	Statistical Analysis Plan
TSC	Trial Steering Committee

16. APPENDIX 2: 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.

17. DOCUMENT HISTORY

Add a brief document history – this can be removed when each full version is formally signed off, but all previous versions should be stored as a record of reviews of the document.

Version number Issue date	Author	Significant changes from previous version
V1.0 15Nov2016	RUTH PICKERING	Not applicable as this is the 1st version.
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