

A multicentre, randomised controlled trial of PDSAFE, a physiotherapist-delivered fall prevention programme for people with Parkinson's

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ABSTRACT

Objective: To estimate the effect of a physiotherapist-delivered fall-prevention programme for people with Parkinson's (PwP).

Methods: People at risk of falls with confirmed Parkinson's were recruited to this multi-centre, pragmatic, investigator blind, individually randomised controlled trial with pre-specified sub-group analyses. 474 PwP (Hoehn and Yahr 1-4) were randomised: 238 allocated to a physiotherapy programme and 236 to control. All participants had routine care; the control group received a DVD about Parkinson's and single advice session at trial completion. The intervention group (PDSAFE) had an individually tailored, progressive home-based fall-avoidance strategy training programme with balance and strengthening exercises.

The primary outcome was risk of repeat-falling, collected by self-report monthly diaries, 0 to 6 months post-randomisation. Secondary outcomes included, Mini-BESTest for balance, chair stand test, Falls Efficacy, freezing of gait, health related quality of life (Euroqol EQ-5D), Geriatric Depression Scale, Physical Activity Scale for the Elderly and Parkinson's disease Questionnaire, fractures and rate of near-falling.

Results: Average age, 72 years and 266 (56%) were men. By 6 months 116 (55%) of the control group, and 125 (61.5%) of the intervention group reported repeat falls (controlled odds ratio 1.21, 95% confidence interval 0.74 to 1.98, $P=0.447$). Secondary sub-group analyses suggested a different response to the intervention between moderate and severe disease severity groups. Balance, falls efficacy and chair stand time improved with near-falls reduced in the intervention arm.

Conclusion: PDSAFE did not reduce falling in this pragmatic trial of PwP. Other functional tasks improved and reduced fall rates were apparent among those with moderate disease.

Trial registration: Trial registration reference is ISRCTN48152791.

INTRODUCTION

Parkinson's disease is a progressive neurological condition that affects more than 10 million people worldwide; falls are common in this group. Prior to the start of the PDSAFE trial, a meta-analysis of fall reduction among the general older population [1] demonstrated a positive exercise effect but it was not until during PDSAFE that a meta-analysis of fall prevention among PwP was published [2]; findings were inconsistent with small overall effect sizes on fall rate ratios and group-based training more favourable than home-based interventions [3-8].

Falls are twice as common among PwP as the healthy aged [1, 7-10]. Impairments of gait, including freezing of gait, cognition and loss of postural control are common risk factors for falling in this population, balance and falls are not easily remedied by medication [11, 12]. The effects of falls in PwP can be profound including loss of mobility, poor function in activities of daily living, fractures and increased care needs [7-9, 12-13] as well as being costly to both individuals and health services [14]. There is some evidence that exercise may be useful for falls prevention in PwP [2]. However, trials conducted to date have usually been small, only 6 out of 25 trials in the meta-analysis recruited 100 or more participants. Most of the larger trials were negative [2] but there were differences in sub-group responses [6, 7, 8]; benefits were demonstrated in higher functioning groups, particularly in people who had sufficient function to enable them to travel to exercise venues and participate in group programmes [6]. Canning et al [6] recruited 231 PwP to an RCT and reported non-significant overall effect but significant interaction with disease severity; those with more severe disease had a greater number of falls following intervention, while there was significant improvement for those with less severe disease.

Our aim was to compare the effect on repeat falling outcomes and other outcomes of an individualised, progressive exercise intervention delivered in people's own home, in addition to usual care. We aimed to recruit a large, pragmatic sample of PwP, and used pre-specified and exploratory sub-group analysis to examine variation in the intervention effect according to baseline disease severity and freezing of gait.

METHODS

Study design

A full protocol has been published[15]. This was a multi-centre, pragmatic, investigator masked randomised controlled trial. Participants were recruited from Parkinson's services in NHS hospital and clinics, community and social services in eight regions across England: Bournemouth and Poole, Truro, Plymouth, Exeter, Winchester and Basingstoke, Newcastle, Portsmouth and Southampton. We also identified recruits via the study web-site. We delivered interventions in the participant's home. The primary endpoint for the trial was 6 months after randomisation. We received funding to allow 12 month follow up on the first 342 recruited into the trial. An economic evaluation and a nested qualitative study of the views of participants will be published elsewhere as will details of the intervention. Trial management, data monitoring and statistical analyses were coordinated at the PDSAFE Trial office, University of Southampton, UK and supported by the Oxford Clinical Trials Unit OCTRU. Ethics approval was granted by the NRES South Central Hampshire B Committee (REC reference 14/SC/0039). Trial registration number is ISRCTN48152791.

Participants

People were eligible if they had a clinically confirmed diagnosis of Parkinson's disease in accordance with UK Brain Bank criteria[16]; were living in their own home; independently mobile with or without an aid; experienced at least 1 fall in the previous 12 months; scored 24 or more on Mini-Mental State Examination [17] (MMSE); had the cognitive ability to give informed consent; were able to understand and follow commands; and considered able to participate in an exercise and strategy programme.

Interventions

All participants continued to receive usual care including medication management, and took part in their usual activities, such as exercise or social groups. Participants assigned to the control group were given a Parkinson's UK DVD with information about Parkinson's. At the end of their time in the trial, control participants received a single session on fall avoidance and a booklet on falls management.

PDSAFE[18] comprised individually tailored, progressive home-based exercise and strategies to avoid falls eg. 'Stepping patterns and sideways stepping in small complex areas to avoid tripping'. Registered physiotherapists made visits to the participants' home to provide 12 supervised sessions of 1 to 1.5 hours duration over 6 months. More supervised sessions were delivered early in the programme, and gradually tapered over time. From the start of the programme, participants were expected to engage in daily,

unsupervised exercise for about 30 minutes, and were provided with a prescription for these and strategies to maximise adherence, such as integration into daily routines. Participants were given a folder with pictures and descriptions of exercises, a rating of perceived exertion scale, an exercise log, and DVDs of both exercise demonstrations and personal videos taken by their physiotherapist of them doing the exercises. Programmes were based on an individualised assessment of fall risk factors, including the home environment and high-risk activities. Exercises included balance training with a gradual decrease in the area of support and use of foam standing pads. Strength training used body weight resistance, and if appropriate, weighted vests, during functional exercises (sit to stand). Strategies for fall and freezing avoidance included transfer practice (turning) in complex environments such as bathrooms and kitchen and adopting wide-based positions during functional task practice.

Intervention fidelity was promoted through a two-day training session, and subsequent observation and feedback during sessions by a specialist physiotherapist with expertise in Parkinson's management. All but one physiotherapist had a background in neurological practice. Monthly 'master classes', weekly teleconferences and regular clinical supervision sessions were implemented. Fidelity checks were undertaken three times during a therapist's first three months of delivering the intervention, and three monthly thereafter. We considered that people who attended the assessment and received one home session to have engaged with the intervention. Those who had 7 or more sessions were considered to have complied with the intervention.

Outcomes

The primary outcome was risk of repeat falling in the first six months after randomisation. A fall was defined as an event which resulted in a person coming to rest unintentionally on the ground or lower level[19]. Secondary outcomes were fractures and the rate of near falling, the Mini-BESTest[20] (high values – good, a test of balance control); the chair stand test[21] (low timing - good) ; medication use; the Geriatric Depression Scale, GDS[22] (15 question version; low scores - good); the International version of the Falls Efficacy Scale, FES[23] (low scores - good); the New Freezing of Gait questionnaire, NFOG[24] (low scores - good); the Parkinson's Disease Questionnaire, PDQ-39[25] (low scores - good, a quality of life measure designed specifically for PwP); the Physical Activity Scale for the Elderly, PASE[26]; high scores - good) at 6 months; the Euroqol (EQ5D 3L) health related quality of life instrument[27]. We recorded all deaths, any hospitalisations were recorded at assessment and serious adverse events were reviewed by medical physician, HR. The PASE, PDQ-39 and GDS were self-completed and returned by post.

Randomisation and blinding

Prior to randomisation, participants completed three months of fall diaries. We then did a baseline assessment after which participants were randomly assigned (50:50) to either the intervention or control group, using an online procedure set up by OCTRUI (a UKCRC registered trials unit). The allocations were sent to the trial manager who informed a treating therapist, to ensure allocation concealment from trial recruiters and assessors. Random allocations were computer-generated, stratified by centre and allocated in blocks with random size of 2, 4, 6 or 8. The trial manager, the treating therapists and the participants were not blinded to the allocated group. At each point of contact, participants were asked not to divulge their group allocation to trial assessors who were blind to group allocation.

Procedure

We trained registered health care professionals to assess eligibility of potential participants, to register and randomise participants, to collect baseline information and administer outcome measures during the follow up period; fidelity checks were routinely made. We collected eligibility and baseline data over two visits, separated by a three month period in which we asked participants to collect falls diary data. At the first eligibility visit we collected the Montreal Cognitive Assessment (MoCA)[28], the number of falls experienced over the previous 12 months, the Mini-Mental State Examination (MMSE)[17], the Hoehn & Yahr Scale of Disease severity[29], demographics and medical history. At the second visit, we re-checked consent, collected the Unified Parkinson's disease Rating Scale, UPDRS[30] (low scores - good, motor section only) and enrolled and randomised the participant. Participants were asked to complete monthly diaries through the follow up period and face to face assessments were taken to collect all other data during home visits at 6 and, for those completing the extend follow up, at 12 months.

Sample size calculation

Based on the results of a previous trial[8] we assumed the risk of repeat falling between 0 and 6 to be 50% in the intervention group and 63% in the control group, yielding a sample size requirement of 228 participants per group at 80% power in a two-sided 5% comparison of proportions. Allowing for 15% (10% before randomisation and 5% after) loss to follow up, for these participants, between approach, randomisation and 6 months, we aimed to recruit 534 participants to the pre-randomisation falls collection period.

Statistical analysis

A statistical analysis plan was finalised before the dataset was locked. The analysis was intention to treat in that all participants were analysed in the group to which they were randomised. For the primary outcome we included participants who had completed a minimum of 50% of diaries, (as recommended by Goodwin et al[7]) and missing falls diary data, for these participants, by imputing the binary indicator of repeat faller (yes/no) from the final assessment if this data were available. The analysis of rates of falling included all participants with any degree of diary completion.

We used logistic regression controlling for site, age, gender, Hoehn and Yahr, the logarithm of retrospectively collected number of falls in the year prior to screening, repeat fall status prior screening, and the logarithm of the prospectively collected rate of falling during the 3 months period prior to randomisation with 0.5 added to numerators so that participants with zero falls during the period were included. These controlling variables were finalised in a blind analysis without access to the group indicator, as specified in the analysis plan. Rates of falling during the periods 0 to 6 and 6 to 12 months post randomisation were examined in negative binomial models with the logarithm of a participant's days of diary follow-up included as an offset. Odds Ratios (OR) and Fall Rate Ratios (FRR) are presented with 95% confidence intervals (CI). The geometric mean of individual participant rates (with 0.5 added to the numerator as before) of falling during 6 month follow-up periods are presented as rates per 6 months to accommodate the skewed distribution across participants. We pre-specified subgroup analysis for falling between 0 and 6 months to MoCA[28] status (≤ 25 and ≥ 26), freezing status, and disease severity UPDRS[30] and Hoehn and Yahr [29]. In addition, and informed by the findings of Morris et al[3,5] we explored sub-group analyses for MoCA, UPDRS and number of falls in the year prior to screening using the tertiles of the baseline distribution. We tested for sub-group effects using statistical tests of interaction. A secondary per protocol analysis excluded participants from the PDSAFE group who received less than 7 of the planned 12 sessions. Analysis was conducted in SPSS (IBM Corp., Armonk, NY) and Stata[31].

Patient Involvement

PPI representatives were involved in the design of the study, the development of participant information sheets, consent forms and intervention resources. A PPI representative was a member of the Trial Steering Committee. The trial was discussed at several Local Parkinson's support groups and representatives were invited to a meeting on interpretation of results and key messages.

RESULTS

Trial progression and recruitment

Recruitment was from July 2014 to August 2016 (study flow summarised in Figure 1). A total of 640 PwP were invited to participate, 99 either did not respond or did not meet the eligibility criteria leaving 541 for consent and completion of the first eligibility visit. At this point, a further 7 people did not reach the MMSE requirement and were excluded. The remainder went on to second eligibility check after which a further 60 people were excluded (reasons provided in Figure 1). The remaining 474 completed a baseline assessment and were randomised to usual care (n= 236) or PDSAFE (n= 238). Withdrawal rates were low at the primary time point, and equivalent across the groups. Falls diary completion was good at the primary time point, with 203/238 (85%) of the usual care group, and 211/236 (89%) of the intervention group providing usable data, see supplementary table. The IQR for the number of diary completion days over the primary 6 month period were 174-183 and 153-183 days in the control and intervention groups respectively. Fourteen trained assessors completed blinded data collection.

Intervention

Eighteen physiotherapists delivered PDSAFE and compliance with the intervention was good. 217/238 (91%) participants received per protocol, 7 or more supervised treatment sessions and 75% (162) of those received the maximum number. The median number of supervised sessions for all participants randomised to the intervention was 12 (IQR 11 to 12). The majority of participants, 236/238, received the exercise assessment and at least one supervised session. Two participants did not start due to a change of mind, 19 received less than 7 sessions. Reasons for withdrawal from the trial included: admission to a nursing home, deteriorating health, commitment was too much, no reason given and caring for others (see figure 1).

Figure 1

Sample

The baseline characteristics of randomised groups were balanced (Table 1). There was a difference in the rate of falling in the run-in-period.

Table 1

Table 2

Outcomes

There was little difference in the rate of falling between groups in the first 6 months (Table 2). Table 3 shows the treatment effect estimates for the primary time point including the primary outcome. Repeat falling in the PDSAFE group at 6 months was slightly higher than in the control group (OR 1.21 (95% CI 0.74 to 1.98, P=0.447)). There was significantly lower risk of near falling (0.67, (95% CI 0.53 to 0.86, P=0.001)) in the PDSAFE compared to control group.

Tables 3 & 4

For the secondary outcomes collected at 6 months (table 3), the exercise group had better balance (between group difference Mini-BEST score 0.95 points (95% CI 0.24 to 1.67 P=0.009); better falls confidence (between group difference 1.60 points (95% CI 3.00 to 0.19, P=0.026); and improved balance and functional strength as assessed by the Chair stand test, CST (P=0.041) (table 4). No material differences from those reported above were found when analyses were repeated on a per protocol basis.

Fig 2

Pre-specified and exploratory sub-group analysis - 6 months

The results of pre-specified sub-group analyses for MoCA and freezing of gait are shown in Figure 2, along with further analysis of subgroups defined by tertiles. People who had freezing of gait at study entry did not respond well to the intervention, and this interaction effect estimate was statistically significant (P=0.025) There were trends toward worse response to treatment in people with cognitive impairment (as measured by the MoCA) (P=0.111 and P=0.088 for the analyses of repeat falls and rate of falling respectively).

Statistically significant differences in the PDSAFE effect in relation to rate of falling were found across subgroups according to UPDRS severity, and retrospectively collected falling in the year prior to screening (interaction $P=0.009$ and 0.050 respectively); with an indication of possible benefit of PDSAFE in the middle subgroups only, while PDSAFE was associated with increased rate of falling in the most severe group. The impact of PDSAFE on near falling, Mini-BESTest and falls confidence was consistently beneficial across the subgroups.

Adverse events and deaths

Two participants died during follow-up in the PDSAFE group and five in the control group (figure 1). During the 6 months following randomisation, five fractures were reported by PDSAFE and nine by control group participants. Nine PDSAFE and twenty control group participants reported hospitalisations, of whom one PDSAFE participant reported two stays, none of these were associated with participation in the intervention.

Extended follow up

During the period 6 to 12 months after randomisation, seven fractures were reported by PDSAFE and three by control group participants; eighteen PDSAFE and 21 control group participants reported hospitalizations of whom two PDSAFE and four control participants reported two hospital stays. No participant fell during exercising.

DISCUSSION

PDSAFE is the largest trial of physiotherapy for fall prevention among PwP, with 474 participants randomised it was more than double the size of the previous largest trial by Canning et al[6] with 231 participants. It was novel with a personalised intervention conducted in the home-setting, and both a three-month pre-randomisation baseline and follow-up counts of falls collected prospectively in diaries. Despite this, we failed to demonstrate PDSAFE was effective in reducing falls in a heterogeneous sample of PwP overall. Our non-significant result was similar to that found by previous researchers of trials with more than 100 participants[5, 6, 7, and 8] and falls as a primary outcome. The exception was a trial of exercises, conducted in an out-patient setting by Morris et al in 2015[3], this positive outcome was not replicated when repeated at home with a lower treatment dose[5]. Two other research groups reported falls reduction as a result of interventions outside of current physiotherapy; virtual reality and treadmill

training[4] and Tai Chi[32]. A meta-analysis of falls interventions prior to this trial demonstrated an inconsistency of effect with a need for higher quality trials[2]. In line with those previous researchers of non-significant trials we found a diverse response to the intervention, those with milder disease responding better to the intervention than those with a more severe condition profile.

It has been suggested that non-significant fall prevention trials have resulted from under dosing of treatment[3] but dosing rehabilitation is complex. Rehabilitation is an interactive educational process designed to improve function and facilitated by a therapist. Each person has to actively participate in rehabilitation, the process of which can be influenced by motivation, age, cognition and severity of condition. Other important features are timing and content of intervention as well as the therapists and training. We will address these issues below and discuss how they may have led to the non-significant finding of our trial.

First, the influence of the therapy content and delivery on rehabilitation dose. A strength of the trial was the evidence-based therapy programme delivered by skilled trained physiotherapists. The PDSAFE training was structured and practice was rigorously tested for fidelity. Ninety-one percent of the intervention-group participants received per protocol, on average 12 face-to-face supervised sessions of 1 to 1.5 hours and were encouraged to complete unsupervised daily practice, meeting the recommendations of Sherrington et al[33] of at least 50 hours of practice. Previous researchers have used a range of different interventions, often poorly described with a great deal of diversity of treatment protocols and dosage. The PDSAFE trial delivered more supervised sessions than any of the other five identified research trials, e.g.: one hour weekly face to face for six weeks[5], one hour weekly group sessions for 8 weeks[6], and one hour weekly group session for 10 weeks[7], one hour monthly group session for 6 month, one hour weekly session for 6 weeks[8], in addition all encouraged independent practice but their recommendations were not as frequent as the PDSAFE mandate of daily routine. In terms of amount of treatment a balance is needed between sufficient time for training and too high an expectation of commitment, if too high participants start to withdraw and even under our procedures we had a greater withdrawal from the intervention group than our control group. Our programme was personalised in order to maximise individual motivation and it was multidimensional, requiring individuals to progress their activities and to integrate their training into everyday functional tasks which needed active participation from them and cognitive reasoning but this may have been too challenging for some. While manageable by those in the moderate to least severe disease groups, attention, reaction and response rates may have been compromised at the more severe end of the spectrum even though the treatment and selection of tasks were personalised.

Second, the influence of individual characteristics on rehabilitation dose. Our sample reflected a typical heterogeneous Parkinson's population and was not dissimilar to the other research trials, it comprised participants with a range of disease severity and fall events; at least one fall in the previous 12 months, some with multiple falls and high disease severity or more complex symptoms, such as freezing. Within Parkinson's, falls are indicative of a changing disease process; PwP with an established pattern of falling will have more global features of decline of age and/or disease association, Lord et al[34] suggest these progressive features create additional challenges for implementing appropriate management and research. Our sample typically included those with and without freezing of gait and, although we screened to exclude individuals with cognitive impairment using the MMSE[17], some participants at baseline and subsequent assessments scored low on the MoCA[28], a test known to be sensitive to frontal and executive function associated with people who fall[35]. The motor learning potential is reduced in people who freeze[36,37] and are cognitively challenged; increasing evidence demonstrate that freezing of gait is an important risk factor of falls, associated with reduced balance[38] and impaired cognition. The inclusion of people who did or did not experience freezing illustrates the diverse range of motor problems present in a community sample of PwP and the range of challenges faced when teaching and learning new skills. Domingeos et al[39] have called for more studies into fall prevention with people with impaired cognition.

That exercise is not uniformly effective across all presentation of Parkinson's had been suggested but not confirmed in three previous smaller trials[6, 7, 8], this informed our decision to pre-specify and undertake sub-group analyses on our data. The recent work of Canning et al 2016[6] and older trials by Goodwin et al 2011[7] and Ashburn et al 2007[8] consistently found in their secondary analysis that those with less severe Parkinson's responded positively to fall reduction programmes but that effect had been counterbalanced with deterioration among those at the worse end of the spectrum producing a non-significant overall result. Although we have a number of sub-group analyses in PDSAFE, the results are consistent with other published estimates reflecting a similar pattern: those in the moderate disease group, and in the middle group with respect to number of falls prior to the trial had a positive effect from PDSAFE with a 30% reduction in FRR (95% confidence interval 50% to 5% reduction) in the first six months following randomisation. However, there was an increase in FRR of 43% (95% confidence interval 4% to 95% helpful for the moderate disease group, more or different supervised therapy may have been required for those with freezing of gait and greater disease severity (more likely to have additional cognitive impairment) as they could have been more challenged by fall avoidance strategies and experienced greater difficulty with engaging in unsupervised sessions, thus limiting the intensity of practice and the effects.

A number of previous trials[2] have shown the benefits of exercise on risk factors for falling. In PDSAFE balance, functional strength and falls efficacy were targeted in the treatment and our analysis of secondary

outcomes demonstrated a consistent improvement across the whole PDSAFE group i.e., those with mild, moderate and severe disease. These results support those of others[2] highlighting the positive effects of exercise for balance and gait ability. Interventions in previous trials have largely been delivered outside the home setting but our current results demonstrate similar findings from interventions within the home environment. A positive PDSAFE effect on near-falls, an indicator of instability and reflective of the improvements in balance, was also reported. Near-falls among PwP have been reported by Gazibara et al[40] and Ashburn et al[8] and are often related to stumbling or balance loss and have been observed to predispose falling in the general older population[41]. As previously highlighted, all participants, even those with cognitive impairments, greater disease severity and freezing of gait showed improvements in their balance scores and fall efficacy scales. We suggest this indicates these participants were able to comply with exercise but were not able to benefit from the more demanding fall prevention programme possibly because of the need to react and respond in a timely way at moments of instability.

A limitation of our research was the incomplete 12 month assessment on our sample, a consequence of restricted funding. All participants in our trial were followed to six months, the point of primary outcome but the last 132 recruits could not be followed to one year post-randomisation resulting in a smaller sample at 12 months impacting on the interpretation of long-term follow-up, including the economic evaluation.

CONCLUSION

PDSAFE did not reduce falls in the overall heterogeneous sample of PwP. The treatments were personalised to individual needs within the structure of the PDSAFE concept but the package may not have adequately addressed the range of profiles across the disease spectrum. Those with more severe disease may have found implementing the fall avoidance movement strategies too challenging or they needed more training time; secondary analysis showed diverse responses to the intervention. Secondary outcome measures demonstrated improvement in balance, functional strength and falls efficacy with a reduction in near-falls across the whole sample. Further confirmatory trials of falls prevention on targeted groups of PwP are recommended.

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Contributions

KS (trial manager) and AA (chief investigator) lead the trial and drafted the manuscript. AA, RP, EM, LR, HR, VG, AN, CB and SL were grant holders and each contributed to study design and management, data interpretation and critical reviewing. AA, SH, LR, AN and VG designed the intervention. RP and IM provided statistical expertise including data cleaning, analysis and interpretation and writing. CF, SH and DK contributed to data collection, fidelity checking, data cleaning and data interpretation.

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Figure Legends:

Figure 1 Flow of Participants through the Trial

Figure 2 Overall and subgroup analysis of falling, near-falling (during 0-6 months) and secondary outcomes (at 6 months).

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Table 1: Baseline characteristics in the PDSAFE and control groups: figures are number (%) unless stated otherwise

		PDSAFE (n=238¹)	Control (n=236²)
Gender	male	147 (62%)	119 (50%)
	female	91 (38%)	117 (50%)
Age (years)	mean (SD)	71 (7.7)	73 (7.7)
	min to max	51 to 91	46 to 88
Disease duration (years)	mean (SD)	8 (6.6)	8 (5.8)
	min to max	0 to 36	0 to 29
MMSE	mean (SD)	28 (1.7)	29 (1.6)
	min to max	24 to 30	24 to 30
MoCA	mean (SD)	26 (2.9)	26 (3.2)
	min to max	15 to 30	9 to 30
	≤ 25 (cognitively impaired)	91 (38%)	93 (39%)
Living status	lived alone	48 (20%)	59 (25%)
	with a spouse/partner	174 (73%)	166 (70%)
	with a friend/family	15 (6%)	10 (4%)
Hoehn and Yahr stage	1	26 (11%)	30 (13%)
	2	78 (33%)	56 (24%)
	3	102 (43%)	112 (48%)
	4	32 (13%)	38 (16%)
UPDRS	mean (SD)	32 (15.2)	33 (17.3)
	min to max	2 to 77	4 to 92
	TD phenotype	21 (9%)	19 (8%)
	PIGD phenotype	194 (83%)	206 (88%)
	indeterminate	20 (8%)	10 (4%)
Freezing of gait in the past month		152 (64%)	139 (59%)
No. of falls in 12 months prior to screening	median (min to max)	3 (1 to 1460)	3 (1 to 1095)
	mean (SD)	26 (132.7)	19 (105.4)
	repeat falling in 12 months	186 (78%)	189 (80%)
Rate of falls/person/3 months prior to randomisation	median (min to max)	1.98 (0 to 319)	0.99 (0 to 73)
	mean (SD)	5.9 (22.8)	3.0 (7.3)
Rate of near falls/person/3 months prior to randomisation	median (min to max)	4.4 (0 to 440)	4.3 (0 to 601)
	mean (SD)	13.8 (35.8)	15.6 (51.4)
Medications	Levodopa	208 (88%)	216 (92%)
	Dopamine agonist	108 (46%)	106 (45%)
	Monoamine oxidase inhibitor	52 (22%)	46 (20%)
	COMT inhibitors	59 (25%)	41 (17%)
	other PD medication	19 (8%)	23 (10%)
GDS score at baseline	> 5 (suggestive of depression)	147/235 (63%)	164/236 (70%)
	≥ 10 (indicative of depression)	50/235 (21%)	49/236 (21%)
Coexisting conditions	orthopaedic	109 (46%)	129 (54%)
	Cardio/Respiratory	85 (36%)	96 (41%)

¹Missing values in the intervention group: living status (1); UPDRS (1); disease duration (1); freezing of gait (1); rate of falling in the 3 months prior to randomisation (1); TD/PIGD/ Indeterminate phenotype (3).

²Missing values in the control group: living status (1); UPDRS (1); TD/PIGD/ Indeterminate phenotype (1).

Table 2: Intention-to- treat analysis of falling outcomes: 0 to 6 and 6 to 12 months

	Period	PDSAFE	Control	PDSAFE/control* OR (95% CI)	P*
		Number (%)			
Repeat falling restricted to ≥50% diaries	baseline	127/231 (55%)	92/230 (40%)		
	baseline**	112/203 (55%)	80/211 (38%)		
	0-6 months	125/203 (62%)	116/211 (55%)	1.21 (0.74, 1.98)	0.447
	baseline**	55/114 (48%)	47/132 (36%)		
	6-12 months	57/114 (50%)	71/132 (54%)	0.86 (0.45, 1.65)	0.657
		Falls/person/6 months***		FRR (95% CI)	
Fall rates	baseline	4.5	3.3		
	0-6 months	3.4	2.7	0.98 (0.80, 1.19)	0.824
	6-12 months	2.7	2.8	0.83 (0.62, 1.11)	0.200
		Near falls/person/6 months***		NFRR (95% CI)	
Near fall rates	baseline	8.0	8.1		
	0-6 months	4.7	5.6	0.67 (0.53, 0.86)	0.001
	6-12 months	3.9	3.7	1.01 (0.67, 1.52)	0.968

* Controlled for site, age, gender, repeat falling or not in the year prior to screening, log number of falls in the year prior to screening, log rate of falling in the pre randomisation falls collection period, and Hoehn and Yahr (NFRR additionally controlled for log rate of near falling in the pre randomisation falls collection period).

** Baseline repeat falling restricted to participants including in the 0-6 and 6-12month analyses

*** Geometric mean of individual fall rates with 0.5 added to all numerators

Table 3: Secondary outcomes at 6 and 12 months

		mean (SD, n)		mean difference (PDSAFE -Control) (95% CI)*	p*
		PDSAFE (n=238)	Control (n=236)		
visit					
MiniBESTest (0-28, lower values worse)	**baseline	18.3 (5.7, n=183)	17.3 (6.1, n=211)		
	6 months	19.4 (5.9, n=183)	17.5 (6.4, n=211)		
	6 months-baseline	1.1 (3.8, n=183)	0.2 (3.8, n=211)	0.95 (0.24, 1.67)	0.009
	***baseline	18.5 (5.8, n=115)	17.5 (6.1, n=126)		
	12 months	17.9 (6.5, n=115)	17.4 (6.7, n=126)		
	12 months-baseline	-0.7 (4.5, n=115)	-0.2 (3.8, n=126)	-0.41 (-1.48, 0.66)	0.449
FES-I (16-64, higher values worse)	**baseline	34.1 (11.0, n=189)	35.1 (11.5, n=211)		
	6 months	33.4 (10.6, n=189)	36.2 (11.4, n=211)		
	6 months-baseline	-0.7 (7.9, n=189)	1.1 (7.2, n=211)	-1.6 (-3.0, -0.19)	0.026
	***baseline	33.4 (10.7, n=119)	33.7 (11.3, n=135)		
	12 months	34.8 (11.2, n=119)	37.2 (11.6, n=135)		
	12 months-baseline	1.3 (8.2, n=119)	3.5 (9.3, n=135)	-1.4 (-3.41, 0.66)	0.184
PASE (0-400, lower values worse)	**baseline	107.8 (73.5, n=153)	100.1 (67.1, n=177)		
	6 months	110.2 (70.4, n=153)	100.6 (68.0, n=177)		
	6 months-baseline	2.4 (50.8, n=153)	0.5 (49.5, n=177)	-1.05 (-11.3, 9.21)	0.841
	***baseline	108.1 (71.9, n=98)	98.6 (61.1, n=115)		
	12 months	99.4 (72.8, n=98)	87.6 (62.3, n=115)		
	12 months-baseline	-8.7 (53.0, n=98)	-11.0 (48.5, n=115)	-0.55 (-13.9, 12.8)	0.935
PDQ39 (0-100, higher values worse)	**baseline	27.4 (14.3, n=126)	28.7 (15.9, n=153)		
	6 months	28.3 (15.0, n=126)	29.5 (16.5, n=153)		
	6 months-baseline	0.8 (8.3, n=126)	0.9 (9.0, n=153)	0.12 (-2.0, 2.28)	0.911
	***baseline	27.2 (13.6, n=77)	28.9 (15.9, n=100)		
	12 months	29.1 (15.4, n=77)	31.7 (15.5, n=100)		
	12 months-baseline	1.9 (8.6, n=77)	2.8 (11.2, n=100)	0.48 (-2.53, 3.49)	0.754
GDS (0-15, higher values worse)	**baseline	7.7 (2.3, n=154)	7.7 (2.1, n=183)		
	6 months	7.8 (2.5, n=154)	8.0 (2.5, n=183)		
	6 months-baseline	0.3 (1.8, n=154)	0.2 (1.9, n=183)	-0.02 (-0.42, 0.39)	0.942
	***baseline	7.7 (2.1, n=96)	8.0 (2.2, n=118)		
	12 months	7.8 (2.5, n=96)	8.5 (2.4, n=118)		
	12 months-baseline	0.2 (2.0, n=96)	0.4 (1.7, n=118)	-0.21 (-0.72, 0.31)	0.421

* Controlled for site, age, gender, repeat falling or not in the year prior to screening, log number of falls in the year prior to falling, log rate of falling in the pre randomisation falls collection period, Hoehn and Yahr, and the outcome in question assessed at baseline.

** Baseline results restricted to existing participant assessment at 6 months

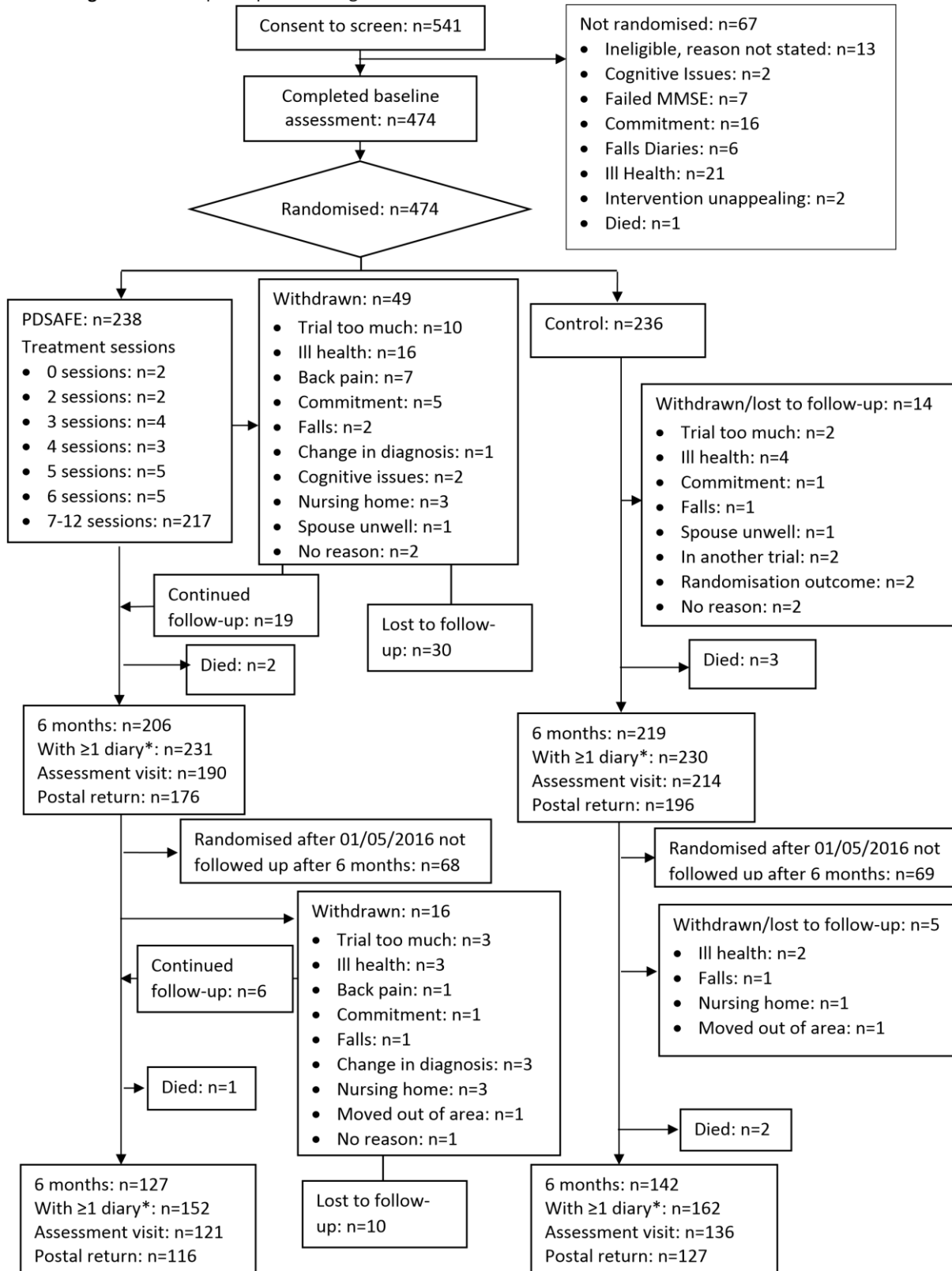
*** Baseline results restricted to existing participant assessment at 6 months

Table 4: Chair Stand Test (CST) at 6 and 12 months

		PDSAFE (n=238)	Control (n=236)	p*	
Baseline amongst participants with 6 month assessment	Unable of those with a CST assessment	29/188 (15%)	35/213 (16%)	0.041 (n=401)	
	CST (seconds) median amongst IQR those able	14 11 to 18 (n=159)	14 11 to 18 (n=178)		
6 month assessment	Unable of those with a CST assessment	27/188 (14%)	47/213 (22%)		
	CST (seconds) median amongst IQR those able	12 10 to 15 (n=161)	13 10 to 16 (n=166)		
Baseline amongst participants with 12 month assessment	Unable of those with a CST assessment	15/119 (13%)	21/134 (16%)		0.163 (n=253)
	CST (seconds) median amongst IQR those able	14 11 to 17 (n =104)	14 12 to 18 (n=113)		
12 month assessment	Unable of those with a CST assessment	23/119 (19%)	38/134 (28%)		
	CST (seconds) median amongst IQR those able	12 9 to 14 (n=96)	13 11 to 15 (n=96)		

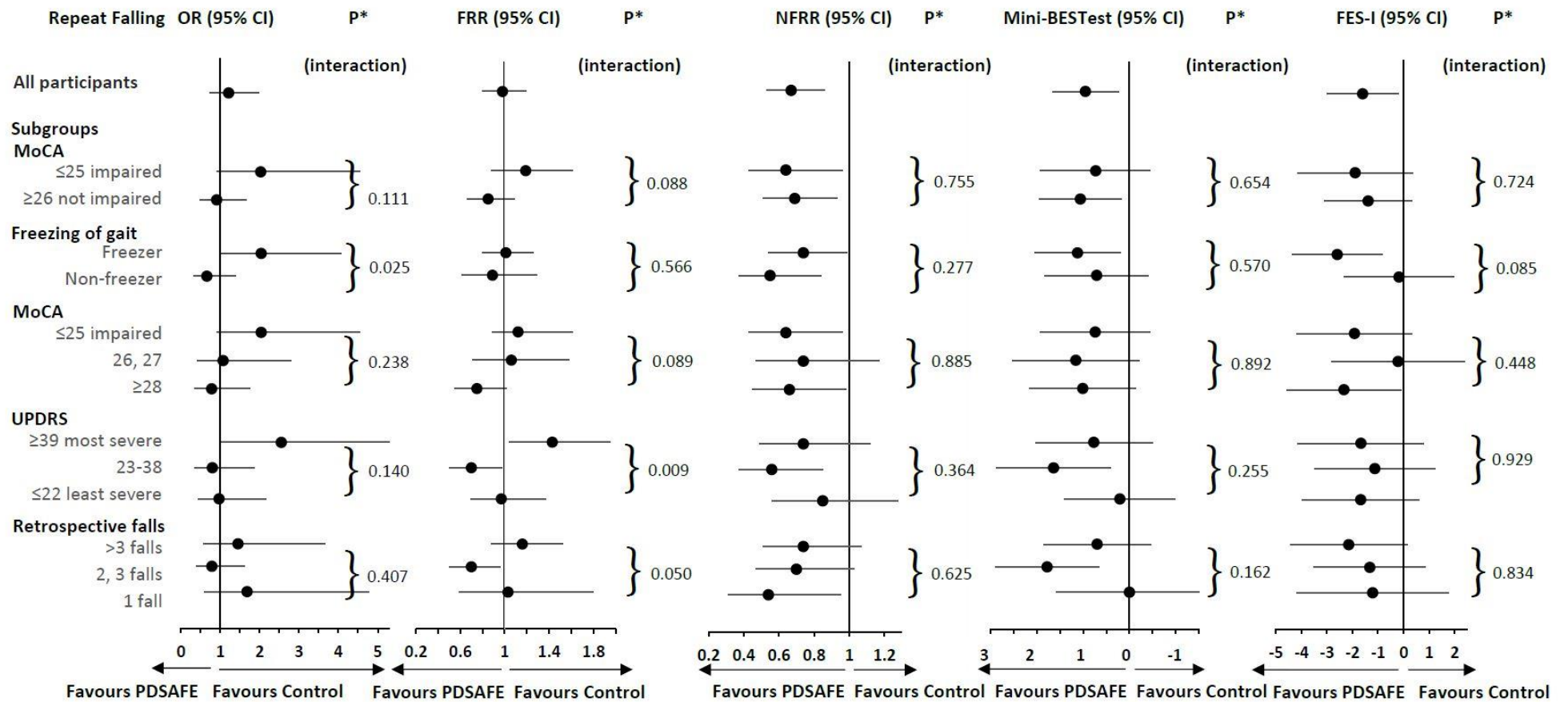
* Mann Whitney U test incorporating participants unable to perform test and times from participants able to perform test.

Figure 1 Flow of participants through trial.



*Number with any diaries during the preceding 6 months

Figure 2: Overall and subgroup analysis of falling, near falling (during 0 to 6 months) and secondary outcomes (at 6 months)



* Test for interaction of PDSAFE contrast differing across subgroups, controlled for site, age, gender, repeat falling or not in the year prior to screening, log number of falls in the year prior to falling, log rate of falling in the pre randomisation falls collection period, Hoehn and Yahr, and the outcome in question assessed at baseline.

**OR= Odds Ratio; FRR= Falls Rate Ratio; NFRR= Near Falls Rate Ratio; Mini-BESTest= Balance Evaluation Systems Test; FES-I= Falls Efficacy Scale International