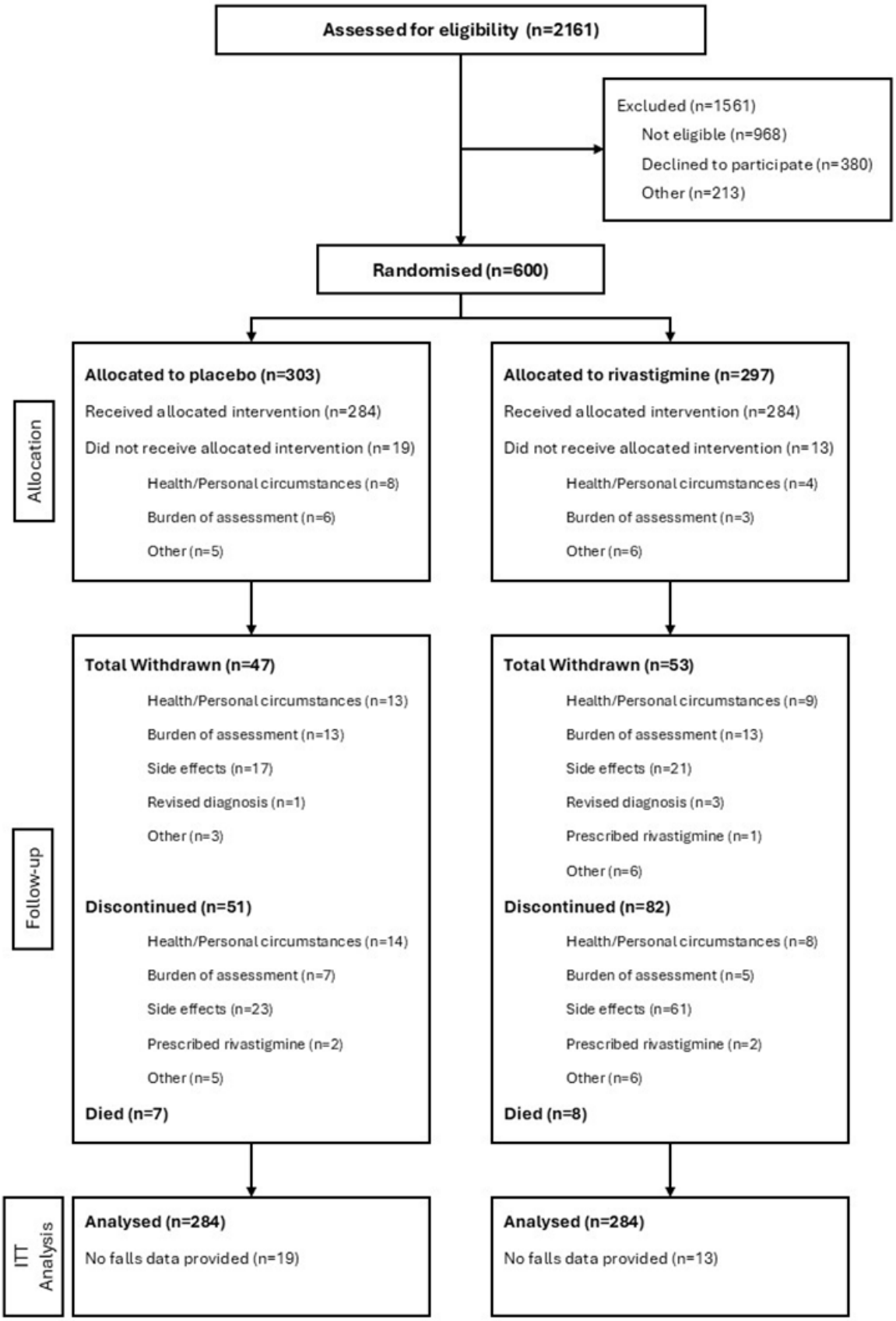
Participant flow



Baseline characteristics

		Rivastigmine		Placebo
	n	***Mean (SD), Median (IQR)* or N (%)**	**n**	***Mean (SD), Median (IQR)* or N (%)**
Total number of participants	297		303	
Falls rate in previous 12-months	297	2·3 (6·1)	303	3·2 (10·5)
Median age (IQR)	297	72·0 (66·0, 77·0)	303	72·0 (66·0, 77·0)
Age range		35, 88		47, 93
Median BMI (IQR):	297	26·4 (23·7, 29·6)	300	26·7 (23·4, 30·2)
Underweight		8 (3%)		4 (1%)
Healthy Weight		98 (33%)		108 (36%)
Overweight		120 (40%)		115 (38%)
Obese		66 (22%)		60 (20%)
Severely Obese		5 (2%)		13 (4%)
Female	297	119 (40%)	303	113 (37%)
Accommodation:	297		303	
Lives in own accommodation or rented		275 (93%)		290 (96%)
Sheltered accommodation		7 (2%)		2 (1%)
Other (e.g. living with family)		15 (5%)		11 (4%)
Education:	238		243	
No formal qualification		41 (17%)		29 (12%)
GCSEs, O-Levels or equivalent		58 (24%)		63 (26%)
A-levels or equivalent		32 (13%)		35 (14%)
Degree/Higher Degree		107 (45%)		116 (48%)
Comorbidities:	297		303	
0 comorbidities		36 (12%)		32 (11%)
1-2 comorbidities		103 (35%)		101 (33%)
3+ comorbidities		158 (53%)		170 (56%)
PD Medication:	297		301	
Levodopa		284 (96%)		291(97%)
COMT inhibitor		77 (26%)		84 (28%)
MAO-B inhibitor		103 (35%)		103 (34%)
Dopamine agonist		132 (44%)		137 (46%)
Device aided therapy		8 (3%)		12 (4%)
Anticholinergic		5 (2%)		2 (1%)
Amantadine		38 (13%)		54 (18%)
Levodopa Equivalent Dose	262	698·3 (422·0)	267	745·4 (477·8)
Cognition – MoCA:	297	25·3 (3·4)	303	25·2 (3·6)
PD severity – MDS UPDRS:				
Part 1: Non-motor	286	14·2 (6·2)	291	14·4 (6·8)
Part 2: Motor symptoms	282	18·2 (7·2)	294	19·1 (7·9)
Part 3: Motor examination	293	34·1 (16·3)	299	34·4 (15·6)
Part 4: Motor complications	284	5·1 (4·6)	290	5·1 (4·6)
Total score	267	71·9 (24·8)	278	72·8 (25·2)
PD severity – Hoehn & Yahr stage	294		297	
Stage 1		33 (11%)		29 (10%)
Stage 2		124 (42%)		126 (42%)
Stage 3		118 (40%)		115 (39%)

Stage 4		19 (7%)		27 (9%)
Frailty – SHARE-FI	270	1·7 (1·6)	270	1·9 (1·6)
Frail		79 (29%)		88 (33%)
Pre-frail		104 (39%)		111 (41%)
Non-frail		87 (32%)		71 (26%)
Physical performance – SPPB				
SPPB balance score	297	3·2 (1·2)	303	3·0 (1·3)
SPPB gait speed score	281	2·7 (1·2)	282	2·7 (1·2)
SPPB chair stand score	297	1·4 (1·3)	303	1·4 (1·3)
Gait speed (normal walk)	281	0·7 (0·3)	282	0·7 (0·3)
Fear of falling – ICON-FES	253	26·6 (6·7)	253	26·8 (6·5)
Freezing of Gait – NFOGQ	269	11·1 (9·4)	280	11·8 (9·8)
Presence of Freezing of Gait	283	191 (68%)	290	193 (67%)
Apathy – SAS	270	15·1 (5·8)	267	15·4 (6·0)
Dysphagia – SDQ	283	8·8 (6·6)	287	8·7 (6·9)
Depression – GDS	287	5·7 (3·6)	294	5·5 (3·6)
Presence of orthostatic hypotension	287	132 (46%)	289	141 (49%)
Presence of anticholinergic medications (Anti-cholinergic Burden = 3)	297		301	
Total Participants		53 (18%)		51 (17%)
Presence of dyskinesia	292		300	
None		168 (58%)		171 (57%)
Slight: ≤ 25% of waking day		88 (30%)		78 (26%)
Mild: 26-50% of waking day		19 (7%)		32 (11%)
Moderate: 51-75% of waking day		4 (1%)		14 (5%)
Severe: >75% of waking day		13 (4%)		5 (2%)
Presence of ON-OFF periods	293		295	
None		98 (33%)		105 (36%)
Slight: ≤ 25% of waking day		144 (49%)		141 (48%)
Mild: 26-50% of waking day		38 (13%)		35 (12%)
Moderate: 51-75% of waking day		7 (2%)		8 (3%)
Severe: >75% of waking day		6 (2%)		6 (2%)
Presence of Visual Hallucinations	297		302	
None		241 (81%)		239 (79%)
Slight		40 (14%)		37 (12%)
Mild		10 (3%)		22 (7%)
Moderate		4 (1%)		4 (1%)
Severe		2 (1%)		0

BMI=Body Mass Index. GCSE=General Certificate of Secondary Education. MoCA=Montreal Cognitive Assessment. COMT=catechol-O-methyltransferase. MAO-B=Monoamine Oxidase B. MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale. SHARE-FI=Survey of Health, Ageing and Retirement in Europe Frailty Instrument. SPPB=Short Performance Physical Battery. ICON-FES=Iconographical Falls Efficacy Scale. NFOGQ=New Freezing of Gait Questionnaire. SAS=Starkstein Apathy Scale. SDQ=Swallowing Disturbance Questionnaire. GDS=Geriatric Depression Scale. Orthostatic hypotension was defined as a drop of 20mmHg systolic or 10mmHg on standing.

Fall rate per arm in the intention-to-treat analysis population, per protocol population and sensitivity analyses.

	Rivastigmine Mean rate (SD, n)	Placebo Mean rate (SD, n)	Unadjusted IRR (95% CI, n)	Adjusted* IRR (95% CI, n)	P value*
Intention-to-treat analysis					
Fall rate (falls per month)	4·8 (13·8, 284)	4·8 (13·1, 284)	0·94 (0·70, 1·27, 568)	1·02 (0·78, 1·34, 568)	0·883
Per protocol analysis					
Falls having taken IMP for at least 1 month	4·5 (12·5, 258)	5·1 (13·6, 260)	0·88 (0·65, 1·18, 518)	0·96 (0·73, 1·27, 518)	0·797
Falls having taken IMP for at least 6 months	5·0 (14·8, 172)	5· 3 (14·1, 211)	0·92 (0·63, 1·33. 383)	1·02 (0·73, 1·43, 383)	0·911
Sensitivity analysis					
Time varying coefficient (by diary)			1·03 (1·03, 1· 04, 568)	1· 03 (1· 03, 1· 04, 568)	<0.001
Removing participants who were unblinded	4· 8 (13· 8, 283)	4· 8 (13· 2, 282)	0· 95 (0· 70, 1· 27, 565)	1· 02 (0· 78. 1· 34. 565)	0· 867
Randomisation time zero	4· 8 (13· 8, 284)	4· 8 (13· 2, 284)	0· 94 (0· 70, 1· 26, 568)	1· 01 (0· 77, 1· 33, 568)	0·919

*Adjusted for age (in years), site, number of falls in the previous year and MoCA score.
IRR=Incident Rate Ratio. IMP=Investigational Medicinal Product.

Serious Adverse Events by arm

	Active		**Placebo**	
	Participants N=297	**Events N=61**	**Participants N=303**	**Events N=88**
Blood and lymphatic system disorders	1 (<1%)	1 (2%)	0	0
Cardiac Disorders	4 (1%)	4 (7%)	9 (3%)	9 (10%)
Endocrine disorders	1 (<1%)	1 (2%)	0	0
Gastrointestinal disorders	4 (1%)	5 (8%)	1 (<1%)	2 (2%)
General disorders and administration site conditions	0	0	4 (1%)	4 (5%)
Infections and infestations	14 (5%)	16 (26%)	19 (6%)	23 (26%)
Injury poisoning and procedural complications	14 (5%)	17 (28%)	22 (7%)	29 (33%)
*Falls**	*13 (4%)*	*15 (25%)*	*20 (7%)*	*27 (31%)*
Metabolism and nutrition disorders	2 (1%)	3 (5%)	1 (<1%)	1 (1%)
Musculoskeletal and connective tissue disorders	3 (1%)	3 (5%)	3 (1%)	4 (5%)
Neoplasms benign, malignant, and unspecified	1 (<1%)	1 (2%)	0	0
Nervous system disorders	4 (1%)	4 (7%)	9 (3%)	9 (10%)
Product Issues	0	0	1 (<1%)	1 (1%)

Psychiatric disorders	1 (<1%)	1 (2%)	1 (<1%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	1 (<1%)	1 (2%)	2 (<1%)	2 (2%)
Surgical and medical procedures	2 (1%)	2 (3%)	0	0
Vascular disorders	2 (1%)	2 (3%)	3 (1%)	3 (3%)
Relatedness of SAEs				
Not related	··	31 (51%)	··	39 (44%)
Unlikely related	··	29 (48%)	··	37 (42%)
Possibly related	··	1 (2%)	··	11 (13%)
Probably related	··	0	··	1 (1%)
Definitely related	··	0	··	0
Severity of SAEs				
Mild	··	16 (26%)	··	22 (25%)
Moderate	··	15 (25%)	··	36 (41%)
Severe	··	30 (49%)	··	30 (34%)
Death in Study Window	8 (3%)	··	7 (2%)	··

Legend: SAEs are listed by MedDRA system organ class groupings for each trial arm. Data are presented as both the number of participants experiencing at least one SAE (Participants) and the total number of events (Events) recorded within each category. One participant in the placebo arm had a SAE reported for bradycardia.

**Falls are a MedDRA lower level term nested within the MedDRA system organ class "Injury, poisonng and procedural complications", and therefore the numbers represent a subgroup of the participants and events which are reported within this MedDRA system organ class.*