Parkinson's Repository of Biosamples and Networked Datasets

PRoBaND

(Tracking Parkinson's)

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This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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Protocol Approval

PRoBaND: Parkinson's Repository of Biosamples and Network Datasets

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ABBREVIATIONS

AE	Adverse event
CDE	Common data elements
CRF	Case report form
COMT	Catechol-O-methyl transferase
DaTSCAN	Dopamine transporter brain scan
DeNDRoN	Dementia and Neurodegenerative Diseases Research Network
eCRF	Electronic case record form
EDTA	Ethylene Diamine Tetra-acetic Acid
EC	Ethics Committee
FPCIT	Fluoro-propyl carbomethoxy iodophenyl tropane, also known as Ioflupane (and also known as DaTSCAN)
GBA	Glucocerebrosidase
GP	General Practitioner
ICH GCP	International Conference on Harmonization of Good Clinical Practice
LREC	Local regional ethics committee
LRRK2	Leucine-rich repeat kinase 2
MAPT	Microtubule-associated protein tau
MDS	Movement disorder society
MoCA	Montreal cognitive assessment
MREC	Multi regional ethics committee
NINDS	National Institute for Neurological Diseases and Stroke
NMS	Non-motor symptoms
PD	Parkinson's disease
PDQ8	Parkinson's disease quality of life scale
PET	Positron emission tomography
PPMI	Parkinson's progression markers initiative
QoL	Quality of life
REM	Rapid eye movement
SAE	Serious adverse event
SCOPA-AUT	Scales for outcomes in Parkinson's disease - autonomic
SPECT	Single photon emission computed tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction
UPDRS	Unified Parkinson's Disease Rating Scale

STUDY SYNOPSIS

Title of Study:	PRoBaND: Parkinson's Repository of Biosamples and Networked Datasets (Tracking Parkinson's)
Coordinating Study Centre:	Institute of Neurological Sciences, Southern General Hospital, Glasgow
Duration of Study:	5 years
Objectives:	To identify genetic and biomarker factors which affect the expression of Parkinson's Disease.
Primary Objective:	To define the severity and rates of progression of clinical features of Parkinson's Disease.
Secondary Objective:	To relate clinical phenomenology of Parkinson's disease to genetic and biomarker changes.
Study Endpoints	**Primary endpoint** Proportion of patients with PD who have gene mutation related to the expression of their disease. **Main Secondary endpoint** Progression rate of key PD features: motor, non-motor, therapy response, cognitive.
Rationale:	PD has varied expression with likely genetic causes.
Methodology:	Prospective multi-centre observational trial.
Sample Size:	3080
Registration/Randomisation:	4:1 active to control for relatives of gene test positive index PD cases.
Inclusion Criteria	• PD diagnosed within 3 years • PD diagnosis at age under 50 • First degree relative of same.
Exclusion Criteria	Other Parkinson disorder, dementia.
Duration of Treatment:	Not applicable
Statistical Analysis	• 5 - 8 % difference for categorical variables detected in 2000 patients assuming 90% power and 5% significance • For continuous measures, 0.33 standardised difference with 200 cases and 200 controls (sampling 10% of the cohort based on a specific feature e.g. gene mutation). • Comparing gene positive and gene negative relatives, 0.42 standardised difference between 100 cases and 150 relatives.

STUDY FLOW CHART 1 - Patients diagnosed for less than three years

	Screening visit	(Baseline) Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
		0 months	6 months	12 months	18 months	24 months	30 months	36 months
Obtain informed consent	X							
Review Inclusion/Exclusion Criteria	X							
Medical/Disease history	X							
Medications review	X		X	X	X	X	X	X
Vital signs (blood pressure, weight)	X							X
Height	X							
Family history	X							
Demographics	X							
Blood sample for DNA		X						
Blood sample for serum		X			X			X
QOL questionnaires		X			X			X
Depression questionnaire		X			X			X
Parkinson's Rating Score		X			X			X
Social history			X					
Non-motor symptom score		X			X			X
PD grading		X			X			X
Diagnostic features				X			X	X
Parkinson's sleep scale		X			X			X
Epworth sleep score		X			X			X
REM sleep disturbance		X			X			X
Impulsive questionnaire		X			X			X
Clinical and Global impression			X			X		
Constipation questionnaire		X			X			X
Cognitive testing		X			X			X
Smell testing			X					
Autonomic features		X			X			X
Personality questionnaire				X				
Environmental exposure questionnaire				X				
Diagnostic factors		X						
L-dopa challenge test *						X		

Scans **		X						X
Tissue Bank						X	X	
Wearing off questionnaire							X	

* L-dopa challenge test will be performed once during the study, in patients who are prescribed L-dopa based treatment. It will be performed in patients who have been on L-dopa for at least 6 months, by scoring the UPDRS part 3 after overnight "off", and after unit dose of L-dopa.
** Structural brain imaging and functional brain imaging. Results of tests undertaken on clinical grounds will be collected.

STUDY FLOW CHART 1A- Interim Extension

	Screening	Treatment		
	On or after Visit 7	Visit 8 (Baseline)		Visit 9
	36 months	42 months		54 months
Obtain informed consent		X		
Review Inclusion/Exclusion Criteria	X			
Medications review		X		X
Blood sample for serum				X
QOL questionnaires				X
Depression questionnaire				X
Parkinson's Rating Score				X
Non-motor symptom score				X
PD grading				X
Parkinson's sleep scale				X
Epworth sleep score				X
REM sleep disturbance				X
Impulsive questionnaire				X
Clinical and Global impression		X		
Constipation questionnaire				X
Cognitive testing				X
Autonomic features				X
Wearing off questionnaire				X

STUDY FLOW CHART 2- Patients with PD onset at less than age 50 years

	Screening Visit 0	(Baseline)Visit 1 0 months	Visit 2 6 months
Obtain informed consent	X		
Review Inclusion/Exclusion Criteria	X		
Medical/Disease history	X		
Medications review	X		
Vital signs (blood pressure, weight, height	X		
Family history	X		
Demographics	X		
Blood sample for DNA		X	
Blood sample for serum		X	
QOL questionnaires		X	
Depression questionnaire		X	
Parkinson's Rating Score		X	
Patient items – social history, non-motor symptoms		X	
Parkinson's medical items		X	
PD grading		X	
Parkinson's sleep scale		X	
Epworth sleep score		X	
REM sleep disturbance		X	
Impulsive questionnaire		X	
Constipation questionnaire		X	
Cognitive testing		X	
Smell testing			X
Autonomic features		X	
Environmental exposure questionnaire			X
Diagnostic factors			X
Scans*		X	
Tissue Bank		X	X
Personality Questionnaire			X
Wearing off Questionnaire			X

* Structural brain imaging and functional brain imaging. Results of tests undertaken on clinical grounds will be collected.

STUDY FLOW CHART 3- Relatives of PD patients

	(Baseline) Visit 1	Visit 2
	0 months	36 months
Obtain informed consent	X	
Review Inclusion/Exclusion Criteria	X	
Medical history	X	
Medications review	X	X
Vital signs (blood pressure, weight)	X	X
Height	X	
Family history	X	
Demographics	X	
Blood sample for DNA	X	
Blood sample for serum	X	X
Depression questionnaire	X	X
Parkinson's Rating Score	X	X
Non-motor symptoms	X	X
Parkinson's medical items	X	X
Parkinson's sleep scale	X	X
Epworth sleep score	X	X
REM sleep disturbance	X	X
Impulsive questionnaire	X	X
Constipation questionnaire	X	X
Cognitive testing	X	X
Smell testing	X	X
Autonomic features	X	X
Global quality of life	X	X
Personality questionnaire		X
Environmental exposure questionnaire	X	
Scans*	X	X
Tissue bank		X

*Structural brain imaging and functional brain imaging. Results of tests undertaken on clinical grounds will be collected.

1.0 INTRODUCTION

Parkinson's disease epidemiology

Parkinson's disease (PD) is a neurodegenerative disorder of increasing incidence and prevalence with advancing age. Between 4 and 20 new cases per 100,000 population are diagnosed each year. Prevalence is approximately 160 per 100,000 in the UK. Around 2% of people over 65 years have Parkinson's disease. The cause of Parkinson's disease is unknown but genetic and environmental causes have both been studied in some detail. The majority of Parkinson's disease cases are sporadic, but a few are inherited. An individual with family history of Parkinson's disease has an approximately doubling of the risk of Parkinson's compared to the rate in the background population. Around 15% of patients have a positive family history of Parkinson's disease. Gene mutations implicated in the development of Parkinson's disease consist of autosomal dominant forms including PARK1 which codes for alpha-synuclein and autosomal recessive forms including PARK6 which codes for the PINK1 protein, and leucine-rich repeat kinase 2 (LRRK2). Some of the cases with gene mutations have variations in age of onset (earlier for PARK6 and PARK7, for example), while some have more problems of motor complication, for example there is more dystonia and more dyskinesia with PARK2. Some gene mutations are associated with a presentation very similar to what is considered to be classic idiopathic Parkinson's disease, and this is the largely the case for age of onset for LRRK2 and clinical appearance, although even here there are some components showing variation, as detailed below.

Parkinson's disease genetics

The gene discoveries in Parkinson's disease have emerged from the study of Mendelian families, which carry rare highly penetrant genetic mutations. More recently genome wide association studies have identified common genetic variation, which increases the risk of developing PD. However, it is considered likely that there are genetic influences on the expression of components of the disease, such as the development and severity of dyskinesia, and the development of cognitive impairment and dementia. Accordingly it is thought valuable to characterize patients in detail from a clinical perspective, and to study groups of patients with variations in expression of their disease, alongside further genetic testing. Technical advances in gene tests allow enhancements in the process of gene discovery in relation to these sub-categories of Parkinson's expression and severity. It is therefore the primary hypothesis of the present study that detailed profiling of patients with Parkinson's disease will distinguish sub-types of clinical presentation relating to variations in motor, cognitive, therapy response, and non-motor features. It is considered likely that these features will have genetic influences which will be the focus of the present study.

Parkinson's disease phenomenology

The PRoBaND study will therefore evaluate further around issues which have already shown some linkage to genetic test results, as follows:

1. ***Motor.*** PD can be broadly divided into tremor-dominant and postural instability gait disorder types (Jankovic et al 1990). A proportion of patients who are tremor-dominant have a more benign course ("benign tremulous PD").
2. ***Cognitive sub-types.*** Neuropsychological tests show that early mild cognitive impairment gives an 88 times greater risk of dementia at 5 years compared to patients with normal baseline cognition (Williams-Gray et al 2009). Baseline results correlate with genetic variations in microtubule-associated protein tau (MAPT). There is partial correlation with genetic variability in the Valine/Methionine component of catechol-O-methyltransferase (COMT) (Williams-Gray et al 2009).
3. ***Therapy response.*** The response to antiparkinson therapy varies from excellent to poor, partly due to coexisting disorders (e.g. cerebrovascular disease, Zijlmans et al 2004). Some patients develop early motor complications, while others are less fluctuant. There is surprisingly limited data about this variation. Biochemical and genetic mechanisms which are likely to underlie this variability require exploration, to find new (probably non-dopaminergic) drug mechanisms.
4. ***Non-motor features.*** These often predate motor features and may be important for example in first degree relatives. Non-motor severity is similar for young and older onset PD when gene test negative, with a range of severity (Chaudhuri and Schapira 2009). Non-motor involvement varies according to genetic sub-type, being significantly less in Parkin positive PD (Kagi et al, 2010). A lower prevalence of sleep disturbance was found in familial versus sporadic PD (Vibha et al 2010).

Genetic sub-types of PD

A proportion of PD patients tested carry highly penetrant pathogenic genetic variance. Some differences have been described in patients carrying specific mutations, although to date this has largely been based on retrospective case note review:

a) Patients positive for Leucine-rich repeat kinase 2 (LRRK2) have a similar onset age, but are more likely to develop dystonia after antiparkinson treatment is introduced, to have leg tremor, and progress more slowly (Healy et al, 2008).
b) Patients positive for Parkin have an earlier onset, and more dystonia (predating antiparkinson therapy). Greater baseline abnormalities are seen on nigrostriatal presynaptic dopamine brain scans, but the rate of progression (clinically and on imaging) is at least 5 times slower than that of idiopathic PD (Pavese et al, 2009). It is likely that genetic factors contribute in a far greater sense than currently understood, to PD expression across the above 4 domains. Understanding the links between gene defects and clinical expression is crucial in exploring the causes, and thereby finding new treatments, for PD.

Recording and scoring key PD features in the PRoBaND study

Multiple elements of varied clinical expression in PD and rates of change over time will be recorded using validated tools. PD gene tests will be run, for patients and first-degree relatives.

Requirement for large sample sizes in PD research

This is now recognised as crucial, nationally and internationally. The common theme in such studies is early and prospective detailed recording of the clinical phenotype, to capture variability. Identification of unaffected subjects (usually relatives of PD patients) is a further theme, to understand better what contributes to the *expression* of PD, e.g. LRRK2 gene-mutation carriers may be spared even in their 80s or 90s (Healy et al 2008). This work is seen as key to the development of biomarkers for easier and earlier disease detection, leading to testing, at an earlier stage and when neuronal damage is milder, of potential neuroprotective therapies.

Collaborative working extends the power and significance of studies especially for rarer features, e.g. international collaboration on penetrance of LRRK2 (Healy et al 2008). PRoBaND will link 25-30 large clinical centres across the United Kingdom, and, with the research office of Parkinson's UK, has developed links to other studies, to aid large scale collaboration.

Combining datasets

Harmonization of datasets assists collaborative research. PRoBaND has adopted the common data elements (CDEs) of the National Institute for Neurological Diseases and Stroke (NINDS), on which 3 of PRoBaND's investigators serve. The NINDS plans to enforce the use of CDEs in future US government funded PD research, which often includes international sites, e.g. the PPMI project. This will enhance compatibility and longevity of PRoBaND's data.

PRoBaND

The PRoBaND study will be carried out at the clinical centres where patients with Parkinson's disease attend for their clinical care. The project will involve interviews and scoring on standardised scales to measure the motor and non motor features and the response to medication in people with Parkinson's disease. Blood tests will be taken at baseline for DNA testing and serum will be collected for storage. At follow-up visits a further blood sample for serum will be collected (timings depend on the type of case, see study flow charts above). These blood specimens will be tested for known genes relating to Parkinson's, but also tested for potential new markers of the disease. The information collected will be kept free of personal details according to rules of good clinical practice and data protection. Participants will travel to their nearest centre – using the wide geographic representation of study centres across the UK.

In addition to people with Parkinson's disease, first degree relatives will be asked to participate in a similar fashion, with visits at baseline and 36 months, and the taking of a blood sample at each visit. The purpose of this part of the study is to determine whether Parkinson's disease can be identified earlier than presently, to open the door for treating symptoms at an earlier stage and ultimately preventing the disease developing.

A total of 3080 subjects will be recruited from 25-30 centres. 2000 patients with PD onset within 3 years, and 750 first degree relatives, will be invited to participate. An additional 240

cases with PD onset under 50 years, and 90 of their first degree relatives, will be invited. All participants will be gene tested for LRRK2 and GBA; under 50s will be tested for Parkin and PINK1. Serum will be sampled serially and DNA will be stored long-term.

Clinical scoring will adopt common data elements of the NINDS to maximise compatibility with other studies, and will include demographic, cognitive, quality of life, depression, autonomic and impulse control recordings. Sampling will be performed largely in conjunction with routine clinic visits, i.e. every 6 months for recent onset PD cases, although the main study observations will be performed at 18 month intervals, for recent onset PD cases. Relatives of PD patients will be assessed at baseline, and for a second time at 36 months. For patients diagnosed at age under 50 years, observations will be made over a 6 month period, but progression data and samples will not be performed. Further detail is described in the study flow charts (above).

The programme is linked to, and will support, prevailing scientific and clinical studies, including young onset PD, mitochondrial, and neuroimaging studies, as well as serving as a biosample and data resource for future studies. Recruitment of participants to the Parkinson's UK Tissue bank (Imperial College, London) will be encouraged. National and international linkage of clinical and scientific data will occur, involving similar cohort studies in the UK – Oxford Discovery Grant, and Non-Motor Longitudinal study, King's College London, which also has a European component – as well as studies in the United States, Italy and potentially other centres.

This is the largest long-term clinical UK study of PD, and will open new doors for discovering the reasons for variability in the way PD affects different people, as well as helping to find ways of detecting the very earliest markers of the disease. The current study is linked to several other large studies in the UK and internationally. With this cooperative effort on a huge scale, the findings will in the future help the testing of treatments in those at risk, so that we can delay disease onset, or prevent the disease from developing.

Interim Extension

This will continue monitoring for patients with Parkinson's of recent onset, extending participation from 3 to 4.5 years.

STUDY RATIONALE - HYPOTHESIS

The primary hypothesis is that genetic and biomarker diversity explains the varied clinical phenotype of Parkinson's disease (PD). Understanding these mechanisms will improve the design and interpretation of basic science and clinical therapeutic studies.

Large sample sizes are needed to test subsets of Parkinson's disease patients characterised by variability in clinical features as follows:

1. **Motor features:** tremor dominant versus postural instability gait disorder.

2. **Cognitive features:** early cognitive impairment (predicting dementia) versus patients with normal cognition.
3. **Response to antiparkinson therapy:** clear dose responsiveness versus poor therapy responses.
4. **Non-motor features:** e.g. autonomic, olfactory, gastrointestinal, the burden of which varies between patients.

The study will therefore collate demographic and disease-specific descriptions of PD, including progression rates, across the 4 key areas described above: motor, cognitive, anti-Parkinson therapy response, and non-motor features. The observations will be linked to gene test results, addressing deficiencies in the genome-wide association studies, which have much more limited diagnostic and progression information.

The interim extension of the main study will continue the hypotheses, to further define variations in progression rate linked to biosamples.

2.0 STUDY OBJECTIVES

Expanding on the four key elements planned for assessment and analysis as detailed above, the PRoBaND study will assess patients as follows:

1. **Motor**: Patients will be divided into tremor dominant and postural instability gait disorder types. Progression rates and the response to medication will be compared between the groups. The association of motor subtype with non-motor burden will be collected and described.
2. **Cognitive sub-types**: Cognitive testing will be undertaken to test the hypothesis that patients with early mild cognitive impairment have a greater risk of subsequent cognitive decline compared to patients with normal baseline cognition. Analysis of this data will also be conducted by linkage of the findings to MAPT and COMT gene tests.
3. **Therapy response**: The response to antiparkinson medication and those changes over time, will be collated. Exploratory analysis of features which are associated with a good therapy response will be undertaken. Therapy response in patients with known genetic types of Parkinson's disease will be clarified.
4. **More non-motor features**: The degree of non-motor involvement compared to genetic subtype will be analysed, to test recent observations suggesting for example that non-motor features are less in for example patients with Parkin positive disease.

3.0 STUDY DESIGN

PRoBaND is a prospective, observational, multicentre study involving PD gene testing in patients with recent onset PD and first degree relatives of patients with recent onset *or* young (under 50 years) onset PD, comparing relatives of gene test *positive* patients, with relatives of gene test *negative* patients. PRoBaND will form the largest and most detailed prospective study of PD in the UK.

3.1 STUDY POPULATION

Eligible patients for inclusion in PRoBaND are defined as follows:

A. **Recent onset Parkinson's Disease patients:** PD diagnosis within the preceding three years, and fulfilling inclusion and exclusion criteria.

B. **Patients with PD onset at less than age 50**: regardless of disease duration.

C. **First degree relatives of PD patients (A and B above) who are** (Table 1):

   i. gene test *positive* will be invited to participate.

   ii. gene test *negative*, and matched for age and sex to first degree relatives of patients with positive gene tests.

A2 – Interim Extension for recent onset Parkinson's disease patients who continue to fulfil inclusion and exclusion criteria.

Table 1: Estimates of numbers related to gene tests.

		Sub-total	Total
Patients (recent onset PD)	Gene test positive Gene test negative	*100* *1900*	2000
First degree relatives (of recent onset PD)	Of gene positive patients Of gene negative patients	*150* *600*	750
Patients (diagnosis under 50)	Gene test positive Gene test negative	*12* *228*	240
First degree relatives (of diagnosis under 50)	Of gene positive Of gene test negative	*18* *72*	90
Total: Patients and relatives			3080

3.2 MAIN INCLUSION CRITERIA

A. Parkinson's Disease patients

i. Diagnosis of Parkinson's disease, based on UK Brain Bank criteria (as detailed in Appendix 6) and made within the preceding 3 years ('recent onset cases') or diagnosed at under 50 years ('under 50 years cases')

ii. Age ≥18 to ≤ 90years

iii. Subject is able and willing to provided informed consent.

iv. Patients are allowed to enter the study after they have started antiparkinson medication.

B. First degree relatives

i. Age ≥18 to ≤ 90years
ii. Resident in the United Kingdom and able to access one of the PRoBaND study centres.
iii. Subject is able and willing to provided informed consent.

3.3 MAIN EXCLUSION CRITERIA

A. Parkinson's Disease patients

i. Patient has severe comorbid illness that would prevent full study participation
ii. Patient has features indicating another type of degenerative parkinsonism, e.g. progressive supranuclear palsy
iii. Drug-induced parkinsonism (Drug-unmasked PD is allowed)
iv. Symmetrical lower body parkinsonism attributable to significant cortical and/or subcortical cerebrovascular disease (patients with 'incidental' small vessel disease on brain imaging are allowed).
v. Negative or normal functional imaging of the presynaptic dopamine system
vi. The presence of UK Brain Bank exclusion criteria will be recorded at baseline, allowing for the presence of 1 or 2 exclusion criteria (e.g. dopamine antagonist Drug used; more than one affected relative) (if justified e.g. by abnormal SPECT).

B. First degree relatives

i. Subject has severe comorbid illness that would prevent study participation
ii. Subject already has a diagnosis of PD.

A2: Interim extension participants will follow the inclusion and exclusion criteria above.

3.4 IDENTIFICATION OF PARTICIPANTS AND CONSENT

Patients with recently diagnosed PD, and first degree relatives of those patients will be invited to participate. The study will be performed at 35-40 centres across the United Kingdom, involving neurology and medicine for the elderly services A patient attending a clinic that is not participating in PRoBaND, will be welcome at their nearest PRoBaND site. First degree relatives will be able to access their nearest PRoBaND centre. The study may be notified to potential participants by means of a mini-poster advertising the study. In addition, study centres may contact patients known to their clinical service by letter or telephone to give them an outline indication of the study and invite them to attend for discussion and consideration of potential participation. DeNDRoN research nurses (where available) will assist in patient identification through local clinic lists and databases. Patients will attend for study visits either in conjunction with or separately from their usual clinic visits, by local and personal preferences.

Parkinson's UK will distribute a form "Expression of Interest in the Tracking Parkinson's Study" to their members, advising of the study and asking them to register any interest with the Study Co-ordinator at the Glasgow Centre, for follow-up with their local PRoBaND site.

Patients and relatives will be given information about the study at their local centre providing care for Parkinson's disease patients. The patient and relative information sheets will be provided, as appropriate.

The patients will be given the opportunity to take the patient information sheet with them to consider the study, involving if they wish their immediate family, and also if they wish their first degree relatives who may wish to take part in the study. The patient and relative's wishes will be taken into account in relation to the time required for them to consider the project. Accordingly, if it is the patient's preference to consent on the day of initial discussion about the project, rather than returning for an additional visit, this will be accepted, while the patients and relatives who require longer to consider and discuss the study will be given the time they request to do so.
Patient and relative identification codes will be generated by random code-generating software. Patient and relative ID codes will then be divided into blocks and assigned to individual study centres. This study ID code will be used for all study related documentation.
After patients complete their 3 year visit for PRoBaND, they will be informed of the interim extension and given information and offered a return visit in 6 months to enrol in the interim extension by the clinicians who have been following them already in the study. They will be given the opportunity to take the Patient Information Sheet with them to review, with a view to providing formal consent at their next routine clinic visit 6 months later. In a small number of centres where research visits take place in a clinical research facility, the arrangements will be adapted to allow for this variation.

Withdrawal of study participants

Patients and relatives may withdraw from the study at any time with no detriment to their future care. They will be asked if their data and blood samples provided up to that point can be retained and used by the study; but if they want them removed from the study entirely then this will be respected.
In addition to the general arrangements for discontinuation of study subjects (such as on the patient's request), patients who lose capacity during the study should be withdrawn from further study procedures. Identifiable data and blood samples already collected with consent will be retained and used in the study, but no further data or blood sampling should be collected, nor any other research procedures carried out in relation to the study subject.
The loss of capacity will be based on deterioration in cognitive performance, reflected in a combination of observations in the clinic, from the subject's family/carers, and the scoring instruments of cognition used in the study.

3.5 STUDY SCHEDULE

Patients diagnosed for less than 3 years

Visit 0: Screening visit

- Obtain informed consent
- Review Inclusion/Exclusion Criteria
- Medical/Disease History
- Medications review
- Vital signs (blood pressure, weight)
- Height
- Family history
- Demographics

Visit 1: Baseline 0 months

- Blood sample for DNA
- Blood sample for serum
- Standard PD questionnaires
- Scans – results of tests undertaken on clinical grounds will be collected
- Completion of CRF
- Adverse event assessment and completion of CRF

Visit 2: 6 months

- Standard PD questionnaires and scoring
- Adverse event assessment and completion of CRF

Visit 3: 12 months

- Standard PD questionnaires and scoring
- Adverse event assessment and completion of CRF

Visit 4: 18 months

- Blood sample for serum
- Standard PD questionnaires and scoring
- Adverse event assessment and completion of CRF

Visit 5: 24 months

- Standard PD questionnaires and scoring
- L-dopa challenge test (in patients prescribed L-dopa treatment)
- Adverse event assessment and completion of CRF
- Information on Parkinson's UK Tissue Bank provided for consideration

Visit 6: 30 months

- Standard PD questionnaires and scoring; wearing off questionnaire
- Adverse event assessment and completion of CRF
- Decision on donating to Tissue Bank requested

Visit 7: 36 months

- Blood sample for serum
- Standard PD questionnaires and scoring
- Scans – results of tests undertaken on clinical grounds will be collected
- Adverse event assessment and completion of CRF

Interim Extension

At or after Visit 7 :

- Review Inclusion/Exclusion Criteria
- Provide patient information leaflet

Visit 8: Baseline (36 + 6 months) 42 months

- Complete informed consent
- Medications review
- Clinical and Global Impression Questionnaire

Visit 9: (36 + 18 months) 54 months

- Medications review
- Blood sample for serum
- Standard PD questionnaires and scoring, including PD Grading.

Patients with PD onset at less than age 50 years

Visit 0: Screening visit

- Obtain informed consent
- Review Inclusion/Exclusion Criteria
- Medical/Disease History
- Medications review
- Vital signs (blood pressure, weight)
- Height
- Family history
- Demographics

Visit 1: Baseline 0 months

- Blood sample for DNA
- Blood sample for serum

- Scans – results of tests undertaken on clinical grounds will be collected
- Standard PD questionnaires and scoring
- Information on Parkinson's UK Tissue Bank provided for consideration

Visit 2: 6 months

- Standard PD questionnaires and scoring; wearing off questionnaire
- Decision on donating to Tissue Bank requested

Relatives of PD patients

Visit 1: Baseline 0 months

- Obtain informed consent
- Review Inclusion/Exclusion Criteria
- Medical/Disease History
- Medications review
- Vital signs (blood pressure, weight)
- Height
- Family history
- Demographics
- Blood sample for DNA
- Blood sample for serum
- Scans – results of tests undertaken on clinical grounds will be collected
- Standard PD questionnaires and scoring

Visit 2: 36 months

- Update medical history
- Update medication review
- Vital signs (blood pressure and weight)
- Blood sample for serum
- Scans – results of tests undertaken on clinical grounds will be collected
- Standard PD questionnaires and scoring
- Information on Parkinson's UK Tissue Bank provided

3.6 BLOOD TESTING / VENEPUNCTURE

Two different types of blood sampling will occur in the PRoBaND study.
Blood for DNA (purple and yellow tubes) and a blood sample (red) tubes to produce Serum for storage.
Blood for DNA is taken only once during the study, which is at the baseline visit. This applies to patients and to relatives.

Blood sample to produce Serum for storage. This happens more than once during the study, depending on the type of case - patient (onset <3y or onset <50 years of age) or relative – see study flow charts 1, 1A, 2 and 3 The processes for handling blood samples and shipping are described in detail in the PRoBaND Blood Sample guide notes.

4.0 GENETIC TESTING PROCESS

Genetic analysis will be performed in Cardiff, and follow the established methodology of their group in PD and other disease areas. The technology to analyse DNA variants is rapidly evolving but will include analysis of putative Mendelian and non-Mendelian factors. Screening and analysis of potential pathogenic and anonymous genetic variations in sporadic and familial patients will be compared to control samples. This will include DNA variants such as point mutations, gene re-arrangements, deletions/duplications, non-coding sequence change and DNA expansions. Analysis will include large scale single nucleotide polymorphism (SNP) analysis and sequence analysis. Definition of Mendelian variants will rely on disease segregation, haplotype analysis, bioinformatics and functional work and determination that disease variants are absent from control samples. Definition of associated variants will depend on case control analysis and determination of the odds ratio related to risk alleles.

Linkage analysis within Mendelian families using either microsatellite markers or single nucleotide polymorphisms. This involves identifying the likely genomic area harbouring DNA sequence variation by tracking anonymous DNA variation in affected and unaffected family members. Family based analysis (linkage) depends on genotyping affected and unaffected individuals to determine the shared chromosomal segment thought to harbour the athogenic gene abnormality. This can take place in a single family (usually with >8 affected individuals), in a pool of smaller families in affected sibling pairs or in parent/offspring groups.

The samples collected from PRoBaND will be linked to the samples collected in the Cardiff Neurological Disease Biobank and Neurogenetics Research Study which itself is linked to prior studies by the same group entitled Genetic Investigation of Parkinsonism and Related Disorders, and Comparative Study of Early and Later Onset Parkinson's Disease. Ethical approval for genetic analysis is covered within the Cardiff Neurological Disease Biobank and Neurogenetics Research Study (CANDAS) ethical approval 09/MRE09/35. We are committed to making large sale genetic data available to other researchers in the collaborative fashion following guidance set down by the Medical Research Council (UK) and the Wellcome Trust.

LRRK2 and GBA will be tested in all PD patients. Parkin (PARK 2) and PINK-1 (PARK 6) will be tested in patients at age of diagnosis of Parkinson's disease under 50 years. The number of patients anticipated as PD gene positive will be relatively low (see Table 1 below), and the number of first degree relatives of those gene positive cases will also be low. The matched control subjects (related to gene test *negative* PD patients) will be invited at a ratio of 4:1

compared to the relatives of gene test *positive* patients. This will maintain blinding as to gene status within the family, although it will mark an increased risk (1 in 5).
Oversampling of young-onset PD. In addition, given the relatively small number of PD patients with onset under 50 years, and expected to have positive genes, oversampling of young-onset PD patients will be undertaken, as follows:

All prevalent younger onset PD cases attending the study centres will undergo gene tests for PARKIN and PINK-1. The clinical phenotype will be summarized, but they will not be followed prospectively. First degree relatives of those patients will be invited for participation, on the same principles as the main study cohort.

Procedure for gene test results

The gene test results from patients and relatives participating in the study will not be given to the study centres, and will therefore not be available for discussion with the patients and relatives participating. Clinicians may wish to organise an NHS based test or referrals in the normal way, if they consider this appropriate for their patient. This might be, for example, in a patient with a very strong family history of Parkinson's disease and/or young onset Parkinson's disease where it may be considered by the treating clinician appropriate for discussion about gene test results, with the appropriate counselling usually involving the available genetic services at the hospital site. Such consideration will be on a case by case basis by the principal investigator or clinician responsible for the patient's care. In such circumstances, an additional blood sample should be taken and sent through local channels for testing. **We still wish such patients to participate in the PRoBaND study,** as we consider the additional information from the study processes of PRoBaND will enhance our knowledge of PD and genetic mechanisms.

5.0 DATA MANAGEMENT AND STATISTICS

5.1 DATA COLLECTION

Data capture will be by local medical and nursing staff, including PD Nurse Specialists where available. Data recording will be undertaken by a password-protected and anonymised web-based electronic data capture system, but a paper stage will be available for centres unable to use the e-system. Guide notes for the completion of the eCRF and paper CRF are in PRoBaND manual: Blood sampling and in case record from guide notes. Further context specific information is provided on the data entry website www.clinbase.co.uk. This website is password protected – username and password will be provided to access the system for each study centre. Missing data points will be pursued at the data centre in Glasgow and communication with the study investigators to complete missing data points. Data options will be restricted on the electronic CRF to limit erroneous data.

5.2 STUDY TIMESCALE

	START DATE	FINISH DATE
Identification of new onset Parkinson's within preceding three years for invitation to study participation	December 2011	December 2013
Identification of Parkinson's diagnosed aged under 50 years	December 2011	December 2015
Invitation of relatives for study participation	December 2011	December 2013
Study visit schedule	Last date *first* visit 30/12/13	Last date *last* visit 30/12/16

	START DATE	FINISH DATE
Identification of participants in PRoBaND reaching the 3 year time point	February 2015	May 2017
Study visit schedule	Last date *first* visit (screening) May 2017	Last date *last* visit November 2018

5.3 STATISTICAL ANALYSIS

The sample size for PD patients is based on known incidence rates and clinic activity levels, adjusted for the initially higher rates by inclusion of cases diagnosed within the preceding 3 years. This calculation was initially based on 24 sites, such that 2880 cases a 70% response rate will give around 2000 recent onset patients. The number of centres has since increased, but we have left the target numbers unchanged, to allow for any delays in centre initiation and other contingencies.

We will use standard statistical methods, (survival curves and Cox proportional hazard models) and more complex multivariate models such as multi-level, latent class and/or growth curve models to examine for heterogeneity in the presenting features and natural history of the cohort.

The large size of the cohort will allow prognostic modeling in a random split sample ("training sample") and testing of validity in the second half of the sample ("validation sample").

Also, collaboration with PD Discovery (and other cohort studies) will give full external validation.

Power calculation.

Assuming 90% power and 5% significance, 2000 patients will detect a difference of 5-8% for a categorical variable with an exposure frequency of between 10-90% if we dichotomise the cohort by a prognostic indicator.

There is greater power for continuous measures. For example if we sampled 10% of the cohort based on a specific feature such as a gene mutation, we could detect a 0.33 standardised difference (z-score) with 200 cases and 200 controls.

For comparison between gene positive patients and gene positive first degree relatives we will be able to detect 0.42 standardised difference (z-score) between 100 cases and 150 relatives. We will have greater power for comparison with gene negative relatives and the ability to test for a trend across these three groups.

Statistical analysis will be undertaken under the supervision of Professor Yoav Ben-Shlomo, at the School of Social and Community Medicine, University of Bristol.

As the study does not involve an intervention, interim analysis is not planned, there is no planned unblinding, and there are no stopping rules.

6.0 SOURCE DATA & DOCUMENTS

6.1 Data handling and record keeping

Data will be primarily handled through the electronic data capture system, involving a paper stage for centres that are unable to use this system. For centres not completing data entry on the electronic CRF, data will be forwarded to the data co-ordinating centre in Glasgow by scanning of the visit record sheets to e-mail, or alternatively by fax. Study centres will maintain a local copy of the data collected until the completion of the study, at which point they will be shredded (for data transferred to e-storage, which will include all items captured on eCRF) or archived (for all other data).

Data will be handled from individual scores in tabular form. The data will be linked by visit and by study ID code to allow calculation and processing of aggregate data. The data will be uploaded from the tabular layout which is captured using ClinBase software (Caspio LLC, Cal., USA) into an Access database (Microsoft LLC, USA) where queries will be generated to populate tables for statistical analysis using Stata Data analysis and statistical software (StataCorp LP, Texas, USA).

6.1.1 Completion of eCRF

The eCRF will be developed by the data co-ordinating centre in Glasgow under the supervision of Dr. Donald Grosset, Chief Investigator. The eCRF and the data flow has been designed in conjunction with Professor Ben-Shlomo in Bristol to allow acquisition of the data into the appropriate statistical programmes used in the Bristol statistical unit. In particular, the ability to analyse data from the PRoBaND study alongside data from the Oxford Discovery Project has

been addressed and has informed the design of the PRoBaND data collection system. Further detail is described under section 6.1.4. Database Software.

6.1.2 Data validation

Data will be reviewed on receipt at the data co-ordinating centre on a regular basis, and not less than weekly, during the study period. Data tables will be analysed using conditional formatting to flag missing data points, and to identify data which appears to be out of expected ranges (out of range data will also be limited during eCRF completion, by predefined ranges and appropriate data fields, e.g. for dates). Incomplete or apparently erroneous data will be identified and data clarification requested from the submitting centre.

6.1.3 Data Security

Data collected on the eCRF is anonymised using the study ID code as the unique identifier. Use of the eCRF on the ClinBase website will require multi-level password access, first to enter the ClinBase website, and second to make individual visit entries. Review of submitted data will be a component of the eCRF system, such that centres can check that data has been successfully submitted, and this will be protected by password. Data acquired on the eCRF will be transmitted using the secure protocol, Hypertext Transfer Protocol Secure (HTTPS), which uses the secure socket layer to encrypt communication and secure identification of the network web server. Individual data entries will be tagged with the user ID and internet address.

All data collected on the eCRF system will follow the above processes, but an additional layer of protection will be applied to two components of the data collection, namely subject date of birth and family history. This data will be collected on the eCRF but will not be available for review by users after submission, as it will undergo an additional level of encryption, and will be removed from online storage as it is submitted. These data elements will be held locally in the Glasgow study centre, in an off-line data table. This step has been designed to reduce the likelihood of inappropriate access to data that might allow identification of study participants through combinations with data that could be acquired from other sources and databases.

Data will be backed up to parallel storage systems which have multi-layered incremental backups, all maintained by dual layer password protection.

6.1.4 Database Software

The eCRF is on the ClinBase system (www.clinbase.co.uk).. The software is compatible with several web browsers, Internet Explorer, Firefox and Safari. The software has high level security and encryption and is an established secure method, allowing the safe handing for example of payment processing including credit card submissions. It has multilevel security, including 256-bit secure socket layer, data encryption for storing sensitive information, and password protection for data entry and retrieval. Access (Microsoft, USA) will be used by the

Bristol statistical centre for database queries. Statistical analysis will then use Stat (StataCorp LP, Texas, USA).

6.1.5 Record retention

Records will be stored for a period of 15 years after study completion.

6.1.6 Archiving

At the end of the study period, or when required during the study, case record forms and other study information will be archived in a suitable secure insured storage facility. This will be arranged by the data coordinating centre in Glasgow, and the costs of such ongoing storage arranged by the Glasgow centre will be met from study funding.

6.1.7 Data sharing

Data will be made available to support other research and audit projects in Parkinson's disease. Such data sharing will be stripped of personal identifiers, including date of birth and detail of family history. Access to such datasets will be on application to the Biosample and Dataset Committee. All studies seeking to use data and/or blood or serum samples will require ethics approval.

7.0 STUDY MANAGEMENT

The study will be overseen by three committees, with input from Parkinson's UK (as the funder and the principal representative of PD patients in the UK).

Steering Group

This will consist of the Chief Investigator and Co-Investigators and trial statistician. The membership of this committee is stated on the contacts' page of this document. The Steering Committee will liaise by teleconference, e-mail, and meetings arranged to coincide with the ABN Special Interest Group, the International Movement Disorder Society, and the PRoBaND Investigators Meetings, and other ad hoc meetings as required. The Steering Committee has the responsibility for design and implementation of the project and also has a liaison role with the Parkinson's sub-group of DeNDRoN.

Data and Biosample Access Committee

This committee will receive and consider requests for access to biosamples and datasets for audit and research projects. The committee will be chaired by Dr. David Dexter, Imperial College London, and membership will include clinician, scientist, epidemiology/statistics representation and also representation from Parkinson's UK,

Independent International Review Committee

This will be constituted and administered by Parkinson's UK, who may wish to include representation of their own body on the committee. Membership of the committee is

provisional as follows – Professor Anthony Lang, Toronto, Canada, Professor Wener Poewe, Austria, Professor Eduardo Tolosa, Spain, Professor Angelo Antonini, Venice.

The international committee will receive an annual report on study progress and review any problems or issues in relation to this, as well as help to develop links with other cohort studies underway or planned in other countries.

The study will be subject to audit according to local policies, usually administered by the Research and Development offices.

8.0 STUDY AUDITING

This study will be audited by designated representatives of the Sponsor. The NHS Greater Glasgow & Clyde audit process will be followed. Site visits for audit will be conducted on a rolling basis. Site selection will be made on the basis of number of patients recruited, and data queries and resolution.

It is the Sponsor's responsibility to inform the investigator(s) of all intended study centre audits. It is the investigators responsibility to ensure appropriate resources at site and that the auditor(s) have access to all study personnel, documentation and patient medical notes as appropriate.

9.0 PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the Chief Investigator and any required amendment forms will be submitted to the ethics committee and sponsor. The Chief Investigator will determine whether an amendment is substantial or non-substantial. Before the amended protocol can be implemented (or sent to participating sites) favourable opinion/approval must be sought from the original reviewing REC and Sponsor. The Chief Investigator and Sponsor's Representative will sign any amended versions of the protocol.

10.0 ETHICAL CONSIDERATIONS

Ethical conduct of the study

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

There are no special ethical considerations pertaining to this study. Favourable ethical opinion will be sought before patients are entered into this study. Participants will only be allowed to enter the study once wither they have provided written informed consent.

The Chief investigator will be responsible for updating the Ethics committee of any new information related to the study.

Informed consent

Written informed consent should be obtained from each study participant. Additional informed consent will be obtained from patients entering the interim extension study. The Research Nurse or investigator will explain the exact nature of the study in writing, by provision of patient information sheet, and verbally. This will include the risks of participating in this study. Study participants will be informed that they are free to withdraw their consent from the study at any time.

11.0 INDEMNITY AND INSURANCE

NHS Greater Glasgow & Clyde is the sponsor of this research governance study. No special insurance is in place for patients in this study other than standard NHS liability insurance providing indemnity against clinical negligence. This does not provide cover for non-negligent harm e.g. harm caused by an unexpected side effect of participating in the study.

12.0 FUNDING

The study, including the interim extension, is funded by Parkinson's UK. This includes funding for study design and data management, statistical analysis, consumables such as blood specimen tubes, packaging and postage for blood samples, the costs of gene testing, DNA extraction and storage, and longer term storage of cell lines and serum. There are limited funds available to support meetings of the participating sites (for study initiation, training, and update meetings), and for the core steering committee and biosample and dataset committee (reasonable travel expenses reimbursed; cost of meeting room hire and light catering). The funding and arrangements for the international review committee will be organized separately, as an independent expert review board, as suggested by and agreed with Parkinson's UK. There is a fund to cover additional travel by patients and relatives participating in the study, which will generally be reimbursed on the basis of receipted expenses (e.g. bus, train) incurred, or on the appropriate average mileage rate prevailing in the Glasgow data coordinating centre at the time the mileage was claimed. (mail to:Alison.Smith@ggc.scot.nhs.uk Tel No. 0141 201 2486)

13.0 SPONSOR RESPONSIBILITIES

The Research Governance Sponsor of this study is NHS Greater Glasgow & Clyde. As Sponsor, the Health Board will ensure that there are proper arrangements to initiate, manage, monitor and finance the study.

A Clinical Study Agreement will be put in place between NHS Greater Glasgow & Clyde and each of the participating sites. This agreement outlines the responsibilities of each party in running the study.

14.0 ANNUAL REPORTS

Annual reports will be submitted to the ethics committee and Sponsor with the first submitted one year after the date that all relevant study approvals are in place.

15.0 DISSEMINATION OF FINDINGS

The study will be registered with clinicaltrials.gov, using the account held by the Glasgow movement disorder research team.

1. **Presentations:** Results will be presented at regional, national, and international meetings, for specialist doctors, nurses, and patient groups, e.g. the Parkinson's UK Research meeting, the DeNDRoN subgroup, the Association of British Neurologists, the British Geriatric Society, the Movement Disorder Society and the World Federation.
2. **Publications:** Results will be submitted to peer-reviewed journals e.g. Movement Disorders, Lancet Neurology, Neurology. Study reports will be updated for the newsletters and website of Parkinson's UK.
3. **Internet:** Study information and updates will be maintained on the study's website (www.proband.org.uk), linked to the websites of Parkinson's UK and collaborating studies (e.g. Oxford Discovery).

The publications arising directly from the study will be reviewed and approved by the steering committee. Publications resulting from access to data and/or biosamples (which will have been approved by the Biosample and Dataset Committee, as described elsewhere) will be requested to acknowledge the PRoBaND study as the source of such data and/or biosamples, and where appropriate and by mutual agreement, to involve members of the PRoBaND consortium as contributors to the design, analysis, or other inputs to the resulting work.

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APPENDIX 1. ASSESSING THE L-DOPA RESPONSE

Patients diagnosed within the past 3 three years should have an L-dopa challenge test performed at Visit 5 (24 months), provided they are prescribed medication including L-dopa. This should be undertaken after they have been taking L-dopa for at least 6 months. Patients diagnosed at age under 50 years, and relatives, will not undergo an L-dopa challenge.

The L-dopa challenge test will follow the standard procedure which is used in research studies and is summarised as follows.

Advise the patient that you would like to assess their Parkinson's Disease, both "ON" and "OFF" medication. Discuss with the patient whether they feel they can manage to come up to the hospital having missed out the morning dose of their usual treatment. If they can, then ask them to miss out the morning dose of all anti-Parkinson medication (L-dopa based, dopamine agonist, and any other adjunctive therapy) but they can take other (non Parkinson's) medication they are on as usual. Also ask them to miss out the last bedtime dose of an oral dopamine agonist, and if they are taking a once daily dopamine agonist at 6.00pm or later from the preceding day when you are going to assess their response "ON" and "OFF" medication ask them to miss that dose out as well.

If the patient does not feel they can manage to attend the hospital having omitted their morning dose of anti-Parkinson treatment, ask if they can come to the hospital after their first morning dose and wait until they are due their next morning dose of L-dopa based treatment.

By following one or other of the above approaches, you will assess the patient in an "OFF" state and perform a standard UPDRS3 motor assessment in the "OFF" state.

Then give the usual morning dose of L-dopa and wait for 20-30 minutes, until the patient feels that the dose has had an effect. In patients who are not aware of dose response in general terms, or from this particular dose, proceed in any case with repeat UPDRS assessment at 30 minutes. Do not look at the previous baseline "OFF" state UPDRS score when you are doing the ON score. This improves the objectivity of the scoring. Once the UPDRS3 scoring is complete at the 30 minute time point, the patient can return to taking their usual medication at the usual times thereafter.

Record the UPDRS on either the eCRF or the paper CRF in the usual fashion.

Patients will not require any adjustment to domperidone usage for this challenge test. If a patient usually takes domperidone with their morning dose of anti-Parkinson medication they

can take it as usual in the morning before coming up to the clinic or alternatively once they come up to the clinic. Patients who do not normally take domperidone should not need it as they only getting their usual dose of their medication. This therefore differs from challenge testing which can be done at an earlier disease stage as a diagnostic test, when domperidone covers is usually recommended.

Recording the L-dopa challenge.- This can be done on the paper CRF and transferred to the eCRF later, or it can be done directly onto the eCRF.

APPENDIX 2

Provision of written information for the patients at visit 4 (18 months) in preparation for the L-dopa challenge at visit 5 (24 months) is considered useful and standardized wording for this to be used at all sites has therefore been added to the protocol version 1.3 dated 12/02/2014. The text is shown below:

L-dopa test dose – Guide notes for patients

We would like to measure the effect of your Parkinson's medication at your next visit in the Tracking Parkinson's Study. A single test dose of your medication is given as below.

This visit is planned for _____ (date) at _____ (time)

Please bring your Parkinson's medication with you, when you attend for this visit.

Please miss out your Parkinson's medicines just before your next visit, as explained below.

Tick where appropriate, and Score through where not applicable.

A. L-dopa preparations

☐ Please miss out your morning dose of _____ on the day of your next clinic visit.

B. Dopamine Agonist: Standard Release

☐ Please miss out your last bedtime dose (the day before your visit) **AND** your first morning dose of _____

C. Dopamine Agonist: Modified Release

☐ Please miss out your _____ which you usually take at _____ p.m. on the evening before your next clinic visit.

D. Dopamine Agonist: Modified Release

☐ Please miss out your _____ which you usually take at _____ a.m. on morning of your next clinic visit.

If you usually take Domperidone treatment (this is used to prevent nausea) then you should take it as usual in the morning before coming to the clinic. Please also take any other medication as usual.

If you do not feel you can manage to attend the hospital having omitted your Parkinson medication, you may come to the hospital after your first morning dose and wait until you are due your next dose of L-dopa-based treatment.

Your Parkinson features will be scored when you come to the clinic, then you will be given your usual morning dose of L-dopa-based treatment, and then after 20-30 minutes you will have a repeat assessment of your Parkinson features.

Thereafter you can return to taking your medication as usual.