Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
PRoBaND: Parkinson's Repository of Biosamples and Network Datasets

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
(●) Other clinical trial or clinical investigation
( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples, other human biological samples and/or data *(specific project only)*
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	(●) Yes	( ) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

[x] England
[x] Scotland
[x] Wales
[ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

( ) England
(●) Scotland

- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which review bodies are you applying to?

- ☑ NHS/HSC Research and Development offices
- ☐ Social Care Research Ethics Committee
- ☑ Research Ethics Committee
- ☐ National Information Governance Board for Health and Social Care (NIGB)
- ☐ Ministry of Justice (MoJ)
- ☐ National Offender Management Service (NOMS) (Prisons & Probation)

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study, or any part of the study, being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the clinical care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

NHS
National Patient Safety Agency
National Research Ethics Service

Application to NHS/HSC Research Ethics Committee

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
PRoBaND: Parkinson's Repository of Biosamples and Network Datasets

Please complete these details after you have booked the REC application for review.

REC Name:

REC Reference Number: **Submission date:**

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

PRoBaND: Parkinson's Repository of Biosamples and Network Datasets: Prospective observational study of Parkinson's disease with repeat clinical assessment and biobanking of blood samples.

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Dr	Donald	Grosset
Post	Consultant Neurologist		
Qualifications	BSc, MB ChB, MD, FRCP		
Employer	NHS Greater Glasgow and Clyde Health Board		
Work Address	Southern General Hospital		
	1345 Govan Road		
	Glasgow		
Post Code	G51 4TF		
Work E-mail	donald.grosset@glasgow.ac.uk		
* Personal E-mail			

Work Telephone	01412327846
* Personal Telephone/Mobile	
Fax	01412327626

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Dr	Steven	Burke
Address	NHS Greater Glasgow & Clyde		
	Research and Development Management Office, Tennant Institute		
	38 Church Street, Glasgow		
Post Code	G116NT		
E-mail	steven.burke@ggc.scot.nhs.uk		
Telephone	0141 232 9429		
Fax	0141 211 2811		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	GN11NE062
Sponsor's/protocol number:	52504/1
Protocol Version:	1.0
Protocol Date:	28/02/2011
Funder's reference number:	PROBAND10

International Standard Randomised Controlled Trial Number (ISRCTN): None

ClinicalTrials.gov Identifier (NCT number): Pending

European Clinical Trials Database (EudraCT) number: None

Project website: www.proband.org.uk

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

This study will be conducted across 25/30 centres in the UK, and will involve patients diagnosed within the previous three years with Parkinson's disease, and patients diagnosed under age 50 at any duration of Parkinson's disease, and for both of these groups will also involve close first relatives (e.g. brother, sister) who do not have a diagnosis of Parkinson's disease but may show markers of a risk of the disease developing in later life. A total of 3080 people will be invited to take part, 2240 people with PD and 860 relatives. The study aims to understand better the reasons for variation in the symptoms and response to medication that Parkinson's disease patients frequently report. We need to understand better, for example, why some patients have significant tremor while others are spared having a tremor; why some patients have involvement of memory and thinking processes while others do not; and why some patients respond extremely well to medication while others have a much poorer response. The study will link the clinical observations of variation in these features to gene tests and other laboratory measurements, to help understand mechanisms causing variation in the severity and progression rates of Parkinson's disease. The programme is funded initially for five years but it is hoped that future funding will make it a long term project throughout the lifetime of the participants.

A6-2. Summary of main issues. *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

The main ethical and design issues relate to the collection of blood samples and the gene testing for known mutations associated with Parkinson's disease, both for patients and for first degree relatives. The study has addressed these issues by following the standard current approach namely that the gene testing is primarily for research purposes and the results will not be communicated to the local investigator, or patient, or relative. However, in a very small proportion of cases where there is a very young onset Parkinson's disease and/or a very strong family history of Parkinson's disease, it is considered appropriate to give the gene test result to the patient and to discuss the genetic issues. This will be addressed following standard clinical practice involving the use of counselling in relation to the genetic issues.

The study will observe first degree relatives of patients with Parkinson's disease prospectively for the development of early pre-motor and very early motor features of Parkinson's disease. First degree relatives of patients Parkinson's disease will be invited to participation, involving both gene test negative and gene test positive index cases (at a ratio of around 4:1). Accordingly the invitation of a subject to participation will not indicate to them that a member of their family has tested positive for a gene test.

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The principal research objective is to prospectively record the clinical features and progression rate of patients with early Parkinson's disease, in order to stratify patients according to different expression of the disease, relating to motor severity, response to anti-parkinson medication, and the presence of non-motor features. These observations will be assessed in relation to the presence of known gene mutations linked to the condition (although these only affect a total of 5% of patients with Parkinson's disease). First degree relatives of patients with Parkinson's disease will also be studied, to determine early features of presentation, before the typical signs of tremor, stiffness and slowness develop - these include symptoms of constipation, depression, loss of sense of smell and sleep disturbance.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

The secondary objectives are to identify features that are of importance in predicting the future course of the disease in individual patients. The study will assess factors identified in a previous single centre study suggesting that early cognitive impairment of a particular type predicts significant cognitive impairment subsequently. If this can be replicated, it has important implications for the choice of anti-parkinson medication in those patients, and for the development of medication aimed at slowing progression rates and treating mild cognitive impairment.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

There is emerging evidence that Parkinson's disease is highly variable between different patients, in the symptoms,in the progression rate, and in the response to treatment. It is likely that patients with Parkinson's disease should be treated on a more targeted individual level according to which symptoms are present and based on the likelihood of future complications such as memory impairment.

The presence of gene mutations associated with Parkinson's disease has been an area of recent significant advance. However these gene mutations together are present in only around 5% of patients with Parkinson's disease. The initial clinical associations with the genetic subtypes of Parkinson's disease have given some clues as

to the variability in expression of Parkinson's disease. It is considered likely that all the more common genetic mutations have by now been described in Parkinson's disease. However there may be gene defects within subsets of Parkinson's disease patients which have not emerged from the methods used to date. For example, patients with a very good response to antiparkinson medication may have a different gene pattern to patients with Parkinson's disease who have a poor response to antiparkinson medication. Understanding the relationship between gene defects and the expression of disease is crucial in taking forward treatment approaches. One of the commonest gene mutations referred to as LRRK2 has for example led to consideration of using kinase inhibitors as an entirely new treatment approach for Parkinson's disease. Given that current drug treatments are virtually all related to the dopamine system, there is a need to open new avenues of drug treatment by understanding better the reasons why certain subtypes of Parkinson's exist.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

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
• 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
• Adverse event assessment and completion of CRF

Visit 6: 30 months
• Standard PD questionnaires and scoring
• Adverse event assessment and completion of CRF

Visit 7: 36 months
• Blood sample for serum
• Standard PD questionnaires and scoring
• Adverse event assessment and completion of CRF

L-dopa challenge test will be performed once during the study, in patients who are prescribed L-dopa based treatment. It will be performed approximately 12 months after commencing L-dopa, by scoring the UPDRS part 3 after overnight “off“, and post L-dopa

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
• Standard PD questionnaires and scoring

Visit 2: 6 months
• Standard PD questionnaires and scoring

Relatives of PD patients
Visit 1: Baseline 0 month
• 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
• Standard PD questionnaires and scoring

Visit 3: 36 months
• Update medical history
• Update medication review
• Vital signs (blood pressure and weight)
• Blood sample for serum
• Standard PD questionnaires and scoring

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [x] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
The study has been reviewed by Parkinson's UK involving the Management Board and Research Advisory Panel, both of which have lay membership. Several issues have been raised by patients and lay members about the study design and conduct which have been addressed in revision to the protocol. In addition, the study will undergo annual review by Parkinson's UK, again involving representation by patients, service users and members of the public linked to those.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

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 ≤90 years
iii. Patient 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 ≤90 years
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

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

MAIN EXCLUSION CRITERIA

A. Recent onset Parkinson's Disease patients, onset under 50 years PD 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.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4

Obtain informed consent	1		15m	Doctor and nurse
Medical history	2	2	5m	doctor / nurse
Medication History	8	8	5m	doctor / nurse
Family History recording	2	2	5m	doctor / nurse
Past Medical History	2	2	5m	doctor / nurse
Hospital anxiety and depression score	3	0	5m	patient
UPDRS scoring of Parkinson's disease	3	0	30m	doctor / nurse and patient
Cognitive testing, Mini Mental State Examination and Montreal Cognitive Assessment	2	0	10m	doctor / nurse
Environmental Exposure Questionnaire	1	0	5m	patient
PDQ-8(Quality of Life) EQ-5D	3	0	10m	patient
"On" and "Off" scoring and Global Impression of Response to Antiparkinson Medication	1	0	60m	doctor / nurse and patient
Olfactory testing	1	0	10m	patient
Sleep questionnaire (Epworth and REM sleep)	2	0	10m	patient
Non motor autonomic questionnaire	3	0	10m	patient
Impulse control questionnaires	2	0	5m	patient

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Blood sample for Parkinson's gene testing.	1	0	5m	doctor / nurse
Blood sample for serum storage for biomarkers	3	0	5m	doctor / nurse

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

36 months

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes

to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Patients - distress of considering genetic issues in Parkinson's disease, distress and uncertainty relating to genetic tests in Parkinson's disease, discomfort from blood sampling. Steps to minimise risk and burden: Patients will be informed of the issues relating to gene test for Parkinson's disease, in particular they will be given information about the lack of a clear relationship between having a positive gene test and developing the disease, e.g. there are cases of positive LRRK2 gene test who do not develop Parkinson's disease until reaching their 80's.

Relatives - Potential risks and burdens relate to gene testing in the presence of a close family member with Parkinson's disease. Patients will be given guidance about the gene test issues and the low rates of positive gene tests in family members of patients with Parkinson's disease, and the low likelihood (for most genes) of developing Parkinson's disease even if a gene test is positive.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

Patients will receive additional information about Parkinson's disease and both the patient and their carers may find benefit from increased clinical observation, to more fully understand the disease and how it is affecting them.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Patients will continue to attend their clinical team who will primarily be in charge of the research programme, allowing a point of continuity for subsequent care of their condition. Subjects who are first degree relatives will be able to access the secondary care services after the end of the study on referral of their general practitioner, and it will be encouraged that patients attend wherever possible to the team who has got to know them during the research programme, e.g. in relation to concern about developing Parkinson's disease after the end of the study period.

A26. What are the potential risks for the researchers themselves? *(if any)*

There is potential risk of needlestick injury or similar from blood sampling and the handling of the blood test specimens.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Patients - Potential participants will be identified by the direct care team supported where available by DeNDRoN research nurses. Where a local disease register or clinic listings with diagnoses are available, these will be utilised for a potential participation of subjects who will be invited to study participation by the direct care team.

Subjects - Potential participants will be identified on interview of their relative who has a diagnosis of Parkinson's disease. The patient will be asked to initiate contact to invite study participation, which can be at any one of the UK centres involved in the project depending on the subject's address.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

◉ Yes ○ No

Please give details below:
Identification of patients with Parkinson's disease will primarily be undertaken by the patient's existing clinical care team.
In addition, the PRO-DeNDRoN registry will be used,as described in A27-3.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

◉ Yes ○ No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).

Participants may obtain information from publicity through websites such as Parkinson's UK, clinicaltrials.gov where the study will be registered, and through publicity relating to the launch and running of the study, e.g. through patient self-help groups.

A contact form will be available on the PRoBaND website with the following text: "If you want to take part in PRoBaND, let us know! We like volunteers! It would help us to know which describes you.

Patient diagnosed in past 3 years
Patient diagnosed age under 50 years
Brother or sister of a person with PD (who is taking part)
Other"

The fields requested for the person to complete will be: Name, E-mail, Postcode (with an explanation "We will use this to see where your nearest centre is."), Title (of the message they are writing) and Message (body text of the message they are writing). It will be indicated at the foot of this page that the contents of the message are encrypted but may not be completely secure (as follows: "Your message will be encrypted but email is not entirely secure. Avoid adding extra personal information such as your full postal address.")

A29. How and by whom will potential participants first be approached?

Patients will first be approached by their clinical care team. This will also apply to patients initially identified by the PRO-DeNDRoN registry.
Subjects who are first degree relatives will first be approached by the patient with Parkinson's disease. An outline information sheet will be provided to patients with Parkinson's disease which they may choose to share with their first degree relatives.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Written information sheet will be provided to the patient followed by discussion regarding potential participation, involving the patient, carer or next of kin where present at the clinic visits, and by the doctor involved in the study supported by the Parkinson's or research nurse specialist, according to availability at each site.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

Patients and subjects will be given time to consider participation. In general, a minimum of one week to decide whether or not to take part in the project will be allowed. A subset of patients and relatives may choose to consent to participation sooner, for example if they would find an extra return visit an additional burden, for reasons of disability level (considering in particular patients diagnosed under 50 years, who may have advanced disease), and travelling distances. In these circumstances, and according primarily to patient/subject choice, completion of the consent process earlier (and at times on the day of initial discussion) will be allowed.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

(●) Yes
( ) No
( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Patients will be able to participate in this observational study if for example they have recently participated or might, during the course of the study, participate in a trial of medication for their Parkinson's disease or another condition.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

We do not routinely offer a translation service for clinical research.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Arrangements will be made to comply with these principles, as there are two study centres in Wales, who have experience in these issues and will implement them for participants in Wales.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Information will be communicated in the form of verbal and written updates to participants during the study. In addition there will be interim updates about the study reported in the newsletters of Parkinson's UK and other linked bodies such as the Cure Parkinson Trust. There will also be updates in the research forums, some of which are open to patients and carers.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

(●) The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

( ) The participant would continue to be included in the study.

○ Not applicable – informed consent will not be sought from any participants in this research.

Further details:

If the patient or relative loses capacity to consent during the study, they would be withdrawn with no further data or blood sampling collected or other research procedures carried out. The loss of capacity will be based in 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.

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☐ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files including X−rays
  - ☑ NHS computers
  - ☐ Home or other personal computers
  - ☐ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:

A unique study code number will be assigned to the patient. This will be recorded on locally held paper-based records and will not be computerised or transmitted at any time.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

Pseudonymised data will be collected in the study using a unique code number but the computerised records will omit personally identifiable information. The linkage of the unique code number to the patient's identifier will be retained locally on manual files rather than computer.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

The NHS R & D offices for each hospital site will have access to participants' personal data for the purposes of local

audit undertaken at each site. A description of the data handling process is provided in the patient information sheet and will form part of the consent process.

Storage and use of data after the end of the study

A43. How long will personal data be stored or accessed after the study has ended?

- (●) Less than 3 months
- ( ) 3 – 6 months
- ( ) 6 – 12 months
- ( ) 12 months – 3 years
- ( ) Over 3 years

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

(●) Yes ( ) No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
Travelling expenses will be reimbursed, following the standard rates for mileage and otherwise based on receipts for public transport expenses.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

( ) Yes (●) No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

( ) Yes (●) No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

(●) Yes ( ) No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

(●) Yes ( ) No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

(●) Yes ( ) No

Please give details, or justify if not registering the research.
The research will be registered on clinicaltrials.gov

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [x] Internal report
- [x] Conference presentation
- [x] Publication on website
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [x] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [ ] Other (please specify)

A53. Will you inform participants of the results?

(●) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
Study results will be presented at the Parkinson's UK Bi-Annual Research Conference, and through the Parkinson's UK website and newsletters.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [x] Review within a multi−centre research group
- [ ] Review within the Chief Investigator's institution or host organisation
- [ ] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The study has been peer-reviewed as part of the assessment process by Parkinson's UK. The following changes were made to reflect the suggestions of the peer review panel: Recording the results of neuroimaging (undertaken in participating subjects on clinical grounds); including an environmental questionnaire (to balance the genetic focus); The following have been considered and not adopted: a suggestion to include the collection of spinal fluid samples; this was decided against this as it is invasive and there are no specific tests relevant to the current research programme.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☐ Review by a statistician within the Chief Investigator's institution
- ☑ Review by a statistician within the research team or multi−centre group
- ☐ Review by educational supervisor
- ☐ Other review by individual with relevant statistical expertise
- ☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Yoav	Ben-Shlomo
Department	Social Medicine		
Institution	University of Bristol		
Work Address	Canynge Hall		
	38 Whatley Road		
	Bristol		
Post Code	BS8 2PS		
Telephone	01179287206		
Fax	01179287325		
Mobile			
E-mail	y.ben-shlomo@bristol.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Progression rate in motor and non-motor features of Parkinson's disease, stratified according to the presence or absence of known genetic mutations related to Parkinson's disease.

A58. What are the secondary outcome measures? *(if any)*

Relatives - Proportion of relatives testing positive for known gene mutations related to Parkinson's disease, according to the presence of gene mutations in the index case.

Proportion of patients with early manifestations of possible Parkinson's disease ("pre-motor presentation of PD"); rate of appearance and evolution of such features.

Patients - Predictability of cognitive decline related to baseline presence or absence of mild cognitive impairment. Relationship of medication response in Parkinson's disease to motor response, in particular early motor fluctuations including wearing off.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 3050

Total international sample size (including UK):

Total in European Economic Area:

Further details:
Parkinson's patients - 2240
Relatives - 860

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

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. In the 24 sites, from 2880 cases a 70% response rate will give around 2000 recent onset patients. 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. 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. We have far 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 could 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.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
First degree relatives of patients with Parkinson's disease will be invited to study participation on the basis of positive gene testing the index case, and random matching patients with negative gene tests. The ratio of negative gene test cases to positive gene test cases will be 4:1. The randomisation of the gene test negative cases will be performed independent of the study centres, who will be informed of the randomly selected cases to be invited for involvement in the study.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

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. The School of Social and Community Medicine, University of Bristol has international experts (Jonathan Sterne, Margaret May) in prognostic models in disease areas. In addition Yoav Ben-Shlomo is a co-applicant on a MRC grant on synthesizing data from diagnostic tests and therefore has access to expert methodological input from other colleagues (Penny Whiting, Roger Harbord).

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co–applicants, protocol co–authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

Title	Forename/Initials	Surname

	Professor David Burn
Post	Professor of Movement Disorder Neurology and Honorary Consultant Neurologist
Qualifications	MB, BSc, FRCP
Employer	Newcastle University
Work Address	Newcastle University Campus for Ageing and Vitality Newcastle Upon Tyne
Post Code	NE4 5PL
Telephone	01912481266
Fax	1912481251
Mobile	
Work Email	d.jburn@newcastle.ac.uk

Title	Forename/Initials	Surname
Dr	Roger	Barker

Post	University Reader in Clinical Neuroscience and Honorary Consultant in Neurology
Qualifications	BA, MBBS, MRCP, PhD
Employer	University of Cambridge
Work Address	Forvie Site Robinson Way Cambridge
Post Code	CB2 0PY
Telephone	01223331184
Fax	01233331174
Mobile	
Work Email	rab46@cam.ac.uk

Title	Forename/Initials	Surname
Professor	Yoav	Ben-Shlomo

Post	Professor in Clinical Epidemiology
Qualifications	BSc(Hons), MB BS, MSc, FFPHM, PhD, Fellow Ed.
Employer	University of Bristol
Work Address	Department of Social Medicine Canynge Hall Bristol
Post Code	BS8 2PR
Telephone	011799287206
Fax	01179287325
Mobile	
Work Email	y.ben-shlomo@bristol.ac.uk

Title	Forename/Initials	Surname
Dr	Nin	Bajaj

Post	Consultant Neurologist
Qualifications	MA, BM BCh, PhD, FRCP
Employer	Nottingham University Hospitals
Work Address	Queen's Medical Centre Campus Derby Road Nottingham

Post Code	NG3 5DX
Telephone	01559249924
Fax	01159249924
Mobile	
Work Email	nin.bajaj@nuh.nhs.uk

Title	Forename/Initials	Surname
Professor	John	Hardy

Post	Chairman
Qualifications	BSc, PhD
Employer	UCL Institute of Neurology
Work Address	Rita Lila Weston Institute Queen Square House London
Post Code	WC1N 3BG
Telephone	02078298722
Fax	02078331016
Mobile	
Work Email	j.hardy@ion.ucl.ac.uk

Title	Forename/Initials	Surname
Professor	Nicholas	Wood

Post	Galton Professor of Genetics
Qualifications	MB, ChB, PhD, FRCP
Employer	University College London
Work Address	Department of Molecular Neuroscience Queen Square London
Post Code	WC1N 3BG
Telephone	02078298756
Fax	02072785616
Mobile	
Work Email	n.wood@ion.ucl.ac.uk

Title	Forename/Initials	Surname
Dr	Huw	Morris

Post	Senior Lecturer
Qualifications	MB, BSc, PhD, FRCP
Employer	University Hospital of Wales
Work Address	Department of Neurology Heath Park Cardiff
Post Code	CF14 4XN
Telephone	02920743660
Fax	02920743660
Mobile	
Work Email	Morrishs@cf.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	NHS Greater Glasgow & Clyde
Given name	Steven
Family name	Burke
Address	Research and Development Management Office, Tennant Institute, 38 Church Street, Western Infirmary
Town/city	Glasgow
Post code	G11 6NT
Country	UNITED KINGDOM
Telephone	0141 232 9429
Fax	0141 211 2811
E-mail	steven.burke@ggc.scot.nhs.uk

Is the sponsor based outside the UK?

( ) Yes (●) No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

Please give details of funding applications.

Organisation	Parkinson's UK
Address	215 Vauxhall Bridge Road London

Post Code	SW1V 1EJ
Telephone	020 7931 8080
Fax	020 7233 9908
Mobile	
Email	hello@parkinsons.org.uk

Funding Application Status: (•) Secured ( ) In progress

Amount: £1,633,503

Duration

Years: 5

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

What type of research project is this?

(•) Standalone project

( ) Project that is part of a programme grant

( ) Project that is part of a fellowship/ personal award/ research training award

( ) Other

Other – please state:

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (•) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Dr	Steven	Burke
Organisation	Research and Development Department		
Address	1st Floor, Tennant Institute		
	Western Infirmary, 38 Church Street		
	Glasgow		
Post Code	G11 6NT		
Work Email	steven.burke@ggc.scot.nhs.uk		
Telephone	0141 232 9429		
Fax	0141 211 2811		
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/06/2011
Planned end date: 31/05/2016
Total duration:
Years: 5 Months: 0 Days: 0

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

The end of the trial will be based on the last visit of the last subject.

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☐ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 41

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

☑ NHS organisations in England	31
☑ NHS organisations in Wales	3
☑ NHS organisations in Scotland	7
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Social care organisations	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent hospitals	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	

Total UK sites in study: 41

A75-1. Will a data monitoring committee (DMC) be convened?

○ Yes ◉ No

If Yes, please forward details of the membership of the DMC, its standard operating procedures and summary reports of interim analyses to the Research Ethics Committee which gives a favourable opinion of the study (or to GTAC if applicable).

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

There are no criteria for this as the study does not involve an intervention.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (NHS sponsors only)

☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Venous blood sample for DNA testing, and for longer term storage. A whole venous blood sample will be collected at study entry for all participants and sent to the Cardiff laboratory for known gene tests for Parkinson's disease. The sample will also be used for testing for new genes related to Parkinson's disease. An additional venous whole blood sample for DNA extraction will be sent to the Genetic Support Service Department of The European Collection of Cell Cultures (ECACC). This will be used to create a cell line for further DNA extraction in future research.

Venous blood sample to derive serum for long-term storage. A venous blood sample will be collected and centrifuged to extract serum which will be sent to Cardiff for freezing and longer-term storage. This will be used for future research projects investigating potential biomarkers of the presence and severity of Parkinson's disease.

The blood samples for DNA and serum are perishable after 2 - 3 days and will therefore be posted in Safe Boxes to the two laboratory facilities, for immediate processing after which samples will be held long term in freezers.

2. Who will collect the samples?

The blood samples will be collected by the study nurses and doctors.

3. Who will the samples be removed from?

☑ Living donors
☐ The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?
◉ Yes ○ No

In future research?
◉ Yes ○ No ○ Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

○ Yes ◉ No

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*
○ Yes ◉ No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*
(●) Yes ( ) No

If Yes, say who will have access to the code and personal information about the donor.

The principal investigator at each study site will have access to the code and personal information about the donor. This information will not be identifiable to researchers in the Cardiff laboratory or in the ECACC laboratory.

In a form in which the donor could be identifiable to researchers?
( ) Yes (●) No

9. What types of test or analysis will be carried out on the samples?

All participants will be gene tested for known Parkinson's genes as follows: LRRK2 and GBA; in addition under 50's will be tested for Parkin and PINK1 which are known to be much more common in this age group. Serum will be sampled serially and DNA will be stored long-term.

Ethical questions arising from gene test analysis will be dealt with as follows.

Results of gene tests will not be made available to participating patients or subjects. This is because the clinical significance of gene test positivity is not clearly understood, even for established gene mutations linked to Parkinson's disease. For example, the presence of LRRK2 positivity, which is the commonest genetic association with Parkinson's disease, has variable penetrance such that a subject positive for LRRK2 may not develop Parkinson's disease at all in their lifetime.
The only exception will be cases where there is a very strong family history and/or very young onset of Parkinson's disease in which there is a stronger relationship between gene test positivity and the development of Parkinson's disease. In this situation, patients with Parkinson's disease will be given the option of counselling through their local services before communication of gene test results. Subjects who are relatives of Parkinson's disease patients will, however, not be given gene test results.

It is a possibility that new gene test findings of medical importance might occur in relation to the study. This is anticipated to be similar to the situation regarding gene mutations that are already known in relation to Parkinson's disease and accordingly these results would not be given to the patients or subjects participating in the study.

There is a possibility that relatives of patients who are invited to take part in the study could become aware of our study design inviting relatives of patients with positive gene test results, and thereby deduce that their families were more likely to be "gene test positive". This has been addressed by including a large control sample such that we are also inviting the relatives of gene test negative patients to participate, at a ratio of 4:1 for gene test negative to gene test positive cases. Accordingly the maximum possibility for a relative participating that they are in a family carrying a Parkinson's disease gene mutation will be 1:5.

10. Will the research involve the analysis or use of human DNA in the samples?

(●) Yes ( ) No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

( ) Yes (●) No

12. If so, will arrangements be made to notify the individuals concerned?

( ) Yes ( ) No ( ) Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

1. MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Henry Wellcome Building, Cardiff. The blood and serum samples will be stored in the MRC Centre for Neuropsychiatric Genetics and Genomics. Tests and analysis will take place in the Henry Wellcome Building, Heathpark, Cardiff. Samples will be stored in dedicated freezer space in a facility established for this purpose and which already performs this function in other disease areas in neurology and psychiatry. The data recording of the samples will follow the standardised protocol in the MRC centre. The security and confidentiality of the specimens will be undertaken by Dr. Nigel Williams at the MRC centre.

Cardiff University is a license holder under the Human Tissue Act (HTA) and the Department of Psychological Medicine and Neurology is one of the authorised sites under this license for specific research projects. The department banks human tissue such as saliva, brain, blood and fibroblast samples. As per the requirements of the HTA, all samples are stored in a computerised trackable format using the Progeny sample tracking system. Risk assessment forms, standard operating protocols and training records for staff are maintained appropriately. Ongoing review is undertaken, most recently (at the time of writing) on 28/01/2011 designated HTA officials from Cardiff University inspected and passed the department premises for compliance with HTA regulations.

Access to the samples will be allowed for the study processes within the MRC centre. For any future studies requesting access to the samples there will be an approval process by the data and sample access committee and the projects will be submitted for ethics approval before the release of any data or samples.

2. The European Collection of Cell Cultures (ECACC), Genetic Support Services, Health Protection Agency, Centre for Emergency Preparedness & Response.

Samples will be stored in the ECACC unit. This is a component of the Health Protection Agency in Porton Down, Salisbury. Access to material held in this unit will also require application to the data and sample access committee, and ethics approval of the study.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☑ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

The samples will be maintained in the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff, for the duration of the study. At the end of the research, it is planned for the samples to remain in the same unit, but be redesignated as a research tissue bank for possible further research. The MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff, has a present licence from the Human Tissue Authority and these processes are planned to be maintained for the unit. Accordingly, the longer term retention of the samples is planned to become a component of the MRC Centre for Neuropsychiatric Genetics and Genomics unit's storage function.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Research site		Investigator/ Collaborator/ Contact	
Institution name	Royal United Hospital	Title	Dr
Department name	Medicine for the Elderly	First name/ Initials	Dorothy
Street address	Combe Park	Surname	Robertson
Town/city	Bath		
Post Code	BA1 3NG		
Institution name	University of Birmingham	Title	Professor
Department name	Clinical Neurology	First name/ Initials	Carl
Street address	Westmere House, Edgbaston	Surname	Clarke
Town/city	Birmingham		
Post Code	B15 2TT		
Institution name	Birmingham City Hospital	Title	Dr
Department name	Department of Neurology	First name/ Initials	David
Street address	Dudley Road	Surname	Nicholl
Town/city	Birmingham		
Post Code	B18 7QH		
Institution name	Royal Bournemouth Hospital	Title	Dr
Department name	Medicine for the Elderly	First name/ Initials	Khaled
Street address	Castle Lane East	Surname	Amar
Town/city	Bournemouth		
Post Code	BH7 7DW		
Institution name	University of Cambridge	Title	Dr
Department name	Department of Clinical Neurosciences	First name/ Initials	Roger
Street address	12 Union Road	Surname	Barker
Town/city	Cambridge		
Post Code	CB2 1EZ		
Institution name	Gloucestershire Royal Hospital	Title	Dr
Department name	Department of Elderly Care	First name/ Initials	Peter
Street address	Great Western Road	Surname	Fletcher
Town/city	Gloucester		

Post Code	GL1 3NN

Institution name	Gloucestershire Royal Hospital	Title	Dr
Department name	Department of Neurology	First name/ Initials	Paul
Street address	Great Western Road	Surname	Morrish
Town/city	Gloucester		
Post Code	GL1 3NN		

Institution name	Royal Devon & Exeter Hospital	Title	Dr
Department name	Medicine for the Elderly	First name/ Initials	Raymond
Street address	Barrack Road, Wonford	Surname	Sheridan
Town/city	Exeter		
Post Code	EX2 5DW		

Institution name	Leicester General Hospital	Title	Dr
Department name	Medicine for the Elderly	First name/ Initials	Nelson
Street address	Gwendolen Road	Surname	Lo
Town/city	Leicester		
Post Code	LE5 4PW		

Institution name	Charing Cross Hospital	Title	Dr
Department name	West London Neuroscience Centre	First name/ Initials	Sophie
Street address	Charing Cross Hospital	Surname	Molloy
Town/city	London		
Post Code	W6 8RF		

Institution name	Imperial College London	Title	Dr
Department name	Department of Neurology	First name/ Initials	Paola
Street address	South Kensington Campus	Surname	Piccini
Town/city	London		
Post Code	SW7 2AZ		

Institution name	Kings College Hospital NHS Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Thomasin
Street address	Guy's Campus	Surname	Andrews
Town/city	London		
Post Code	SE1 1UL		

Institution name	King's College Hospital NHS Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Ray
Street address	Denmark Hill	Surname	Chaudhuri
Town/city	London		
Post Code	SE5 9RS		

Institution name	National Hospital for Neurology and Neurosurgery	Title	Dr
Department name	Neurology and Neurosurgery	First name/ Initials	Tom
Street address	Queen Square	Surname	Foltynie
Town/city	London		
Post Code	WC1N 3BG		

Institution name	UCL Institute of Neurology	Title	Dr
Department name	Department of Molecular Neuroscience	First name/ Initials	Nicholas
Street address	Queen Square	Surname	Wood
Town/city	London		
Post Code	WC1N 3BG		

Institution name	Royal Free Hospital NHS Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	James
Street address	Pond Street	Surname	Rakshi
Town/city	London		
Post Code	NW3 2QG		

Institution name	Royal Free Hospital NHS Trust	Title	Professor
Department name	Department of Neurology	First name/ Initials	Tony
Street address	Pond Street	Surname	Schapira
Town/city	London		
Post Code	NW3 2QG		

Institution name	Royal Free Hospital NHS Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Anette
Street address	Pond Street	Surname	Schrag
Town/city	London		
Post Code	NW3 2QG		

Institution name	St. George's, Tooting and Frimley Park in Surrey	Title	Dr
Department name	University of London	First name/ Initials	Jeremy
Street address	Cranmer Terrace	Surname	Stern
Town/city	London		
Post Code	SW17		

Institution name	The Walton Centre NHS Foundation Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Malcolm
Street address	Lower Lane	Surname	Steiger
Town/city	Liverpool		
Post Code	L9 7LJ		

Institution name	Salford Royal NHS Foundation Trust Hope Hospital	Title	Dr

Department name	Department of Neurology	First name/ Initials	Monty
Street address	Stott Lane	Surname	Silverdale
Town/city	Manchester		
Post Code	M6 8HD		

Institution name	Milton Keynes Hospital NHS Foundation Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Michelle
Street address	Standing Way, Eaglestone, Milton Ke	Surname	Hu
Town/city	Buckinghamshire		
Post Code	MK6 5LD		

Institution name	Newcastle-Upon-Tyne NHS Hospitals Trust	Title	Professor
Department name	Clinical Ageing Research Unit	First name/ Initials	David
Street address	Newcastle University	Surname	Burn
Town/city	Newcastle-Upon-Tyne		
Post Code	NE4 5PL		

Institution name	Northumbria Healthcare NHS Foundation Trust	Title	Dr
Department name	Department of Elderly Medicine	First name/ Initials	Richard
Street address	Rake Lane	Surname	Walker
Town/city	North Shields		
Post Code	NE29 8NH		

Institution name	Norfolk & Norwich University Hospital NHS Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Paul
Street address	Old Watton Road	Surname	Worth
Town/city	Norfolk		
Post Code	NR4 7TD		

Institution name	Guys and St. Thomas'NHS Trust	Title	Dr
Department name	Department of Elderly Care Medicine	First name/ Initials	Finbarr
Street address	Lambeth Palace Road	Surname	Martin
Town/city	City of London		
Post Code	SE17EH		

Institution name	University of Sheffield	Title	Dr
Department name	Academic Neurology Unit, Department of Science	First name/ Initials	Oliver
Street address	385A Glossop Road	Surname	Bandmann
Town/city	Sheffield		
Post Code	S10 2HQ		

Institution name	Southampton University	Title	Dr
Department name	Department of Geriatric Medicine	First name/ Initials	Helen
Street address	University Road		

Town/city	Southampton	Surname	Roberts
Post Code	SO17 1BJ		

Institution name	Part of Brighton and Sussex University Hospitals NHS Trust	Title	Dr
Department name	Department of Medicine for the Elderly	First name/ Initials	Martin
Street address	Lewes Road, Hayworth Heath	Surname	Jones
Town/city	West Sussex		
Post Code	RH16 4EX		

Institution name	Brighton and Sussex University Hospitals	Title	Dr
Department name	Department of Neurology	First name/ Initials	Dennis
Street address	Eastern Road	Surname	Chan
Town/city	Brighton		
Post Code	BN2 5BE		

Institution name	Western General Hospitals NHS Trust Edinburgh	Title	Dr
Department name	Department of Neurology	First name/ Initials	Richard
Street address	Crewe Road South	Surname	Davenport
Town/city	Edinburgh		
Post Code	EH4 2XU		

Institution name	Greater Glasgow and Clyde NHS Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Donald
Street address	1345 Govan Road	Surname	Grosset
Town/city	Glasgow		
Post Code	G51 4TF		

Institution name	Greater Glasgow and Clyde NHS Trust	Title	Dr
Department name	Department of Medicine for the Elderly	First name/ Initials	Graeme
Street address	1345 Govan Road	Surname	Macphee
Town/city	Glasgow		
Post Code	G51 4TF		

Institution name	Greater Glasgow and Clyde NHS Trust	Title	Dr
Department name	Department of Medicine for the Elderly	First name/ Initials	David
Street address	Langside Road	Surname	Stewart
Town/city	Glasgow		
Post Code	G42 9TY		

Institution name	Tayside University Hospitals NHS Trust	Title	Dr
Department name	Department of Neurology	First name/ Initials	Ian
Street address	Taymount Terrace	Surname	Lightbody
Town/city	Perth		
Post Code	PH1 1NX		

Institution name	University of Aberdeen	Title	Dr
Department name	Division of Applied Health Sciences	First name/ Initials	Carl
Street address	Foresterhill	Surname	Counsell
Town/city	Aberdeen		
Post Code	AB25 2ZD		

Institution name	NHS Tayside Acute Services Division	Title	Dr
Department name	Clinical Neurosciences, Department of Neurology	First name/ Initials	Rob
Street address	Ninewells Road	Surname	Swingler
Town/city	Dundee		
Post Code	DD1 9SY		

Institution name	Betsi Cadwaladr University Health Board	Title	Dr.
Department name	Department of Neurology	First name/ Initials	Huw
Street address	Hospital Road	Surname	Morris
Town/city	Llandudno		
Post Code	LL30 1LB		

Institution name	County Durham and Darlington NHS Foundation Trust	Title	Dr
Department name	Pierremont Unit, Medicine for the Elderly	First name/ Initials	Peter
Street address	Hollyhurst Road	Surname	Carr
Town/city	Darlington		
Post Code	DL3 6HX		

Institution name	County Durham and Darlington NHS Foundation Trust	Title	Dr
Department name	Medicine for the Elderly	First name/ Initials	Richard
Street address	Hollyhurst Road	Surname	Prescott
Town/city	Co Durham		
Post Code	DL3 6HX		

Institution name	South Teeside Hospitals NHS Foundation Trust	Title	Dr
Department name	Medicine for the Elderly	First name/ Initials	Debbie
Street address	Marton Road	Surname	Bathgate
Town/city	Middlesbrough		
Post Code	TS4 3BW		

Institution name	Northumbria Healthcare NHS Foundation Trust	Title	Dr
Department name	Medicine for the Elderly	First name/ Initials	Brian
Street address	Wansbeck Hospital, Woodhorn Lane	Surname	Wood
Town/city	Ashington		
Post Code	NE63 9JJ		

Institution name	North Wales NHS Trust	Title	Dr
Department name	Care of the Elderly	First name/ Initials	John
Street address	Llandudno Hospital	Surname	Hindle
Town/city	Llandudno		
Post Code	LL301LB		

Institution name	Hurstwood Park Neurological Centre	Title	Dr
Department name	Neurological Centre	First name/ Initials	Adam
Street address	Lewes Road, Haywards Health	Surname	Harper
Town/city	West Sussex		
Post Code	RH164EX		

Institution name	University College London, National Hospital for Neurology and Neurosurgery	Title	Dr
Department name	Department of Neurology and Neurosurgery	First name/ Initials	Andrew
Street address	Queen Square	Surname	Lees
Town/city	London		
Post Code	WC1N 3BG		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the main REC or the GTAC (as applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the main REC, in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs.
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- [x] Chief Investigator
- [ ] Sponsor
- [ ] Study co-ordinator
- [ ] Student
- [ ] Other – please give details
- [ ] None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

- [ ] I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name:

Date: *(dd/mm/yyyy)*

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Signature: .....

Print Name:

Post:

Organisation:

Date: *(dd/mm/yyyy)*