Contact details

PD GEN Sample Storage
Professor K Morrison, Molecular Neurology Laboratory, The Medical School, University of Birmingham, Birmingham, B15 2TT
Tel: 0121 414 3943 e-mail: k.morrison@bham.ac.uk

PD MED Trial and PD GEN Trial Co ordination
Dr C. Rick, University of Birmingham Clinical Trials Unit, Robert Aitken Institute, Edgbaston, Birmingham, B15 2TT
Tel: 0121 415 9129 e-mail: c.e.rick@bham.ac.uk

PD GEN Organisation
Professor C E Clarke, Department of Neurology, City Hospital, Birmingham, B18 7QH
Tel: 0121 507 4073 e-mail: c.e.clarke@bham.ac.uk
Contents

CONTENTS .................................................................................................................................................. 2

BACKGROUND ........................................................................................................................................ 3

PARKINSON’S DISEASE ............................................................................................................................. 3
THE CASE FOR GENETIC RESEARCH ........................................................................................................ 3
POTENTIAL GENETIC STUDIES USING A PARKINSON’S DISEASE DNA BANK ........................................ 4
THE PRESENT NEED FOR THE COLLECTION ........................................................................................... 5

OBJECTIVES ............................................................................................................................................... 6

METHODS .................................................................................................................................................. 6

PATIENTS .................................................................................................................................................. 6
CONSENT, ETHICS AND CONFIDENTIALITY ............................................................................................... 8
DNA EXTRACTION ..................................................................................................................................... 9
DATA STORAGE ......................................................................................................................................... 9
FEEDBACK TO CLINICIANS ..................................................................................................................... 9
MANAGEMENT COMMITTEE AND ACCESS TO SAMPLES ......................................................................... 9

REFERENCES ............................................................................................................................................. 10

APPENDIX 1 PATIENT INFORMATION SHEET .......................................................................................... 11
APPENDIX 2 PATIENT CONSENT FORM .................................................................................................. 14
APPENDIX 3 CARER INFORMATION SHEET .............................................................................................. 15
APPENDIX 4 CARER CONSENT FORM .................................................................................................... 18
APPENDIX 5 PATIENT INVITATION LETTER ............................................................................................ 19
APPENDIX 6 CARER INVITATION LETTER ............................................................................................... 20
APPENDIX 7 PD GEN SUPPLEMENTARY QUESTIONNAIRE .................................................................... 21
APPENDIX 8 GENERAL PRACTITIONER INVITATION LETTER ................................................................. 24
APPENDIX 9 GENERIC PATIENT AND CARER SECOND LETTER ............................................................. 25
APPENDIX 10 GENERIC PATIENT INVITATION LETTER FROM TRIAL SITE ............................................ 26
APPENDIX 11 GENERIC CARER INVITATION LETTER FROM TRIAL SITE ............................................... 27
Background

Parkinson’s disease

Parkinson’s disease (PD) affects around 100,000 patients in the United Kingdom and is the most common neurodegenerative condition after Alzheimer’s disease. With an exponential rise in its prevalence with age, the ageing of the UK population over the next 20 years will significantly increase the burden of this neuro-degenerative condition. The prevalence of PD of 100,000 compares with around 100,000 hospital admissions with stroke in the UK each year, although this figure will fall for stroke with better primary and secondary prevention. Therapy for PD remains symptomatic with no agent proven to slow the progression of the disease. As a result, patients continue to die in excess of their peers.

The case for genetic research

The aetiology of PD is unknown. Family studies continue to suggest a strong genetic component with the possibility of autosomal dominant inheritance with incomplete penetrance. Twin studies have been hampered by the short duration of follow-up of the potentially affected co-twin and thus have given variable results. The latest US Veterans Administration Twin Study confirms a strong genetic component with age of onset of the disease below 50 years and a follow-up PET study in twins suggested a concordance rate of dopaminergic dysfunction of 75% in monozygotic twins compared to 22% in dizygotic twins suggesting a significant genetic component in nigrostriatal dopaminergic dysfunction.

An increasing number of monogenic forms of PD have been identified in large kindreds (Table 1). However, most PD is not familial but sporadic and genetic defects such as those in α synuclein and LRRK 2 are only rarely seen in sporadic disease. Thus, most work to date on genetic factors in PD has focussed on studies of genetic markers hypothesised to predispose susceptibility to the disease. Such genetic association studies have, to date, failed to produce replicable results, thus there is a clear role for well-conducted association studies in a large well-characterised heterogenous PD population with appropriately matched controls. Large randomised controlled trials such as PD MED, PD REHAB, PD SURG and PD COMM will also enable pharmacogenetic association studies to be performed to study susceptibility genotypes affecting disease progression, development of motor fluctuations, dyskinesias, dementia, and mortality. Such studies will be able to be increasingly readily performed with the development of SNP (single nucleotide polymorphism) maps.
### Table 1. Identified gene loci in Parkinson's disease

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chromosomal location</th>
<th>Inheritance</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1</td>
<td>4q21</td>
<td>AD</td>
<td>α synuclein</td>
</tr>
<tr>
<td>PARK2</td>
<td>6q25.2-27</td>
<td>AR</td>
<td>Parkin</td>
</tr>
<tr>
<td>PARK3</td>
<td>2p13</td>
<td>AD</td>
<td>?</td>
</tr>
<tr>
<td>PARK4</td>
<td>4q21</td>
<td>AD</td>
<td>α synuclein</td>
</tr>
<tr>
<td>PARK5</td>
<td>4p14</td>
<td>AD</td>
<td>UCH-L1</td>
</tr>
<tr>
<td>PARK6</td>
<td>1p36</td>
<td>AR</td>
<td>PINK1</td>
</tr>
<tr>
<td>PARK7</td>
<td>1p36</td>
<td>AR</td>
<td>DJ-1</td>
</tr>
<tr>
<td>PARK8</td>
<td>12p11.2-13.1</td>
<td>AD</td>
<td>LRRK2</td>
</tr>
<tr>
<td>PARK9</td>
<td>1p36</td>
<td>AR</td>
<td>?</td>
</tr>
<tr>
<td>GBA</td>
<td>1q21</td>
<td>Susceptibility factor</td>
<td>Glucocerebrosidase</td>
</tr>
</tbody>
</table>

AD - autosomal dominant, AR – autosomal recessive, FTDP – frontotemporal dementia and parkinsonism, UCH-L1 – Ubiquitin hydrolase L1

---

### Potential genetic studies using a Parkinson's Disease DNA Bank

The creation of a Parkinson's Disease DNA Bank will allow a considerable number of novel research projects to be performed which will have significant implications regarding the understanding of the disease and its treatment. Some of the potential studies include:

1. **Susceptibility genotyping studies** The pathogenesis of the majority of cases of sporadic PD is believed to be multifactorial, but certain genes may confer increased susceptibility to the condition. Examples include the apolipoprotein ε4 allele and a recently identified mutation in the promoter of α synuclein. The size of the PD MED study will enable large association studies of sufficient power to be performed which will enable more definitive analysis of candidate loci such as CYP2D6, where previous smaller studies have given inconclusive results.

2. **Pharmacogenomic studies** Pharmacogenomic studies will enable genotype-phenotype correlations with drug response in the PD MED trial. Such studies may help identify genetic variation in genes involved in the metabolism and pharmacology of anti-parkinsonian drugs, as well as genes involved in generating an oxidative response and mitochondrial uncoupling. Examples of these include: catechol-O-methyltransferase, monoamine oxidase B, N-acetyltransferase (NAT 1 and 2), glutathione S-transferase (GSTT 1, M1, M3, P1) and members of the cytochrome P450 super-family. Similarly, the ability to remain on dopamine agonist monotherapy in early disease without adverse events may be predictable genetically. If so, then it may be possible to target the more expensive agonist therapy only to those who will benefit.
3. **Genotype-phenotype association studies** There may be genetic markers for the dementia, depression, and psychosis seen in some patients with PD which could inform better therapeutic decisions. The PD GEN DNA collection will also allow study of genetic predictors of the rate of disease progression and the incidence of levodopa-induced motor complications (i.e. dyskinesias and motor fluctuations) in relation to the medication to which patients are randomised (e.g. polymorphism in the DRD2 gene).16

4. **Studies in atypical Parkinsonian syndromes** Although PD MED will recruit only patients who clinically have idiopathic PD, the error rate in this diagnosis is up to 24%.17 We will inevitably collect DNA from patients with alternative diagnoses such as Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA). This will allow studies of genetic aspects of these conditions and link with the work of the European Study Group on Atypical Parkinsonism (ESGAP) which will include examining the genetic basis of the tau haplotype in PSP.18,19 This type of work will also link in with the large epidemiological study underway in Newcastle under the auspices of Dr D Burn.

5. **Known Parkinsonian loci** Although the majority of Mendelian forms of PD are exceedingly rare, recent work has identified that mutations in the parkin gene are responsible for up to 77% of cases of juvenile PD, and have a much broader phenotype and age of presentation than previously thought.20 The DNA bank would enable prevalence studies to be performed on parkin and other, as yet unidentified, Mendelian forms of PD to establish whether they have a wider role in sporadic PD in a large population of patients and controls. We may then be able to better characterise PD patients by genotype rather than phenotype.

6. **Gene-environment interactions** The PD MED genetic database will enable the performance of complex gene-environment studies, such as interactions between smoking use and susceptibility to PD.21,22

7. **Familial PD studies** The PD MED study will enable the recruitment of further PD families as part of the ongoing European Consortium on Genetic Susceptibility in Parkinson’s disease collaboration.23

*The present need for the collection*

The collection will have immediate use as part of existing collaborations such as the European Consortium on Genetic Susceptibility in Parkinson’s disease (Dr NW Wood) and the European Study Group on Atypical Parkinsonism (ESGAP; Dr D Nicholl & Professor AC Williams).6 In addition, the collection will have a direct wider relevance to the global PD genetics research community.
Objectives

- To develop a Birmingham-based DNA bank from patients with PD and controls using samples from large pragmatic randomised controlled trials (RCT) such as PD MED, PD REHAB, PD SURG and PD COMM.

- To distribute these samples to approved researchers working in the field.

Methods

Patients

Patients for the Parkinson's Disease DNA Bank will be recruited from the PD MED trial which commenced in Autumn 2000. Patients will also be recruited from a smaller trial of surgical intervention in the disease (PD SURG) and a trial examining the effectiveness of combined occupational and physiotherapy (PD REHAB) as well as the pilot trial examining the effectiveness and cost effectiveness of Lee Silverman voice training versus Standard NHS speech and language therapy versus no therapy (PD COMM). As a result, the rate of recruitment to the Bank will be governed by recruitment to the trials from multiple centres across the UK.

We estimate that around 8,000 new cases of PD are diagnosed each year in the UK. If around 8% of these enter PD MED then a total of 2,500 patients can be recruited over 4 years. In addition, around 1,500 patients with more advanced disease requiring adjuvant therapy will be randomised in the trial from the pool of 100,000 in the population. Table 2 summarises likely recruitment to the DNA Bank.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of patient</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD MED</td>
<td>Monotherapy</td>
<td>2,500</td>
<td>2,000</td>
<td>4,500</td>
</tr>
<tr>
<td>PD MED</td>
<td>Adjuvant therapy</td>
<td>1,500</td>
<td>1,200</td>
<td>2,700</td>
</tr>
<tr>
<td>PD SURG</td>
<td>Advanced</td>
<td>500</td>
<td>400</td>
<td>900</td>
</tr>
<tr>
<td>PD REHAB</td>
<td>Variable</td>
<td>750</td>
<td>600</td>
<td>1,350</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>5,250</strong></td>
<td><strong>4,200</strong></td>
<td><strong>9,450</strong></td>
</tr>
</tbody>
</table>

The designs of the trials are summarised below:-

PD MED Trial

This is a large pragmatic multicentre randomised control trial based in the University of Birmingham Clinical Trials Unit (BCTU) and funded by the NHS Research and Development Programme with approximately £940,000. The Trial has two sections:-

1. 1,500 – 3,000 patients with early and previously untreated PD will be randomised to receive treatment with levodopa, any dopamine agonist or any selegiline preparation.

2. 1,000 – 2,000 patients with PD who have developed levodopa-induced motor complications will be randomised to receive treatment with any dopamine agonist, any selegiline preparation or any COMT inhibitor (presently only entacapone licensed).
The 2-fold variation in patient numbers reflects the minimum number needed to achieve adequate statistical power and an upper target which would improve the power of the study and allow more reliable subgroup analysis.

The main outcome measures will be quality of life (PDQ-39 and EuroQol EQ-5D), the development of motor complications (monotherapy group), health economics assessment, and mortality. The latter will be monitored in the early disease patients in view of the debate concerning selegiline and the possibility that dopamine agonists and selegiline may be neuro-protective.

Patients will be followed for at least 5 years but an independent Data Monitoring Committee will evaluate the data as it becomes available on an annual basis.

Adding the DNA banking project and the associated demographic acquisition to this large trial at such an early stage will be simple and relatively inexpensive.

**PD SURG Trial**

This trial, funded by the MRC and the UK Parkinson's Disease Society, will compare any form of subthalamic surgery with deferred surgery in later Parkinson's disease. It will recruit around 500 patients. The main outcome measures in this trial will be quality of life (PDQ-39 and EuroQol EQ-5D), health economics, and Unified Parkinson's Disease Rating Scale (UPDRS). Follow up will be for 10 years. Both the patients and their carers in this study will be asked to join PD GEN.

**PD REHAB Trial**

This trial, funded by the HTA, will compare the effectiveness and cost-effectiveness of combined occupational and physiotherapy for participants whose PD is affecting their activities of daily living. It will recruit up to 750 participants and their carers. The main outcome measures will be quality of life (as measured by the Nottingham extended activities of daily living index, PDQ-39 and EQ-5D scales), resource usage will also be assessed. Follow up will be for 15 months.

**PD COMM Trial**

The PD COMM randomised controlled clinical trial (including a pilot study) which will compare the effectiveness and cost effectiveness of NHS Speech and Language therapy versus Lee Silverman Voice Training versus no therapy for participants whose PD is affecting their speech. Both participants and their carers in this study will be asked to join PD GEN.

The diagnostic criteria for idiopathic Parkinson's disease used in PD MED, PD REHAB, PD SURG and PD COMM are the standard Parkinson's Disease Society Brain Research Centre criteria. Inclusion is otherwise based on the uncertainty principle in all trials. With these ‘real life’ trials, there will be few exclusion criteria other than inability to give written informed consent and dementia. The resulting heterogeneity of the study population will mean the conclusions are more generalisable than in previous trials.
Consent, ethics and confidentiality

After randomisation in the PD MED, PD REHAB, PD SURG or PD COMM trials, patients will be informed about PD GEN by the clinician. They will then be given an information sheet to consider before giving written consent to enter PD GEN (see Appendices 1 & 2 for Patient Information Sheet and Consent Form). Through the patients, we will also approach their carers to act as controls (see Appendices 3 & 4 for Carer Information Sheet and Consent Form).

Some units will find it difficult to assist with PD GEN because of time constraints. In these centres, with the investigator’s permission, we will approach patients directly to volunteer for PD GEN. The patients will be sent an invitation letter (Appendix 5) along with an invitation letter to their carer (Appendix 6), if they have one, the standard information sheets and a stamped addressed envelope. If they wish to participate in the study, they will be asked to return the invitation letters with the preliminary consent slip signed. A duplicate copy of the letter will be kept by the patient/carer. The Molecular Neurology Laboratory will then send to the patient, and carer if appropriate, an envelope containing a consent form, the epidemiology questionnaire (Appendix 7), sealed packs containing sample tubes and phlebotomy equipment and an explanatory letter for the patient’s general practitioner (GP; Appendix 8). They will be asked in a covering letter (Appendix 9) to sign the consent form, complete the epidemiology questionnaire, ask their GP or one of their nursing staff to take the blood samples and then return all material to the Molecular Neurology Laboratory. This method of collecting genetic samples through GPs has been used successfully in several large cancer studies in the past and preliminary enquiries with local GPs has indicated their willingness to help with this type of work.

Other units may also find it difficult to assist with PD GEN because of the lack of nurse or research nurse support within the clinicians’ busy clinics. In these centres with the principal investigator’s permission, the units will approach the participant directly by an invitation letter to the patient (Appendix 10) along with an invitation letter to their carer (Appendix 11). If the patient indicates that they are interested in participation in the PD GEN DNA bank, the site will then contact them directly by phone to arrange a suitable appointment and then follow the usual directed procedures at the given appointment.

To preserve patient confidentiality, clinical data from consenting patients and carers will be stored at the Birmingham Clinical Trials Unit. The DNA will be stored in the Molecular Neurology Laboratory of the University of Birmingham. These two buildings are geographically separate and procedures will be adopted to maintain the anonymity of the samples in each location but also to maintain a link to the demographic and outcome data when required via the patient’s trial reference number.

Information about the results of studies performed with material from the Bank will be fed back to patients and carers in the form of scientific publications, clinical meetings, and Parkinson's Disease Society publications. We will not automatically provide patients or carers with their own individual results because single genetic test results may have no useful value to them. However, if a patient or carer makes a subject access request under the Data Protection Act 1998 or any subsequent legislation the information will be supplied in accordance with the statutory provision. In order to provide the required genetic counselling to understand the result concerned, the PD GEN Management Committee will then ensure that the patient is referred to their local clinical genetics department, together with the appropriate data requested. The appropriate statutory fee operating at this time will be payable to the University of Birmingham for this service.
**DNA extraction**

Blood collection packs and packaging (conforming to new UN602 regulations), demographic data acquisition forms, information sheets and consent forms will be posted to participating clinicians before the recruitment of patients to the study. Samples (20 ml of blood in EDTA tubes) will be returned by first class post to the Molecular Neurology Laboratory, The Medical School, University of Birmingham, where they will be coded and anonymised. DNA will be extracted by standard techniques using Nucleon II (Scotlab) DNA Extraction Kits which are reliable, efficient, and cost-effective and give an estimated yield of 400 $\mu$g of DNA per 10 ml blood sample. DNA will be stored at -70°C pending use in research projects.

**Data storage**

Additional data will be recorded by those patients and carers choosing to donate to the Parkinson's disease DNA Bank (Appendix 7). This will include documentation of: any family history of PD, other movement disorders, or dementia; smoking history; ethnicity; well water exposure and rural living; their present and previous occupations; concomitant medical conditions; exposure to potential toxic chemicals and pesticides; and other relevant environmental factors.

**Feedback to clinicians**

We believe it is of crucial importance that work done on individual genes by remote laboratories is recorded centrally and made available to other groups in the future to assess gene-gene interactions. Some limited information on environmental exposure will also be collected to examine gene-environment interactions (Appendix 7). This will be co-ordinated in the BCTU with the advice of Professor Morrison.

**Management committee and access to samples**

Access to the samples for both academic and commercial researchers will be vetted by a Management Committee. This will be appointed by the University of Birmingham acting in the capacity of ‘owners’ of the samples. It is noted that the Medical Research Council (MRC) may develop regionally based laboratories to store the samples from this and other similar DNA Banks. If the PD GEN DNA collection is to moved to a central laboratory, this will be the subject of discussion between the University of Birmingham, the MRC and West Midlands Regional Ethics Committee.

The Management Committee will consist of:-

1. Professor Carl Clarke, Professor of Clinical Neurology, University of Birmingham and grant holder (Chair)
2. Professor Karen Morrison, Professor of Neurology, University of Birmingham
3. Professor Keith Wheatley, Professor of Medical Statistics, University of Birmingham
4. Doctor Caroline Rick, Neurosciences Trials Team Leader, University of Birmingham

The Committee will judge the scientific merit of the proposed work and if necessary arrange for further external peer review. All proposals must undergo scrutiny by the West Midlands Regional Ethics Committee before final approval by the Management Committee.

If more than one group contacts the Committee about the same or similar research programmes, they will be encouraged to collaborate on the work. Any researcher to whom we release the samples will have exclusive rights to study that specific topic for one year. Thereafter, this exclusive right
will be subject to annual review by the Management Committee, pending the approval of a written report from the investigators.

If approved, samples will be prepared and sent to the investigators at their own expense. Before the release of the samples, investigators must agree to destroy or return all surplus material and to provide the Committee with the results of their work either as a formal report or a published paper. The Committee will ensure that information released to other investigators regarding the patients will not jeopardise the reporting of the primary PD MED, PD REHAB, PD SURG & PD COMM studies.

References

Appendix 1 Patient Information Sheet

Invitation to join the national Parkinson’s Disease DNA Bank

In collaboration with this hospital and Health Trust
For further information please contact:
Dr                                      Telephone No
Nurse                                  Telephone No

You are being invited to take part in a large national research study called the Parkinson's Disease DNA Bank. This is an additional part of the PD MED, PD REHAB, PD SURG and PD COMM studies, one of which you have already agreed to take part in.

You do not have to take part in the Parkinson's Disease DNA Bank. If you choose not to, you do not have to give a reason and this will not affect the standard of care that you receive. Before you decide, it is important for you to understand why the study is being done and what it involves. Please take time to read the following information carefully and discuss it with your family, friends or your GP if you wish.

What is the Parkinson’s Disease DNA Bank?

This is a collection of blood samples from patients with Parkinson's disease and their carers who have already agreed to help by joining the PD MED, PD REHAB, PD SURG or PD COMM Trials. DNA is the material in our genes that determines our genetic makeup. It can be extracted from a small blood sample. The DNA will be kept securely in the Molecular Neurology Laboratory in the University of Birmingham in the UK. The samples will be kept indefinitely. Small amounts of everyone’s sample will be sent to other laboratories to perform medical research. This research will look at DNA sequences in many different genes to see which are important in causing Parkinson's disease and the complications of its treatment. Other genetic research may become possible on the samples in the future.

Before any of the DNA Bank samples are released to other researchers, all research projects will be approved by a management committee after considering the scientific merit of the project and its ethics. The proposed research work will also undergo evaluation by an independent medical ethics committee. Research requests to work on these samples may come from individual researchers, groups or commercial organisations.

It may be necessary to use information from your medical records for the study but this will be done in the strictest of confidence by responsible people from the Parkinson's Disease DNA Bank study team or from other organisations involved in the research.

Why have I been invited?

As someone who has agreed to help with the PD MED, PD REHAB, PD SURG or PD COMM Trials, you are eligible to join this additional study if you choose to do so.

What is involved in the Parkinson’s Disease DNA Bank?

You will be asked to supply some additional information about your family and occupational background. A small blood sample (20 ml = 4 teaspoons) will then be taken from a vein in your arm.

Are there any medical risks in taking part in this study?

Taking the blood sample may be a little painful and may result in short-lived bruising.

Are there any benefits for me from taking part in the study?

Not directly. These samples will allow new research into Parkinson's disease which would otherwise not have been possible. From the legal point of view, this sample will be taken as a gift. You will not have any legal right to share any profits that might arise from research using the sample.

Do I have to take part in the study?
No, you do not have to take part in the study, or give a reason if you choose not to. Before deciding, you should read this leaflet carefully and ask your doctor questions if there are things that you do not understand. If you do decide to take part, we will ask you to sign a consent form indicating that you understand what the study involves. Your hospital doctor will then enter you into the study.

Can I withdraw from the study?

Yes, you can decide to withdraw from the study at any time. Signing the consent form does not commit you to joining the study and withdrawal will not affect the standard of care that you receive in the future. If you withdraw from the study, the stored sample will be destroyed along with any information we have collected.

Will participation in the study affect my legal rights?

No. Whether or not you take part, you will retain the same legal rights as any other patient treated by the NHS. There are no special arrangements for compensation in the very unlikely event of a mishap as a result of taking part in the study.

All information collected in the study will remain strictly confidential in the same way as your other medical records. The information will be put into a computer and analysed, but you will not be identified when the results are reported.

What will happen to the results of the study?

Both the samples and any information about you will be kept confidential at all times. The overall results of the research will be publicised in the medical press and elsewhere. Individuals taking part will not be identified in the results.

We will not automatically provide you with your own results because individual genetic test results may have no useful value to you. However, if you want the result of a particular genetic test, you may apply for this to the specialist who normally cares for you. In order to provide the required genetic counselling to understand the result concerned, your specialist will refer you to your local clinical genetics department. The consultant clinical geneticist will then apply to the University of Birmingham who will arrange via the PD GEN Management Committee and any research laboratory involved in the work for the result to be passed back to you in appropriate terms. The standard fee operating at the time will be payable for this service.

Who is organising and funding the study?

The central study organiser is the University of Birmingham Clinical Trials Unit, which has experience of running very large trials. The study was initially funded by the Medical Research Council. Subsequently we have obtained funding from Parkinson’s UK, the National Institute for Health Research (NIHR), University Hospitals Birmingham Charities and the Midlands Neurosciences Teaching and Research Fund. The doctors involved are not being paid for recruiting patients into the study. The study has also been reviewed by regional and local research ethics committees.

Do you have any other questions?

We hope that you will choose to take part in the Parkinson’s Disease DNA Bank. If you still have questions about the study now or later feel free to ask your hospital doctor or nurse. Their names and telephone numbers are given at the front of the sheet. If you would prefer to delay your decision, perhaps to discuss with friends or relatives, then you can make an appointment to come back later. But, please remember to keep this information sheet in a safe place and write the names and telephone numbers in your diary or address book.

Thank you for taking the time to consider taking part in this study.

What if my first language is not English?
If your first language is not English, we will obtain an interpreter so that the study can be fully explained to you.
Study Coordination: Neurosciences Trial Office, University of Birmingham Clinical Trials Unit, Robert Aitken Institute, Edgbaston, Birmingham B15 2TT. Tel 0121 415 9129. Contact Professor Karen Morrison, 0121 414 3943. e-mail k.morrison@bham.ac.uk

Version 7 Dated 27/01/2012
Appendix 2 Patient Consent Form

Parkinson’s Disease DNA Bank
In collaboration with this Hospital and Health Trust

For further information please contact:

Please initial box each box

Dr                                      Telephone No
Nurse                                    Telephone No

1. I have read the Patient Information Sheet on this project (version 7, dated 27/01/2012) and have been given a copy to keep. I have had the opportunity to ask questions about the project and understand why the research is being done and any foreseeable risks involved.

2. I agree to give a sample of blood for research in this project. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without giving a reason and without my medical treatment or legal rights being affected. I understand that the study is aimed at understanding the genetic influences in Parkinson's disease, but that the results will not have any implications for me personally.

3. I give permission for my medical records to be looked at and information taken from them to be analysed in strict confidence by responsible people from the Parkinson's Disease DNA Bank study team or from other organisations involved in the research.

4. I understand that the information may be kept indefinitely.

5. I understand that the results of any research will be published in medical journals and other publications but that I will not be identified.

6. I understand that I will not financially benefit if this research leads to the development of a new treatment or medical test.

7. I know how to contact the research team if I need to.

………………………………………  ………………  …………………
Name of patient (CAPITALS)    Date    Signature

………………………………………  ………………  …………………
Name of researcher    Date    Signature

Study Coordination: Neurosciences Office, University of Birmingham Clinical Trials Unit, Robert Aitken Institute, Edgbaston, Birmingham B15 2TT, Tel 0121 415 9129. Contact Professor Karen Morrison, 0121 414 3943. e-mail: k.morrison@bham.ac.uk

1 copy for patient; 1 copy for BCTU; original for hospital/GP notes
Version 7 Dated 27/01/2012
Appendix 3 Carer Information Sheet

Invitation to join the national Parkinson’s Disease DNA Bank
In collaboration with this Hospital and Health Trust

For further information please contact:
Dr
Tel:

Nurse
Tel:

You are being invited to take part in a large national research study called the Parkinson's Disease DNA Bank. This is an additional part of the PD MED, PD REHAB, PD SURG and PD COMM studies one of which your relative or friend with Parkinson's disease has already agreed to take part in.

You do not have to take part in the Parkinson's Disease DNA Bank. If you choose not to, you do not have to give a reason and this will not affect the standard of care that the person you care for receives. Before you decide, it is important for you to understand why the study is being done and what it involves. Please take time to read the following information carefully and discuss it with your family, friends or your GP if you wish.

What is the Parkinson’s Disease DNA Bank?

This is a collection of blood samples from patients with Parkinson's disease and their carers who have already agreed to help with the PD MED, PD REHAB, PD SURG or PD COMM Trials. DNA is the material in our genes that determines our genetic makeup. It can be extracted from a small blood sample. The DNA will be kept securely in the Molecular Neurology Laboratory in the University of Birmingham in the UK. The samples will be kept indefinitely. Small amounts of everyone’s sample will be sent to other laboratories to perform medical research. This research will look at DNA sequences in many different genes to see which are important in causing Parkinson's disease and the complications of its treatment. This research relies crucially on identifying differences in the DNA sequences in people with Parkinson's disease compared to people without the disease, hence the need for blood samples from individuals without the disease for this work.

Before any of the DNA Bank samples are released to other researchers, all research projects will be approved by a management committee after considering the scientific merit of the project and its ethics. The proposed research work will also undergo evaluation by an independent medical ethics committee. Research requests to work on these samples may come from individual researchers, groups or commercial organisations.

Why have I been invited?

As someone who has agreed to help with the PD MED, PD REHAB, PD SURG or PD COMM Trial, you are eligible to join this additional study if you choose to do so.

What is involved in the Parkinson’s Disease DNA Bank?

You will be asked to supply some additional information about your family and occupational background. A small blood sample (20 ml = 4 teaspoons) will then be taken from a vein in your arm.

Are there any medical risks in taking part in this study?

Taking the blood sample may be a little painful and may result in short-lived bruising.

Are there any benefits for me from taking part in the study?

Not directly. These samples will allow new research into Parkinson's disease which would otherwise not have been possible. Samples from people who do not have Parkinson's disease are necessary to compare with those from patients with the condition. These are called ‘control’
samples. From the legal point of view, this sample will be taken as a gift. You will not have any legal right to share any profits that might arise from research using the sample.

**Do I have to take part in the study?**

No, you do not have to take part in the study, or give a reason if you choose not to. Before deciding, you should read this leaflet carefully and ask your doctor questions if there are things that you do not understand. If you do decide to take part, we will ask you to sign a consent form indicating that you understand what the study involves. The hospital doctor caring for your relative or friend will then enter you into the study.

**Can I withdraw from the study?**

Yes, you can decide to withdraw from the study at any time. Signing the consent form does not commit you to joining the study and withdrawal will not affect the standard of care that your friend or relative with Parkinson's disease receives in the future. If you withdraw from the study, the stored sample will be destroyed along with any information we have collected.

**Will participation in the study affect my legal rights?**

No. There are no special arrangements for compensation in the very unlikely event of a mishap as a result of taking part in the study. Whether or not you take part, you will retain the same legal rights to care that are provided to any other person in the NHS.

All information collected in the study will remain strictly confidential in the same way as your other medical records. The information will be put into a computer and analysed, but you will not be identified when the results are reported.

**What will happen to the results of the study?**

Both the samples and any information about you will be kept anonymous and confidential at all times. The overall results of the research will be publicised in the medical press and elsewhere. Individuals taking part will not be identified in the results.

We will not automatically provide you with your own results because individual genetic test results may have no useful value to you. However, if you want the result of a particular genetic test, you may apply for this to the specialist who normally cares for you. In order to provide the required genetic counselling to understand the result concerned, your specialist will refer you to your local clinical genetics department. The consultant clinical geneticist will then apply to the University of Birmingham who will arrange via the PD GEN Management Committee and any research laboratory involved in the work for the result to be passed back to you in appropriate terms. The standard fee operating at the time will be payable for this service.

**Who is organising and funding the study?**

The central study organiser is the University of Birmingham Clinical Trials Unit, which has experience of running very large trials. The study was initially funded by the Medical Research Council. Subsequently we have obtained funding from Parkinson’s UK, the National Institute for Health Research (NIHR), University Hospitals Birmingham Charities and the Midlands Neurosciences Teaching and Research Fund. The doctors involved are not being paid for recruiting patients into the study. The study has also been reviewed by regional and local research ethics committees.

**Do you have any other questions?**

We hope that you will choose to take part in the Parkinson’s Disease DNA Bank. If you still have questions about the study now or later feel free to ask your hospital doctor or nurse. Their names and telephone numbers are given at the top of the sheet. If you would prefer to delay your decision, perhaps to discuss with friends or relatives, then you can make an appointment to come back later.
But, please remember to keep this information sheet in a safe place and write the names and telephone numbers in your diary or address book.

Thank you for taking the time to consider taking part in this study.

**For further information please contact:**

**What if my first language is not English?**

If your first language is not English, we will obtain an interpreter so that the study can be fully explained to you.

Study Coordination: Neurosciences Office, University of Birmingham Clinical Trials Unit, Park Robert Aitken Institute, Edgbaston, Birmingham B15 2TT. Tel 0121 415 9129. Contact Professor Karen Morrison, 0121 414 3943. e-mail k.morrison@bham.ac.uk
Appendix 4 Carer Consent Form

Parkinson’s Disease DNA Bank
In collaboration with this Hospital and Health Trust
For Further information please contact:
Dr Tel: 
Nurse Tel: 

Please initial box each box

1. I have read the Carer Information Sheet on this project (version 7, dated 27/01/2012) and have been given a copy to keep. I have had the opportunity to ask questions about the project and understand why the research is being done and any foreseeable risks involved.

2. I agree to give a sample of blood for research in this project. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without giving a reason and without my medical treatment or legal rights being affected. I understand that the study is aimed at understanding the genetic influences in Parkinson’s disease, but that the results will not have any implications for me personally.

3. I give permission for my medical records to be looked at and information taken from them to be analysed in strict confidence by responsible people from the Parkinson’s Disease DNA Bank study team or from other organisations involved in the research.

4. I understand that the information may be kept indefinitely.

5. I understand that the results of any research will be published in medical journals and other publications but that I will not be identified.

6. I understand that I will not financially benefit if this research leads to the development of a new treatment or medical test.

7. I know how to contact the research team if I need to.

…………………………………………………………..…………..……………………
Name of carer (CAPITALS) Date Signature

…………………………………………………………..…………..……………………
Name of researcher Date Signature

Study Coordination: Neurosciences Office, University of Birmingham Clinical Trials Unit, Robert Aitken Institute, Edgbaston, Birmingham B15 2TT. Tel 0121 415 9129. Contact Professor Karen Morrison, 0121 414 3943. e-mail k.morrison@bham.ac.uk

I copy for carer; 1 copy for BCTU; original for hospital/GP notes of the patient
Version 7 Dated 27/01/2012

18
Appendix 5 Patient Invitation Letter

Address
Date

Dear <Name >

Re: Volunteering to help with PD GEN – a Parkinson’s disease DNA database

Recently you have kindly agreed to help research into Parkinson's disease by volunteering for either the PD MED, PD REHAB, PD SURG or the PD COMM Trials. We are now writing to you to ask if you would like to volunteer to help with another piece of research called the PD GEN study.

In PD GEN, we are collecting one small blood sample and a simple two page questionnaire about lifestyle and work history from patients and their carers who have helped with the PD MED, PD REHAB, PD SURG or the PD COMM trials. The blood is being sent to the Molecular Neurology Laboratory of the University of Birmingham where genetic material called DNA is extracted. This will then be used in a large number of research projects into Parkinson's disease for many years to come. The additional questionnaire will allow us to compare people’s background and genetic make up with their response to medication or surgery. This type of research work will be immensely useful over the next few decades.

If you are interested in helping with this project, please read the enclosed Patient Information Sheet for more details of the study.

If you have registered as having a carer as part of PD MED, PD REHAB, PD SURG or PD COMM, we have also included an invitation letter for your carer along with a Carer Information Sheet. Please pass these on to them on our behalf.

If you would like to help with PD GEN, please sign the slip at the bottom of this letter and return the whole letter back to the University of Birmingham Clinical Trials Unit using the enclosed stamped addressed envelope.

We will then send you an envelope containing a consent form and the questionnaire to complete. The envelope will also contain an explanatory letter for your general practitioner and a sealed pack containing sample tubes. We would like you to make an appointment with your GP to ask them if they or their nurse would take the blood sample and then post this back to us with the consent form and the questionnaire in the stamped addressed envelope which we will provide.

We are most grateful to you for considering helping with this important study.

Yours sincerely

Professor C E Clarke, Professor of Clinical Neurology

Professor K Morrison, Professor of Neurology

I would like to help with the PD GEN study.

Signature ................................................. Date ...................................................

Version 7 dated 27/01/2012
Appendix 6 Carer Invitation Letter

Address
Date

Dear <Name>

Re: Volunteering to help with PD GEN – a Parkinson’s disease DNA database

As the carer of a person with Parkinson's disease, you have kindly agreed to help research into the condition by volunteering to help with either the PD MED, PD REHAB, PD SURG or the PD COMM Trials. We are now writing to you to ask if you would like to volunteer to help with another piece of research called the PD GEN study.

In PD GEN, we are collecting one small blood sample and a simple two page questionnaire about lifestyle and work history from patients and their carers who have helped with the PD MED, PD REHAB, PD SURG or the PD COMM trials. The blood is being sent to the Molecular Neurology Laboratory of the University of Birmingham where genetic material called DNA is extracted. This will then be used in a large number of research projects into Parkinson's disease for many years to come. The additional questionnaire will allow us to compare people’s background and genetic make up with their response to medication or surgery. This type of research work will be immensely useful over the next few decades.

If you are interested in helping with this project, please read the enclosed Carer Information Sheet for more details of the study.

If you would like to help with PD GEN, please sign the slip at the bottom of this letter and return the whole letter back to the University of Birmingham Clinical Trials Unit using the enclosed stamped addressed envelope.

We will then send you an envelope containing a consent form and the questionnaire to complete. The envelope will also contain an explanatory letter for your general practitioner and a sealed pack containing sample tubes. We would like you to make an appointment with your GP to ask them if they or their nurse would take the blood sample and then post this back to us with the consent form and the questionnaire in the stamped addressed envelope which we will provide.

We are most grateful to you for considering helping with this important study.

Yours sincerely

Professor C E Clarke, Professor of Clinical Neurology

Professor K Morrison, Professor of Neurology

I would like to help with the PD GEN study.

Signature ............................................. Date ..............................................

Version 7 dated 27/01/2012
**Appendix 7 PD GEN Supplementary Questionnaire**

<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Please tick - Patient □ or Carer □</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Initials of name</th>
<th>Date of birth …./…./….</th>
<th>Sex (please circle)</th>
<th>Male / Female</th>
</tr>
</thead>
</table>

**What is your ethnic origin? (please circle)**

<table>
<thead>
<tr>
<th>Asian (Indian origin)</th>
<th>Asian (Pakistani origin)</th>
<th>Asian (Chinese origin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian (Other)</td>
<td>Black (Caribbean origin)</td>
<td>Black (African origin)</td>
</tr>
<tr>
<td>Black (Other)</td>
<td>White</td>
<td>Other (please specify)</td>
</tr>
</tbody>
</table>

In which country were you born? ...............................

**Employment**

Present or last type of employment if retired? ..................................

How long have (had) you been in this job? ............years...............months........

What other jobs have you had? List the main six (with dates).

(1) ..................................................  (2) ..................................................
(3) ..................................................  (4) ..................................................
(5) ..................................................  (6) ..................................................

**Have you ever been admitted to hospital due to intoxication by chemical compounds? (please circle)**  Yes / No

If YES, what was the name of the chemical ..........................................................

**Have you worked with:**

- Hydrocarbons (e.g. paints, dry cleaning industry)?  Yes / No
  - What was the name of the chemical ......................

- Pesticides or insecticides?  Yes / No
  - What was the name of the chemical ......................

**How long did you work with hydrocarbons/pesticides?  ...................... years**

**Have you lived most of your life in:**

- The countryside?  Yes / No
- A town or city?  Yes / No
- A mixture of the two?  Yes / No

**Have you drunk water from a well for more than 6 months of your life at any time?  Yes / No**
Do you smoke NOW (includes all forms of tobacco)? (please circle)  Yes / No

If YES, in what year did you start smoking?  ..........

How many cigarettes (or the equivalent) on average do you smoke daily? (please circle)  

0-10 per day  11-20 per day  More than 20 per day

If NO, have you smoked in the past? (please circle)  Yes / No

In what year did you start smoking?  ..........

In what year did you stop smoking?  ..........  

How many cigarettes (or the equivalent) on average did you smoke daily? (please circle)  

0-10 per day  11-20 per day  More than 20 per day

How many cups of coffee on average have you drunk each day over the last 10 years? (please circle)  
None  One  Two  Three  Four  Five  Six or more

Is there or has there been anyone in your family with Parkinson's disease?  Yes / No

If Yes, please list their names and relationship to you (e.g. brother, mother, etc):-  
Name  Relationship
.................................................................
.................................................................
.................................................................
.................................................................
.................................................................
.................................................................

Is there a family history of dementia such as Alzheimer’s disease?  Yes / No

If Yes, please list their names and relationship to you (e.g. brother, mother, etc):-  
Name  Relationship
.................................................................
.................................................................
.................................................................
.................................................................

Other Neurological conditions
Have you ever had a serious head injury that put you in a coma?  Yes / No

Have you ever had meningitis (i.e. infection of the lining of the brain)?  Yes / No

Have you ever had encephalitis (i.e. a severe infection of the brain tissue)?  Yes / No
Please return this form with the blood sample in the prepaid envelope to:
Professor K.E. Morrison, Dept. of Neurology, The Medical School, University of Birmingham, Vincent Drive, Birmingham. B15 2BR

Version 7 dated 27/01/2012
Appendix 8 General Practitioner Invitation Letter

Date

Dear Colleague

Re: PD GEN – a Parkinson’s disease DNA database

Your patient has kindly agreed to help research into Parkinson's disease by volunteering to join either the PD MED, PD REHAB, PD SURG or the PD COMM Trials. We have recently written to them to ask if they would like to volunteer to help with another piece of research called the PD GEN study. They have replied in the affirmative which is why they have approached you with this explanatory letter.

In PD GEN, we are collecting a single blood sample and a two page epidemiology questionnaire from patients and their carers who have helped with the PD MED, PD REHAB, PD SURG or the PD COMM trials. The blood is being sent to the Molecular Neurology Laboratory of the University of Birmingham where DNA is extracted. This will then be used in a large number of research projects into Parkinson's disease including pharmacogenomic studies attempting to find genetic predictors of the response to different anti-Parkinsonian medications. This type of work will be immensely useful over the next few decades.

We fully appreciate the numerous calls on your time these days. However, we hope that you will agree that this type of work is crucially important. If so, we hope that you will agree to take the blood sample that we require or to ask one of your nursing staff to do so.

We have provided the equipment required to take the blood in the pack that we sent to the patient (Vacutainer sample tubes, needle and barrel).

Once the sample has been taken, please package the tubes carefully in the box provided then send in the stamped addressed envelope to the Molecular Neurology Laboratory. The blood samples do NOT need to be refrigerated at any time.

The final envelope should contain:-

1. Box containing samples
2. Consent form completed by patient and countersigned by yourself or the nurse
3. Epidemiology questionnaire

We are most grateful to you for your help with this study.

Yours faithfully

Professor C E Clarke, Professor of Clinical Neurology

Professor K Morrison, Professor of Neurology

Version 7 dated 27/01/2012
Appendix 9 Generic Patient and Carer Second Letter

Address
Date

Dear <Name>

Re: Volunteering to help with PD GEN – a Parkinson’s disease DNA database

Thank you for agreeing to help with the PD GEN study.

In this package you will find everything you and your general practitioner (GP) need to complete the study.

We would like you to:

1. Read the consent form then, if you still would like to help with the study, please initial the boxes on the right hand side of the form and then sign it at the bottom
2. Complete the epidemiology questionnaire
3. Book an appointment with your GP
4. Give the GP invitation letter in this package to your GP along with the sample tube pack
5. Ask your GP or one of their nurses to take the blood samples and countersign the consent form
6. Return our copy of the consent form, the questionnaire and the blood samples in the packaging sent to you. The blood samples do NOT need to be refrigerated at any time.

We are very grateful to you and your general practitioner for helping with this important study.

Yours sincerely

Professor C E Clarke, Professor of Clinical Neurology

Professor K Morrison, Professor of Neurology
Appendix 10 Generic Patient invitation letter from trial site

Dear <participant name>,

Re: Volunteering to help with PD GEN – a Parkinson’s disease DNA database

Recently you have kindly agreed to help research into Parkinson's disease by volunteering for either the PD MED, PD REHAB, PD SURG or the PD COMM Trials. We are now writing to you to ask if you would like to volunteer to help with another piece of research called the PD GEN study.

In PD GEN, we are collecting one small blood sample and a simple two page questionnaire about lifestyle and work history from patients and their carers who have helped with the PD MED, PD REHAB, PD SURG or the PD COMM trials. The blood is being sent to the Molecular Neurology Laboratory of the University of Birmingham where genetic material called DNA is extracted. This will then be used in a large number of research projects into Parkinson's disease for many years to come. The additional questionnaire will allow us to compare people’s background and genetic make up with their response to medication or surgery. This type of research work will be immensely useful over the next few decades.

If you are interested in helping with this project, please read the enclosed Patient Information Sheet for more details of the study.

If you have registered as having a carer as part of PD MED, PD REHAB, PD SURG or PD COMM, we have also included an invitation letter for your carer along with a Carer Information Sheet. Please pass these on to them on our behalf.

If you would like to help with PD GEN, please sign the slip at the bottom of this letter and return the whole letter back to the <hospital contact address>. We will then call you to make an appointment for you to come see us.

We are most grateful to you for considering helping with this important study.

Yours sincerely

<Site Principal Investigator>

I would like to help with the PD GEN study. TNO: <to be completed by site>

<Patients name>

Signature ……………………………………. Date …………………………….

Version 7 dated 27/01/2012
Appendix 11 Generic Carer invitation letter from trial site

Dear <participant Name>

Re: Volunteering to help with PD GEN – a Parkinson’s disease DNA database

As the carer of a person with Parkinson's disease, you have kindly agreed to help research into the condition by volunteering to help with either the PD MED, PD REHAB, PD SURG or the PD COMM Trials. We are now writing to you to ask if you would like to volunteer to help with another piece of research called the PD GEN study.

In PD GEN, we are collecting one small blood sample and a simple two page questionnaire about lifestyle and work history from patients and their carers who have helped with the PD MED, PD REHAB, PD SURG or the PD COMM trials. The blood is being sent to the Molecular Neurology Laboratory of the University of Birmingham where genetic material called DNA is extracted. This will then be used in a large number of research projects into Parkinson's disease for many years to come. The additional questionnaire will allow us to compare people’s background and genetic make up with their response to medication or surgery. This type of research work will be immensely useful over the next few decades.

If you are interested in helping with this project, please read the enclosed Carer Information Sheet for more details of the study.

If you would like to help with PD GEN, please sign the slip at the bottom of this letter and return the whole letter back to <hospital contact address>. We will then call you to make an appointment for you to come see us.

We are most grateful to you for considering helping with this important study.

Yours sincerely

<Principal Investigators Name>

I would like to help with the PD GEN study. TNO: <to be completed by site>

<Carers Name>

Signature ........................................ Date ................................................

Version 7 dated 27/01/2012