A large, randomised, long-term assessment of the relative effectiveness of surgery for Parkinson’s disease

PROTOCOL

In Parkinson’s disease (PD), levodopa (LD) initially controls the symptoms of most patients, but after a few years of treatment motor complications develop. Dopamine agonists (DAs) or monoamine oxidase type B inhibitors (MAOBI s) have been used, either alone or with reduced doses of LD, in an attempt to delay the onset of motor fluctuations. Once motor complications develop, DAs or MAOBI s may be introduced if not previously used, as may catechol-O-methyltransferase inhibitors (COMTIs), but in many patients these eventually fail to maintain adequate control of symptoms. At this point (or potentially earlier), surgical intervention may be considered. Alternatively, apomorphine may be tried, often with some success if the patient is having bad “off” periods but reasonable “on” time. Surgery may be performed at three sites (thalamus, globus pallidum or subthalamic nucleus) using two techniques (radio-frequency lesioning or electrical stimulation). There is very little reliable evidence available as to the optimal site, technique and timing of surgery. Few randomised trials have addressed these questions, and those that have been performed have been small. Most published reports relate to small non-randomised series, which cannot provide reliable evidence because of the potential selection biases involved. There is, therefore, an urgent need for large randomised trials of surgery for PD to be undertaken.

The PD SURG trial will evaluate the role of subthalamic (STN) and pallidal (GPi) surgery, by either stimulation or lesioning, compared to medical therapy (with surgical intervention delayed as long as possible) in patients with advanced PD that is not adequately controlled by their current medical treatment. Patients allocated to medical therapy will receive whatever drug treatment is considered appropriate (this may include continuous apomorphine infusion). Although surgery may produce clear and rapid clinical improvements, it is also important to evaluate the safety and long-term effects of the procedure and to use endpoints of relevance to the patient.

PD SURG is a large, simple, “real-life” trial that will determine reliably whether early surgery is more effective than medical therapy (with surgery deferred) for advanced PD.

In order to obtain the large number of patients needed to provide reliable answers, and to maximise the clinical relevance of the findings, the trial is designed to fit in with routine practice as far as possible and to impose minimal additional workload by keeping extra clinic-based tests and evaluations to a minimum. A health economic evaluation will be undertaken alongside the trial. Because the success of the trial depends entirely on the whole-hearted collaboration of many surgeons, neurologists, nurses and others, publication of the main result will be in the name of the collaborative group and not those of the central organisers.
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## CONTENTS

1. BACKGROUND .......................................................................................................... 1
   1.1. Parkinson’s Disease............................................................................................. 1
   1.2. Drug therapy for PD ............................................................................................. 1
   1.3. Surgery for PD ...................................................................................................... 1
      1.3.1 Lesioning ............................................................................................................ 2
      1.3.2 Deep brain stimulation ........................................................................................ 2
   1.4. Thalamic surgery .................................................................................................. 2
   1.5. Globus pallidus surgery ........................................................................................ 2
   1.6. Subthalamic surgery ............................................................................................. 3
   1.7. The choice of questions to be asked .................................................................... 3
   1.8. The need for a large simple trial of surgery for PD ............................................... 4

2. TRIAL DESIGN........................................................................................................... 5

3. ELIGIBILITY................................................................................................................ 5
   3.1. Simple eligibility .................................................................................................... 5
   3.2. Eligibility and randomisation based on “uncertainty” ............................................ 6
   3.3. Types of patient to be entered .............................................................................. 6
   3.4. Non -trial patients ................................................................................................. 7

4. LARGE, SIMPLE TRIAL: MINIMAL EXTRA WORKLOAD .......................................... 7

5. RANDOMISATION ..................................................................................................... 7
   5.1. Patient and carer information leaflet ..................................................................... 7
   5.2. Randomisation ..................................................................................................... 7

6. TREATMENT AND FOLLOW-UP ............................................................................... 8
   6.1. Surgical technique ................................................................................................ 8
   6.2. Medical treatment ................................................................................................. 8
   6.3. Serious and unexpected adverse events ................................................................ 9
   6.4. Follow-up assessments ...................................................................................... 10
   6.5. Other management at discretion of local doctors ............................................... 10

7. OUTCOME MEASURES .......................................................................................... 11
   7.1. Endpoints ........................................................................................................... 11
   7.2. Health economic outcomes ................................................................................ 12

8. ACCRUAL AND ANALYSIS...................................................................................... 13
   8.1.Projected accrual................................................................................................. 13
   8.2. Sample size ........................................................................................................... 13
   8.3. Stratification variables ........................................................................................ 13
   8.4. Independent Trial Steering Committee ............................................................... 14
8.5. Data Monitoring and Ethics Committee: determining when clear answers have emerged ................................................................. 14

9. ORGANISATION ............................................................................. 15

9.1. Centre eligibility .......................................................................... 15

9.2. Local Co-ordinator at each centre .............................................. 15

9.3. Central co-ordination: supply of all trial materials, randomisation service, and data collection and analysis ........................................ 15

9.4. Funding and Cost implications ..................................................... 16

9.5. Indemnity ..................................................................................... 16

9.6. Publication and ancillary studies .................................................. 16

10. REFERENCES ............................................................................. 17

APPENDIX A PATIENT INFORMATION SHEET ........................................ 20

APPENDIX B: PATIENT AND CARER CONSENT FORM ..................... 23

APPENDIX C: GP LETTER ..................................................................... 25

APPENDIX D: RANDOMISATION NOTEPAD ......................................... 26

APPENDIX E: ENTRY FORM ................................................................. 27

APPENDIX F: PDQ-39 ......................................................................... 28

APPENDIX G: EUROQOL EQ-5D .......................................................... 31

APPENDIX H: UPDRS .......................................................................... 33

APPENDIX I: HOEHN & YAHR STAGING SYSTEM ............................. 42

APPENDIX J: NEUROPSYCHOLOGICAL EVALUATION ....................... 43

APPENDIX K: SF36 VERSION 2 ............................................................. 44

APPENDIX L: POST-OPERATIVE FORM ............................................... 48

APPENDIX M: SIX MONTH POST-OP FORM ....................................... 50

APPENDIX N: RESOURCE USAGE ....................................................... 51

APPENDIX O: ANNUAL FOLLOW-UP FORM ......................................... 52

APPENDIX P: SERIOUS ADVERSE EVENT FORM .............................. 55

APPENDIX Q: TOXICITY ..................................................................... 56
1. BACKGROUND

1.1. Parkinson’s Disease

Parkinson’s disease (PD) is a progressive neurological disorder caused by the loss of pigmented dopaminergic neurones in the brain and the consequent depletion of the neurotransmitter dopamine. This leads to increasing problems with movement, including tremor, rigidity, slowness, postural disturbance and loss of balance. PD is one of the commonest causes of disability in older people. It is estimated that about 8,000 new cases of PD are diagnosed in the U.K. each year. Average life expectancy is about 15 years, leading to a minimum prevalence of 100,000 cases. Only about 5% of patients are aged under 40 years at diagnosis, and incidence increases rapidly with age, with most patients developing the initial symptoms of PD between 50 and 70 years of age. There is currently no curative therapy for PD, and treatment is directed towards the alleviation of symptoms.

1.2. Drug therapy for PD

A wide range of medical treatments for both early and more advanced PD have been employed. Levodopa (LD) provides symptomatic relief for most patients with PD. However, after a few years of treatment, motor complications (“wearing-off” and “on-off” fluctuations and dyskinesia) develop and drug-induced hallucinations are common. A number of other agents, including dopamine agonists (DAs) and dopamine degradation inhibitors (DDIs), have been used, either alone or with reduced doses of LD, in an attempt to delay the onset of motor fluctuations. Once “wearing-off” and “on-off” fluctuations develop with LD monotherapy, DAs (including apomorphine), and DDIs, such as monoamine oxidase type B inhibitors (MAOBIIs) and the newer catechol-O-methyltransferase inhibitors (COMTIs), may be introduced. Eventually, after a few years, these may fail to control the symptoms of PD adequately.

1.3. Surgery for PD

Surgical procedures for PD first proved successful in the 1950s, but their use declined rapidly after the introduction of LD and other dopaminergic agents in the late 1960s. However, in the mid 1980s the development of elaborate techniques to increase the precision of surgical interventions together with a greater understanding of basal ganglia anatomy and pathophysiology led to a resurgence of interest in surgical procedures to relieve parkinsonian symptoms. The Manchester group, amongst others, have, in a series of important publications, highlighted the role of the subthalamic nucleus, which becomes overactive in PD. Other new options for the treatment of PD include foetal nigral cell grafts and continuous parenteral administration of apomorphine (with marked reduction of concomitant oral therapy). However, the use of human foetal tissue transplantation has been limited by ethical and logistical (shortage of tissue) issues. These may be resolved or overtaken by “gene therapy” in which case the infrastructure legacy from the current trial for symptomatic relief may prove of value for establishing future trials of semi-curative approaches.

Currently, stereotactic neurosurgical operations for PD are performed at three sites: thalamus, globus pallidus (GP) and subthalamic nucleus (STN) and involve either lesioning or deep brain “stimulation”. Both methods are stereotactic neurosurgical procedures, which involve fixing a frame to the patient’s skull under local anaesthesia and mild sedation. The brain is then imaged using either computerised tomography (CT) scan, magnetic resonance imaging (MRI) or intraoperative ventriculography, where a contrast dye is injected into the ventricles of the brain. All of these imaging methods allow the precise localisation of target structures in the brain. A small hole is then drilled in the skull.
and a brain needle inserted. The procedures differ in which part of the brain is targeted and what is done to them.

1.3.1 Lesioning
The aim of these procedures is to produce improvement by placing a lesion in the appropriate target structure. A high frequency electric current destroys the brain region. This lesion should be large enough to provide long-term benefit but small enough to avoid irreversible neurological deficits.

1.3.2 Deep brain stimulation
This procedure is essentially identical to lesioning except for the final part when the stimulating electrode is placed in the target instead of making a lesion. Since deep brain stimulation mimics the effects of a lesion, it is probable that the high frequency stimulation used results in inhibition, rather than stimulation, of neurons surrounding the electrode tip. Thus, an electrode is implanted into the desired brain area and connected to a battery-powered circuit, which is implanted under the skin below the clavicle. The circuit sends electrical signals to the desired structure of the brain to regulate neuronal activity. An external computer, which programs the pacemaker via radio waves, can control the stimulation. Stereotactic neurostimulation may provide a suitable tool for functionally inactivating the target structure in PD patients without producing a permanent lesion. Furthermore, the electrodes can either be turned off or removed at any time. A new stimulator has just been introduced by Medtronic after many years of development allowing bilateral stimulation from a single device.

1.4. Thalamic surgery
Thalamotomy: Prior to the advent of levodopa therapy, thalamotomy offered the most effective means of controlling parkinsonian tremor. However, published outcomes for total abolition of tremor after unilateral thalamotomy vary considerably. Furthermore, despite often permanent relief of tremor and rigidity, thalamotomy had no effect on akinesia, the core disabling feature of PD. In addition, although unilateral surgery in this disease was associated with low morbidity, as the disease progressed a second, contralateral lesion was often made with a high incidence of speech and swallowing problems along with some psychiatric morbidity. With the introduction of dopamine replacement therapy in the late 1960s, the first treatment that dramatically alleviated akinesia, use of this surgical treatment for PD declined rapidly.

Thalamic Stimulation: While using a stimulating electrode to guide lesion placement, Benabid et al discovered that high frequency discharges from this electrode could abolish tremor. Since then deep brain stimulation of the ventral intermediate (Vim) thalamic nucleus, has proved very successful in patients with PD and essential tremor. The functional nature of the stimulation, which makes all the effects reversible, is the main advantage over the permanent surgical lesion of thalamotomy. In addition, stimulation seems to induce less adverse effects than traditional destructive thalamotomy, particularly when bilateral. However, as with the ablative surgery in this region, thalamic stimulation does not improve akinesia nor does it help dyskinesias.

1.5. Globus pallidus surgery
Pallidotomy: Stereotaxic lesions of the posteroventral GP were introduced by Leksell in the early 1950s prior to dopamine replacement therapy. During the 1990s it regained popularity with Laitinen et al reporting a dramatic improvement in rigidity and akinesia as well as tremor. Two recent randomised controlled trials in pallidotomy have confirmed these benefits. The procedure is also associated with the reduction of dyskinesias and “off” period disability. Many groups have since investigated pallidotomy in PD.
Generally unilateral pallidotomy dramatically reduces contralateral, and mildly reduces ipsilateral, dyskinesias. For unilateral and bilateral pallidotomies some groups have reported negligible morbidity, but others have experienced some deaths and strokes as a result of haemorrhage, infarct or misplaced lesions. Pallidotomy carries the additional risks of injury to the optic tract or the internal capsule which are both near the optimal lesion location and hence prone to injury.

**Pallidal stimulation:** High frequency stimulation of the globus pallidus appears to have an efficacy similar to that of pallidal lesions\(^ {13,14} \). Pallidal stimulation offers significant improvement in duration in the “on” state accompanied by a reduction in dyskinesias. Depending on the location of the stimulating electrode, pallidal stimulation has a variable effect on parkinsonian features versus LD-induced dyskinesias. A randomised study in Argentina compared lesion versus stimulation of the posteroventral pallidum but was too small to provide reliable evidence on their comparative efficacy\(^ {15} \).

**1.6. Subthalamic surgery**

**Subthalamotomy:** Beneficial effects from lesioning of the STN were first reported in parkinsonian monkeys\(^ {16} \). Since then it has been demonstrated that ischaemic or haemorrhagic STN lesions in patients with PD also alleviate symptoms\(^ {17} \). To date there is only limited experience with STN lesions in humans because of the fear of inducing hemiballism (proximal high amplitude flinging movements). However, the first stereotactic lesions involving the STN have been recently reported in two groups of Cuban and British patients\(^ {18,19} \). These studies suggest that subthalamotomies can be performed safely with major benefit to parkinsonism. Furthermore, in contrast to pallidotomy, dopaminergic drug requirements seem to be dramatically reduced by these lesions, which may account for the low incidence of dyskinesias\(^ {18,19} \).

**Subthalamic stimulation:** Greater experience has been gained with implantation of STN stimulators. Since the small subthalamic nucleus is overactive in PD and is the major excitatory driving force of the basal ganglia, blockade of its excitatory output has the largest potential to normalise the excessive and abnormal discharge patterns of other basal ganglia structures, thereby improving all the motor features of PD. Such stimulation has been shown to have a much greater effect on underlying parkinsonism including tremor, balance, speech and freezing of gait\(^ {20,21,22} \). As with STN lesioning, the antiparkinsonism effect is so striking that, in contrast to pallidotomy, LD dosage can be drastically reduced, with consequent reduction of dyskinesias\(^ {22,23} \).

**1.7. The choice of questions to be asked**

Although there has been a resurgence of functional neurosurgery for PD, there is still a paucity of information on timing, technique and site, and the cost-effectiveness of surgery. Lesions have the advantage that the effects are permanent, but morbidity might be higher than deep brain stimulation. Stimulation is reversible but is much more costly and requires multiple post-operative visits to tune the stimulator and, in due course, indefinitely for periodic battery replacement.

The great majority of studies looking at surgery for PD have been small non-randomised case series. Over 10,000 patients have been included in more than 470 reported studies, with an average of approximately 22 patients per study and an average follow-up of 15 months per patient. While these studies demonstrate that surgery is clearly beneficial for some patients in the short term, it is impossible to assess reliably the long-term role of surgery from such small non-randomised studies due, for example, to the potential for substantial selection bias among the patients included and because small series which look promising are more likely to be reported than those which look unpromising.
(“publication bias”). Certainly, anecdotal reports from neurologists and neurosurgeons in UK and USA reveal a different picture from the published literature with regard to the safety and efficacy of surgery.

To date, six published randomised controlled trials (RCTs) have been identified for surgery in PD. These trials, although randomised, are mainly single-centre trials and contain small numbers of patients (204 patients in total and an average of 34 patients per trial). These RCTs are also characterized by relatively short-term follow-up averaging only 6 months follow-up per patient. Unfortunately, the many reported benefits of surgery for PD are weakened by the overall limited quality of the available evidence. This further highlights the need for a multi-centre randomised controlled trial to evaluate the surgical techniques available for the treatment of PD.

A survey of opinion among neurosurgeons and neurologists and discussions at three workshops demonstrated that the greatest interest was in subthalamic surgery (with less enthusiasm for the thalamus or pallidum as targets). There was substantial uncertainty as to the optimal timing of surgical intervention for PD. A consensus on the trial design was reached and finalised. However, surgery for PD is a rapidly changing area. Unfortunately, some of these changes are not made on the basis of reliable evidence, so designing a "clean" trial with a comparison between two precisely specified approaches is not feasible, while modern trial design theory makes it unnecessary. The trial design therefore needs to be pragmatic, with some flexibility built in, so that if views change substantially the trial could, after consultation, adapt.

1.8. The need for a large simple trial of surgery for PD

As demonstrated above, there remain substantial uncertainties about fundamental aspects of surgery for PD. The few previous trials have been much too small to evaluate reliably the relatively moderate differences that can realistically be expected between the various treatment modalities. Furthermore, while there is reasonably sound evidence that surgery can be effective in the short term, there are few data on the long-term effects. Previous studies have concentrated on short-term outcome (most involving only 6 months follow-up) with physician-based assessment. It is essential in a disease with a long time course such as PD to evaluate the long-term effectiveness and safety of surgery, based on clinically and socially important outcomes, and to assess the patients’ perceptions of benefit (using appropriate quality of life measures), as well as that of clinicians. In addition, none of the trials have compared STN surgery with medical treatment. These studies have, therefore, provided very little reliable evidence as to the optimal site, technique and timing of surgery. As a result there is, an urgent need for collaborative work involving large, multi-centre randomised controlled trials to evaluate the surgical techniques available for the treatment of PD, with long-term follow-up, to be undertaken.

Thus, the combination of a new site and technique and a new stimulator provide a window of opportunity, which might not recur, for undertaking a uniquely reliable evaluation of the role of stereotactic neurosurgery, and in particular, deep brain stimulation in PD.

The results of this trial will allow decisions on how to treat PD patients to be evidence-based (i.e. the trial will determine whether surgery is a beneficial and cost-effective intervention and, if so, the optimal timing in addition to a reliable unbiased evaluation of the relative merits of surgery compared to medical therapy), leading to more patients receiving the most appropriate therapy and to more cost-effective use of the available clinical resources.
2. TRIAL DESIGN

This is a large, simple, “real-life” randomised trial to evaluate the role of surgery as therapy for PD.

The fundamental question being addressed in this trial is:

- Does early surgery provide more or less effective long-term control than medical therapy (with surgery deferred for as long as possible)?

If allocated to surgery, the procedure may be performed by either stimulation or lesioning at either the subthalamic nucleus or the globus pallidus. The procedure planned will need to be decided in advance and specified at the time of entry (it is also anticipated that, in due course, it will be possible to introduce a sub-randomisation to stimulation versus lesioning and/or STN versus GPi). Surgery should ideally be performed within one month of entry and within 3 months at the latest. If surgery cannot be scheduled within this timeframe, the baseline assessments and randomisation should be deferred.

If allocated to medical treatment, the therapy given will be at the discretion of the medical team responsible (but again the planned therapy, i.e. whether or not apomorphine will be used, needs to be decided in advance).

3. ELIGIBILITY

3.1. Simple eligibility

Patients will be eligible if:

- They have PD as diagnosed by the UK Brain Bank Criteria
- They have PD that is not controlled by current medical therapy.
- They are considered able to withstand surgical intervention, reached by consensus with the clinical team and patient.
- They are unlikely to be considered to definitely require, and be able to receive, surgery within one year of entry.
- They are not demented, as determined by the DRS-II (see section 7.1).
- They are able to understand and complete the trial questionnaires (non-English speaking patients may be entered if they have a carer, relative or other person who can help them).
- They have given written informed consent.

Definite indications for, or contraindications against, any of the therapies in the trial are not specified by the protocol, but by the responsible clinician. Eligibility will be based on the uncertainty principle (see Section 3.2).
Neuropsychological evaluation forms part of the clinical assessment to determine a patient’s suitability for surgery. In some centres, data on the pre-operative neuropsychological state will be collected as part of the trial and repeated at one year (Appendix J). Other centres should use their standard local psychological tests.

3.2. Eligibility and randomisation based on “uncertainty”

There is no consensus as to the optimal timing of surgery for PD. Some clinicians may consider that surgery should be performed at a relatively earlier stage of the disease than others, while factors such as the level of disability of a patient are also potential determinants of the appropriateness of different treatments. In the UK, the previous restrictions in the availability of surgery will have skewed the type of patients previously receiving surgery, so the trial will allow a more heterogeneous population to receive surgery, as well as provide reliable data.

In view of these considerations, this trial adopts a pragmatic approach and eligibility is based not on rigid entry criteria but on the "uncertainty principle". That is, if the clinical team is substantially uncertain which treatment (surgery or medical therapy) a particular patient should be offered at the current time, that patient is eligible to be randomised. If, on the other hand, the clinical team considers, for any reason, that there is a definite contraindication against surgery, then the patient is not eligible for randomisation. Usually, the same considerations would apply to patients for whom surgery is considered to be definitely indicated. However, in PD SURG, patients with a definite indication for surgery can also be randomised into the trial if it would not be possible to perform the surgery outside the trial within one year (i.e. patients allocated to surgery will get it more quickly than otherwise, while those allocated to medical treatment will not have to wait longer than they would outside the trial). In these circumstances randomisation is both scientifically and ethically preferable to the uninformative alternative of not randomising and treating patients in an ad hoc way outside of a study. (Those patients for whom surgery is considered to be definitely indicated can be offered this treatment off-study but do not contribute any useful information on the real value of that treatment.) Eligibility based on uncertainty has been used in many previous trials (e.g. the "ISIS" heart disease trials, the MRC Carotid Endarterectomy Trial, and the QUASAR Colorectal Cancer trial) and has been shown to simplify trial procedures and to facilitate large-scale recruitment of an appropriately heterogeneous group of patients.

The clinical team should be clear as to which type of surgery (stimulation or lesioning) is to be performed and to which target (STN or GPi), if surgery is allocated. Similarly, the clinical team should decide before randomisation whether to introduce or continue apomorphine if allocated to medical management, although the decision as to whether apomorphine will be delivered continuously or intermittently, by pump or by penject, need not be specified in advance.

3.3. Types of patient to be entered

It is envisaged that patients in three broad categories may be considered for entry:

1. Patients with very advanced PD for whom all medical therapy options have been tried and surgery remains the only option. Currently, these patients often have to wait over a year for their surgery, while in some regions it is effectively unavailable. Within PD SURG it will be possible to schedule surgery within 4 weeks for these allocated to surgery, thus permitting half of these patients to receive it early.

2. Patients with advanced PD for whom their current medical therapy does not provide adequate control and for whom either surgery or alternative medical therapy (e.g.
apomorphine, a second oral agonist or further adjustments of levodopa preparations) might be considered. It is anticipated that this group of patients will be the largest.

3. Patients with less advanced disease (e.g. onset of motor complications) for whom medical options are available (e.g. dopamine agonists, COMT inhibitors) but for whom early surgery is also considered to be an option.

With eligibility based an uncertainty (Section 3.2), clinicians will be free to enter patients in any of these categories. With a broad spectrum of patients in the trial, it will be possible to evaluate the optimal timing of surgery more reliably (see Section 8.3 for details of subgroup analyses).

3.4. Non-trial patients

Patients who decline to enter PD SURG will not be disadvantaged and will be put on the normal waiting list for PD surgery. Patients for whom surgery is considered definitely indicated without delay should be treated immediately if circumstances permit. Experience from the pilot phase of the trial suggests acceptance is high and few patients will refuse to participate.

4. LARGE, SIMPLE TRIAL: MINIMAL EXTRA WORKLOAD

In order to obtain the large number of patients necessary for the reliable evaluation of surgical intervention for PD, the trial will need the participation of several centres. To make this practicable, trial procedures need to be kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to treat their patients. This will be achieved by simple entry procedures (a single phone/fax call to the randomisation office), the use of standard local treatment regimens, routine follow-up of patients (with few additional hospital visits or tests to be performed above those done as part of standard care), minimising documentation and largely patient-based evaluation of outcome. This information will be supplemented by the use of national mortality records to ensure long-term follow-up. Regular newsletters will keep collaborators informed of trial progress, and regular meetings will be held to report progress of the trial and to address any problems encountered in the conduct of the study.

5. RANDOMISATION

5.1. Patient and carer information leaflet

The conduct of the trial will be in accordance with the Medical Research Council (MRC) Guidelines for Good Clinical Practice 1998 and any subsequent amendments. The patient's written informed consent (according to usual local practice) to participate in the trial must be obtained before randomisation and after a full explanation has been given of the treatment options and the manner of treatment allocation. Patient information sheets (Appendix A) and consent forms (Appendix B) will be provided so that patients and their carers can find out more about the trial before deciding whether or not to participate. If the patient identifies a regular carer, he/she will also be asked for consent to contribute information to the study. The patient's GP should be notified, with the patient's consent, and a specimen "Letter to GP" is supplied (Appendix C).

5.2. Randomisation

Randomisation notepads (Appendix D) will be provided to participants and may be used to collate the necessary information prior to randomisation. Patients are entered and randomised into the trial by one telephone call (0800 953 0274) or fax (0121 415 9135) to the toll-free randomisation service. The telephone randomisation number from outside the
UK is +44 (0)121 415 9129. The person randomising will need to answer all of the telephone questions before a treatment allocation is given. Randomisations are available Monday-Friday, 09:00-17:00 GMT.

6. TREATMENT AND FOLLOW-UP

6.1. Surgical technique

Patients in the study who are allocated to surgery will undergo one of the following options:

- bilateral STN stimulation
- unilateral pallidal stimulation
- bilateral pallidal stimulation, either as staged or single session procedure
- unilateral pallidotomy
- unilateral subthalamic lesioning

Patients randomised to surgery should ideally have their surgery completed within 4 weeks of being entered into the trial, and within 3 months at the maximum. If it is unlikely that surgery, if allocated, can be performed within this time frame, randomisation should be delayed until the necessary arrangements can be made.

The techniques of stereotactic localisation of the STN or GPi will vary considerably between centres depending on available equipment and expertise. As it would not be possible to standardise the surgical technique, centres will be allowed to use the methods with which they are most familiar.

Several targeting methods are commonly used in the target localization: both anatomical and physiological. Anatomical methods include both direct and indirect techniques. Direct targeting involves specific MRI sequences that enable visualization of the target boundaries. The indirect methods are based on the use of brain atlases typically using the anterior commissure (AC) and posterior commissure (PC) as internal landmarks to co-register the atlas with the patient. The three-dimensional (3-D) coordinates of the AC and PC are variably determined by using ventriculography, computerized tomography scanning, magnetic resonance imaging (MRI) or ventriculography coupled with MRI. Physiological methods, which include macroelectrode stimulation and microelectrode recording (MER), are used in conjunction with the anatomical coordinates to adjust or confirm final placement of the lesion or stimulator; and performed intraoperatively with the patient awake they can adjust for brain shifts resulting from cerebrospinal fluid loss.

However, as outcome may depend on the quality of the localisation of target organ, post operative MRI will be performed on patients who are lesioned to confirm that the lesion is located in the target structure; with stimulators, MRIs may still be used but there is a lot of artefact (new technology may overcome some of these problems). However, it may be more appropriate to use a functional test, i.e. UPDRS with stimulator switched on versus switched off. Surgical data that will be collected will include details of localisation methods both radiological and physiological, and, in stimulation, type of electrode and stimulator (see Appendix K). Details of all additional surgery will also be recorded e.g. replacement of pulse generator, revision of electrodes, leads, etc. In stimulation patients, stimulation parameters will be recorded after stabilisation of the disease by the stimulator (see Appendix I).

Morbidity of surgery will be recorded (see Appendix P for summary of the most frequent side-effects). All significant and non-transient effects should be reported.
6.1.1 Deep Brain Stimulator Systems

Two dual-channel neurostimulator systems are now licensed and available in the UK: Kinetra™ from Medtronic and NeuroCor™ marketed by InterMedica. Both products allow bilateral stimulation through a single device and have other benefits, e.g. easier to programme and less prone to extraneous interference. Either system can be used within PD SURG and the make and model number are recorded on the Post-Operative Form (Appendix L).

6.2. Medical treatment

The medical treatment received by patients allocated to medical therapy is at the discretion of the clinical team responsible. It will fall into two main categories:

**Apomorphine:** Treatment should be initiated during an in-patient or day case stay following pre-treatment with domperidone 20-30mg three times daily for 3 days. The patient should not receive any oral medication for a minimum of 4-6 hours before the challenge in order to provoke an “off” period. A test dose of 1.5mg subcutaneous apomorphine should be administered and the patient’s motor response observed for 30 minutes. If there is no response or a poor response, a subsequent dose of 3mg should be given and the patient observed. Incremental doses of 5mg then 7mg should be given until a response is seen. If no response is seen using 7mg, the patient is likely to be a non-responder.

Intermittent injections using a penject system may be suitable for patients who experience “off” periods of less than 1hr duration and fewer than 6-8 times per day and for treating painful dystonias. Patients who have a good “on” period response but whose overall control remains unsatisfactory using intermittent injections or those patients who require many frequent injections may be commenced on, or transferred to, continuous waking day infusion administered via a syringe driver.

Oral dopamine agonists and dopamine decarboxylase inhibitors may be withdrawn gradually over two weeks and the infusion or injection rate is increased if required up to a maximum of 150mg daily. Levodopa may be reduced by 50 mg each week until the lowest tolerated dose is achieved.

**Other drug therapy:** For patients with less advanced PD, other standard medical options may not have been exhausted and therapy with a dopamine agonist (or a different one, or two together), COMT inhibitor, amantadine (to decrease dyskinesia) or other appropriate agent may be initiated if not previously received.

Details of medical treatment received will be recorded at baseline and follow-up for all patients, including those allocated to surgery.

6.3. Serious adverse events

Since there may mortality and morbidity associated with surgery for PD, all serious adverse events believed to be due to the procedures (or due to the drug therapy administered in the medical therapy arm) should be reported by fax to the trial office as soon as possible. This report should be followed within 2 weeks by a completed SAE form. Events that might reasonably be expected to occur in PD patients receiving the study treatments do not need to be reported in this way.

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* For the purposes of this study, “serious” adverse events are those which are fatal, life-threatening, disabling or require hospitalisation. It is not required to report in this way side-effects or events that might reasonably be expected, such as disease progression or death from PD (such deaths should be reported on the standard follow-up forms).
6.4. Follow-up assessments

Post-operative assessments for patients receiving surgery will be according to local practice. Late adverse events post-surgery, medical therapy and stimulation parameters will be collected in the surgical arm only at 6 months. All patients will be assessed at 1 year, 2 years, 3 years, 5 years, 7 years and 9 years after entry to the trial. The principal evaluations will be by means of questionnaires to be completed by patients and their carers (see Section 7). The Unified Parkinson’s Disease Rating Scale (UPDRS) will be used for clinical assessment of all patients, and there will be a neuropsychological evaluation in selected centres. There will also be a simple bi-annual questionnaire to clinicians to ascertain changes in disease status and changes in medical therapy. National mortality statistics will be used to monitor long-term survival. The trial therefore involves little additional administration and paperwork on the part of clinicians and their staff.

Assessments in parentheses, i.e. (X), are optional and will be performed on a subset of patients. Centres that wish to undertake these evaluations should perform them in all randomised patients irrespective of the arm to which they are allocated.

<table>
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<td>Adverse events (surgery only)</td>
<td>Clinician</td>
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<td>X</td>
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</tbody>
</table>

6.5. Other management at discretion of local doctors

Apart from the trial treatments allocated at randomisation, all other aspects of patient management are entirely at the discretion of the local doctors. Patients are managed in whatever way appears best for them, with no other special treatments, no special investigations, and no extra follow-up visits.

6.6. Dementia

As the trial proceeds, some patients may become demented, as defined by the clinical team responsible for the patient or by a score of less than 5 on the age and education adjusted Dementia Rating Scale 2. This does not require that the patient be withdrawn from the trial: it is important that as much data as practical is collected during follow-up. The shorter version of the PDQ-39, the PDQ-8, will be sent directly to the patient together with the EuroQol E5-ED and the clinical follow-up information will continue to be obtained from the patient's current doctors.
6.7. Death
Death of a participant should be reported on the clinical follow-up form within two weeks of notification to the randomising hospital. If the death occurs because of a serious adverse event (see section 6.3), a SAE form should also be submitted. This information will be supplemented by national mortality statistics to monitor long-term survival.

7. OUTCOME MEASURES
7.1. Endpoints
The primary endpoint will be the patient’s self-evaluation of their functional status using the PDQ-39 questionnaire.

Secondary endpoints will evaluate other aspects of functioning, as well as safety:
- Quality of Life (EuroQol).
- Cognitive decline (Dementia Rating Scale-II)
- Clinical assessment of functioning (UPDRS, Hoehn & Yahr stage).
- Neuropsychological evaluation
- Carer psychological wellbeing (SF-36)
- Health Economics.
- Toxicity and side-effects, including mortality rates.

PDQ-39: A clinically and socially meaningful endpoint needs to address matters of most concern to the individual with PD. These concerns will be assessed by means of the PDQ-39 (Appendix E), specifically developed and tested for use in clinical trials by two of the Trial Management Group members (CJ, RF). This self-completed questionnaire was developed by qualitative in-depth interviews involving patients with PD and items reflect their concerns in relation to eight aspects of PD: mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, bodily discomfort. The instrument has been extensively tested for validity, reproducibility, and sensitivity to change in both clinic and population survey applications. For example, the instrument has high convergent and discriminant validity in relation to neurologists' assessments of PD severity using conventional clinical scores, such as Hoehn and Yahr, Columbia and UPDRS, and is sensitive to changes considered of importance to patients but not identified by clinical ratings. It has been translated and used in most European, Australasian and North American countries and has been widely used as outcome measure in trials of drugs, neurosurgery and nursing care packages.

The PDQ-39 includes additional items to assess self-rated severity of PD symptoms. However it is expected that, additionally, potential side-effects of treatment will need to be assessed by a patient-based instrument developed specifically for the study.

EuroQol EQ-5D: The main outcome measure for the economic evaluation will be the EuroQol EQ-5D (Appendix F). Responses will be given valuations derived from published UK population tariffs and the mean number of quality adjusted life-years (QALYs) per patient and incremental QALYs will be calculated.
Cognitive Decline - Dementia Rating Scale-2: About 40% of PD patients ultimately develop dementia. The trial aims to determine whether therapies prevent or decrease the decline of cognitive function as measured by the DRS-II. The DRS has the ability to assess the level of cognitive impairment in different clinical populations and to differentiate between types of dementia. Age and education corrected norms are available and the instrument is sensitive to differences at the lower end of functioning, although it may not be sensitive to cognitive defect in individuals of higher intelligence. The test can be administered and scored by a trained PD nurse specialist and only patients with an age adjusted score of greater than 5 will be eligible at the baseline assessment. Borderline scores should be viewed in the context of other psychological assessments and should be referred to the trial psychologist in case of doubt.

Clinical Assessment: The UPDRS (Appendix G) and Hoehn & Yahr staging system (Appendix H) will be used to provide a standard neurological assessment against which to further validate the PDQ-39. The UPDRS must be performed in full, in both the “on” and “off” states. If, at the follow-up time-points, it is considered too distressing to withdraw drugs and stimulation to induce the “off” state, the “off” UPDRS assessment can be omitted. Other information regarding status and current therapy will be collected at each time-point (Appendix N).

Neuropsychological evaluation: This assessment will comprise a short semi-structured interview (to briefly quantify relevant neuropsychiatric dimensions), patient & carer-rated questionnaires (to quantify depression/anxiety and carer-rated dysexecutive behaviours), and a battery of psychometric tests known to be sensitive to STN, pallidal or thalamic lesions/stimulators. The battery will include measures of premorbid ability, verbal fluency, attention/working memory, executive functions, memory/new learning ability and spatial skills (Appendix I). The full battery will be performed in a limited number of centres, whilst other centres will have the option of contributing data from a core subset of the above battery.

Carers’ psychological well-being: Little work has gone into researching the effect of anti-parkinsonian treatment on carer attitudes, stress or physical and psychological morbidity. The person identified by the patient as their primary carer will be assessed by the SF36 version 2 (Appendix J), a well-validated measure of health status.

7.2. Health economic outcomes

Direct Medical Costs: An economic evaluation will be undertaken as part of the trial. The intention will be to estimate the incremental cost of all types of surgery compared to medical therapy, the incremental effectiveness measured in life years and quality adjusted life years, and the incremental cost-effectiveness.

Costs: Costs will be measured by recording resource volumes used per patient and attaching appropriate unit costs. Data to be collected will include: duration of surgery, types of electrodes, stimulators, pulse generators, leads, and batteries; medications, clinic visits, adverse events, hospitalisations and institutionalisation to nursing or other home. These data will be collected as an integrated part of the trial case forms. Further details of hospitalisations, including main reason for admission, length of stay, and any procedures performed, will be collected from the relevant hospitals. In addition, patients will be asked at the specified trial follow-up intervals to complete a simple (one A4 sheet) questionnaire covering GP consultations, physiotherapy out-patient visits, hospital stays, and other health care resources used since the previous follow-up point, and the volume and opportunity cost of informal care received. This questionnaire is given in Appendix M.
All resources used will be costed using current unit costs derived from national statistics and from participating centres, and a mean net cost per patient in each trial arm and incremental cost per patient will be calculated, together with associated measures of variance.

**Other Endpoints:** Progression of PD may lead to increased requirements for formal domiciliary or residential care as the limits of informal care are exceeded in some patients. Transitions to more intensive forms of care can be viewed both as outcome and as costs. The transitions to formal or paid inputs of care will impose costs either on the public sector or families. Public sector costs are likely to be borne initially by the NHS in terms of short term admissions (geriatrics, neurology), followed by individual needs assessment by the Local Authority Social Services (LASS), leading in turn to packages of domiciliary care and later, if and as appropriate, to placement in a residential care or nursing home. If surgery for PD delays these transitions, it may reduce costs. The economic evaluation will include both informal and formal costs, both those borne by the NHS and by LASS or privately by patients or their families.

8. ACCRUAL AND ANALYSIS

8.1. Projected accrual
There are at least 8,000 new cases of PD diagnosed in the UK each year and, in a substantial proportion of these, the disease will, in due course progress to the stage where surgical intervention becomes an option. Currently in the UK, only a small number of centres are performing surgery, but this number is increasing steadily. On a conservative estimate, if only ten centres were to collaborate and were to randomise just one patient per month, then over 400 patients could be entered in 4 years. More optimistically, there are large numbers of patients potentially eligible for surgical intervention and, with the additional resources available through this trial, larger centres may be able to randomise considerably more than one patient per month. This, along with the expansion of recruitment to a larger number of centres (collaboration internationally will be actively sought), could lead to much larger numbers of patients being entered and it is not unrealistic to anticipate accrual of up to 600 patients.

8.2. Sample size
To detect reliably realistically modest differences requires large trials, with hundreds (rather than tens) of patients randomised. For example, to detect (at $p=0.05$ with 90% power) a 15% difference between two treatments of (e.g. 75% disability reduced to 60%) would require about 200 patients in each arm, while to detect a 10% difference would require about 450 patients in each arm. Alternatively, a 10 point difference between arms on the PDQ-39 would be considered clinically important and to detect this (assuming $SD=30$, $p=0.05$, power=90%) would require about 400 patients in total. Due to a lack of data on patients with advanced PD, more precise estimates of the likely differences between the treatments under comparison can not be made. Thus, the trial adopts a pragmatic approach and will aim to recruit between 400 and 600 patients (this number should be achievable and should allow relatively modest, but clinically meaningful, differences to be detected). If larger than anticipated differences were to be observed, this would be picked up at the annual DEMC reviews (see Section 8.4) and accrual to the trial could be stopped early or modified as appropriate.

8.3. Stratification variables
Within the randomisations, there will be subgroup analyses by years since initial diagnosis of PD (<5 years, 5-9 years, 10-14 years, 15+ years), age at entry (<60, 60-69, 70+ years),
disease stage (Hoehn & Yahr stage \( \leq 2.0; 2.5; 3.0, \geq 4.0 \)), reason for considering surgical intervention (tremor, dyskinesia, severe "off" periods, other reason), type of surgery (stimulation, lesion) and site (STN, GPi) to be performed if allocated surgery and type of medical therapy to be given if allocated medical therapy (apomorphine, other). A subgroup analysis by time period, to investigate “learning curve” effects, will also be performed. Due the serious risk of foreknowledge, the randomisation will not be minimised by surgeon. A retrospective stratification and sub-group by surgeon will be performed to examine the effect of expertise and technique. Because of the serious dangers of misinterpretation, all subgroup analyses will be interpreted cautiously.

The randomisation will be ‘minimised’ by the parameters and strata listed above.

8.4. Independent Trial Steering Committee

The TSC provides independent supervision for the trial, providing advice to the principal investigators and the MRC on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the clinical co-ordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the trial office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8.5. Data Monitoring and Ethics Committee: determining when clear answers have emerged

If surgery for PD really is substantially better or worse than medical therapy with respect to the main endpoints, or survival, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that surgery is definitely more, or less, effective than medical therapy. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt”* that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TSC, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.
9. ORGANISATION

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial:

9.1. Centre eligibility

The Department of Health (and Scottish Executive Health) requires all UK centres undertaking stereotactic neurosurgery to undergo a formal accreditation process, to ensure that surgeons have obtained sufficient expertise from recognised experts, to set minimum standards for the service and to guarantee adequate clinical governance measures are in place. The process is coordinated by the National Specialist Commissioning Advisory Group in England and Wales and the National Services Division in Scotland.

The PD SURG Trial is independent of the accreditation process and it is not required that centres have to be accredited to participate. However, to be recognised as a designated centre for stereotactic surgery for movement disorders by the Department of Health, the centre must be accredited.

9.2. Local Co-ordinator at each centre

Each Centre should nominate one neurosurgeon and one neurologist to act as the Local Co-ordinators. Close collaboration between neurological and surgical teams is particularly important in PD SURG in order that patients for whom surgery is an option can be identified sufficiently early for entry. The responsibilities of the local co-ordinator will be to ensure that all medical and nursing staff involved in the care of PD are well informed about the study. This will involve distributing protocols and patient information sheets to all relevant staff, displaying the wall-chart where it is likely to be read, and the regular newsletters. The local coordinator should liaise with the clinical research fellow and trial coordinator on clinical and administrative matters connected with the trial.

Chief Nursing Co-ordinator at each centre: Each participating centre should also designate one nurse as Local Nursing Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline patient and carer data (e.g. PDQ-39, EuroQoL EQ-5D, SF-36, UPDRS, DRS-2) and for administering the follow-up evaluations (e.g. UPDRS, DRS-2). Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

9.3. Central co-ordination: supply of all trial materials, randomisation service, and data collection and analysis

The Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all trial materials, including the trial folders containing printed materials and the update slides. These will be supplied to each collaborating centre, after relevant ethics committee approval has been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment) and for analyses. The Trial Office can also provide lists of local doctors who have expressed interest in the trial, and help resolve any local problems that may be encountered in trial participation.

The trial organisers have obtained Multi-centre Research Ethics Committee (MREC) approval, which should greatly simplify obtaining Local Research Ethics Committee

ISRCTN34111222 Version 6.2 29th April 2009
(LREC) approval. The Trial Office is also able to help the Local Co-ordinator by applying for LREC approval on behalf of their centre. As soon as LREC approval has been obtained, the Trial Office will send a folder containing all trial materials to the local co-ordinator. Entry of patients into the trial can then begin.

9.4. Funding and Cost implications

The research costs of the trial are funded by a grant from the UK Medical Research Council and UK Parkinson’s Disease Society awarded to the University of Birmingham.

The trial has been designed to minimise extra ‘service support’ costs for participating hospitals, with no extra visits to hospital and no extra tests (for centres where UPDRS is standard practice). Several centres have research nurses funded by the MRC/ PDS award and further support is available for the psychological assessments in selected centres. For other centres, additional costs associated with the trial, e.g. gaining consent, for nurses to explain the questionnaires to patients, etc, should be met by accessing the Trust’s Support for Science budget, which will require centres to submit an estimate of the resources required.

All centres will be required to sign an Investigator’s Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice and confidentiality. Deviations from the agreement will be monitored and the MRC Trial Steering Committee will decide whether any action needs to be taken, e.g. withdrawal of funding for nurse, suspension of centre.

It is a pre-requisite of the trial that centres must be competent in the surgical techniques being evaluated, so infrastructure service development costs will not necessarily be incurred in participating centres. The Department of Health in the UK has agreed to part-fund the treatment costs (surgery costs and the cost of the stimulator) from a central subvention and an agreement has been reached with Health Authorities/ Primary Care Trusts to guarantee the funding of trial and non-trial patients. For further information, please contact the Trial Office.

Centres outside of the UK will be required to fund the clinical costs of the trial locally.

9.5. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so ABPI/ABHI guidelines on indemnity do not apply. The manufacturer of stimulators has not been involved in any way in the design of the trial and will not be involved in its conduct. The normal NHS indemnity liability arrangements for clinician-initiated research will operate in this case. However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial.

9.6. Publication and ancillary studies

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the PD SURG Trial that use Trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some patients (e.g. special investigations in selected hospitals) be referred...
to the Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

**10. REFERENCES**


APPENDIX A PATIENT INFORMATION SHEET

Invitation to join a national study of surgical treatment for Parkinson’s disease

You are being invited to take part in a large national research study, called PD SURG, of surgery for Parkinson’s disease (PD for short). You do not have to take part in PD SURG. 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.

Surgery for Parkinson's disease

There are a number of types of surgery that can be performed on patients with PD. There are two areas of the brain that can be operated upon: the subthalamic nucleus (or STN for short) or the globus pallidum (or GPi for short). There are also two types of operation that can be performed: either a small region of the brain can be destroyed by a small electrical current (this is called “lesioning”), or an electrode can be inserted which produces an electrical current (this is called “stimulation”). Therefore the possibilities are STN stimulation, STN lesioning, GPi stimulation or GPi lesioning (also called pallidotomy).

Why might surgery be of benefit to me?

Your PD has progressed such that the drugs you have been taking until now are no longer able to control the symptoms effectively. It is possible that surgery will help provide greater control of your symptoms and may slow down the progress of the disease, though we know that surgery is not a cure.

If surgical treatments are available why do we need a clinical trial?

Although we know that surgery for patients with advanced PD can produce clear short-term improvements, we do not know when is the best time to perform the surgery. At the current time, this uncertainty means that some doctors prefer to operate earlier in the course of the disease and others like to wait a bit longer. It is important to find out reliably which of these strategies is the best. Also, in a disease with a long time course such as PD, it is very important to assess the long-term impact of surgery on the daily life of people with PD (and on their carers). PD is, unfortunately, a common condition and we need to be absolutely sure that any new – and expensive – operations really are effective, and find out when is the best time to perform them, before they become standard treatment. This means weighing up all the advantages and disadvantages of surgery compared to drug treatment, and seeing which is best overall. This is what we hope to find out from the PD SURG study.

Why have I been invited?

Your hospital consultant has agreed to take part in this large, national study of surgery for PD. Patients can enter the study if their current drug therapy is not working well enough and it is thought that surgery might help. You are in this group and so are eligible to participate in the study, should you choose to do so. The study is aiming to recruit up to 600 patients in total.

Which patients will get surgery and which will get drug treatment?
Since we do not know when is the best time to perform surgery, we need to compare these two options to find out. In order to do this, patients will be allocated to one of two groups at random by a computer at the central study office. You will have an equal chance of drawing any of the treatments, either: 1) early surgery, or 2) medical treatment (with surgery deferred for as long as possible). If you are allocated to group 1, the surgery will be performed as soon as possible, and ideally within one month. Your surgeon will decide whether you receive STN or GPI surgery, and whether it will be by lesioning or stimulation. If you are allocated to group 2, the surgery will be delayed for at least twelve months until your medical team considers it definitely necessary, unless there becomes a clear clinical reason to operate earlier. During this time you will receive whatever drug treatment is considered best for you (this may include treatment with a drug called apomorphine which is given continuously) and your doctors will discuss with you all the various options. Thus, half of the patients will receive early surgery and one half of the patients will receive drug therapy. Whatever treatment you receive during the study, you will still have access to the same medical and nursing support that would be provided if you were not in the study.

What does the PD SURG Study involve?

Entry into the study does not require any extra physical tests at all and no extra clinic visits are necessary as part of the study. You will be asked to complete a straightforward set of questions when you enter the study, then at 1, 2, 3, 5, 7 and 9 years after entry. In addition, a nurse, or other researcher, will assess the severity of your PD at the same time points during your routine visits to the hospital and may perform a psychological evaluation. Your carer, if you have one, will also be asked to answer some questions so that we can find out how helping to look after someone with PD affects their life. It is important that you tell your doctor of any changes in your symptoms so that the treatment you are receiving can be reviewed.

What are the risks of surgery for PD?

As with all forms of surgery, there are some risks from the procedure. Adverse events may be related to the surgery (e.g. bleeding in the brain, which at worst could cause a stroke, possibly leading to weakness of the opposite side of the body and speech problems), the device (infection necessitating removal of the stimulator, malfunction including disconnection of the stimulator) or the stimulation (an increase in writhing movements and double vision, which is reversible on stopping stimulation). Although many of these events are rare, they may be serious when they do occur. The risk of death from surgery is less than one in a hundred.

Your doctors will tell you about the possible adverse effects of the drugs that you might receive. One of the main aims of the study is to determine whether the risks of surgery outweigh the benefits, or vice versa. If new information comes to light during the course of the study, your doctors will tell you about it and discuss with you whether your treatment should be changed.

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

All of the treatments being used in this study are known to help control the symptoms of PD and are already widely used, so the treatment you receive will be at least as good as that available outside the study. We hope that the information from this study will help us to treat patients with PD more effectively in the future.

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. It is up to you to decide and, before doing so, 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, and your carer if you have one, to sign a consent form indicating that you understand what the study involves. Your hospital doctor will then call the study organisers to enter you into PD SURG.

**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 receiving the treatment allocated and withdrawal will not affect the standard of care that you receive subsequently. If you do change your mind later you do not have to give a reason, but it would help our research if you could still complete the questionnaires to let us know how you are doing.

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

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

**Will information about me be kept confidential?**

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. Members of the research team may look at your notes to check that the study is being carried out correctly. We would also like your permission to tell your GP that you are taking part in the study.

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

At the end of the minimum follow-up period for the trial, the answers you provide in the questionnaires, along with the other assessments, will be analysed and a report written for a leading medical journal. The NHS will help ensure that UK doctors are aware of the results, so that patients can be treated with proven, effective treatments.

**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 like PD SURG. The study is funded by a grant from the Medical Research Council and the Parkinson’s Disease Society. 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?**

Having read this leaflet we hope that you will choose to take part in PD SURG. 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 on the cover 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.

**What if I have other concerns?**

If you have any problems, concerns or other questions about this study, you should preferably contact the investigator first – [name, address and telephone number of local investigator]. If you have any complaints about the way the investigator has carried out the study, you may contact [name, address and telephone number of appropriate complaints department]
APPENDIX B: PATIENT AND CARER CONSENT FORM

PD SURG: A large randomised assessment of the relative cost-effectiveness of surgery for Parkinson’s disease

Patient Consent Form

I confirm that I have read and understand the information sheet dated 10/10/03 (version 4) for the above study and have had the opportunity to ask questions.

I have been informed about the PDSURG study and agree to enter it. I hope to complete the study, but I understand that I am free to withdraw from the study at any time without necessarily giving a reason. If I do withdraw, I can continue to expect the highest standard of care from my doctors.

I understand my doctors will provide information about my progress, in confidence, to the central organisers. I understand that the information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status.

I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting +of the results.

I understand that sections of any of my medical notes may be looked at by responsible individuals from the Birmingham Clinical Trials Unit or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

I give consent to my GP being informed about my participation in this study.

Patient’s signature: ____________________________________________
Print name: ___________________________ Date: ______/_____/_______

Clinician’s signature: ___________________________ Date: ______/_____/_______
Print name: ___________________________
PD SURG: A large randomised assessment of the relative cost-effectiveness of surgery for Parkinson’s disease

Carer Consent Form

I confirm that I have read and understand the information sheet dated 10/10/03 (version 4) for the above study and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time without my legal rights being affected.

I understand that the information I supply may be looked at by responsible individuals from the Birmingham Clinical Trials Unit and will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results.

I agree to take part in the above study and to provide information about how the patient’s disease affects me.

Carer’s signature: ________________________________
Print name: ________________________________ Date: __________/________/_______

Clinician’s signature: ________________________________
Print name: ________________________________ Date: __________/________/_______
APPENDIX C: GP LETTER

Doctor
Practice
Street
City
Postcode
NAME                   DATE RANDOMISED
DATE OF BIRTH          PDSURG NUMBER
HOSPITAL NUMBER

Dear Dr gp

Your patient, named above, has agreed to take part in PDSURG, a randomised assessment of the relative effectiveness of surgery for Parkinson’s disease (PD) in which we, and several other centres in the UK and Europe, are participating. PDSURG is organised by the University of Birmingham Clinical Trials Unit and funded jointly by the Medical Research Council (MRC) and Parkinson’s Disease Society (PDS). PDSURG is a large, simple, “real-life” trial that aims to determine reliably whether surgery is more, or less, effective than drug treatment in advanced PD. The trial is designed to fit in with routine practice as far as possible and to impose minimal additional workload.

The above patient has been allocated:

Surgery/Medical therapy.

and will receive STN stimulation/ STN lesioning/ GPi stimulation/ pallidotomy/ continuous apomorphine/ medical therapy other than apomorphine.

The local co-ordinator for the trial is Dr participant, Department of Neurology/Neurosurgery, hospital. The trial has been approved by Trent Multicentre Research Ethics Committee and region Local Research Ethics Committee.

If you require any further information about the study, it can be obtained from the PDSURG trial co-ordinator (see address below).

Please file this letter in the patient’s notes. I would appreciate being notified if he/she is no longer one of your patients.

Yours sincerely

Local co-ordinator

PDSURG Trial Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Edgbaston, Birmingham, B15 2TT

Tel: 0121 415 9129  Fax: 0121 415 9135  Email: pd-trials@bham.ac.uk
APPENDIX D: RANDOMISATION NOTEPAD

Prepare for the randomisation questions by filling in sections A, B C and D on this pad before telephoning the toll free randomisation service on 0800 953 0274 for immediate randomisation, or fax form to 0121 415 9135 for allocation by next working day.

PART A: IDENTIFYING DETAILS
Randomising consultant: .......................................................... Hospital name: ..........................................................
Patient’s full name: .......................................................... Sex: Male □ Female □
Date of birth: .........../........./......... Hospital number: ..........................................................

PART B: PATIENT’S MEDICAL DETAILS
Date of initial diagnosis of PD (mo/yr): .........../......... Hoehn & Yahr stage: ........... 
Has the patient previously received?
Dopamine agonist No □ Yes □
Selegiline No □ Yes □
COMT inhibitor No □ Yes □
Apomorphine No □ Yes □
Reason for considering surgery (more than one box may be ticked):
Tremor □ Dyskinesia □ Severe “off” periods □ Other, specify: ..........................................................

PART C: PLANNED TREATMENT
If allocated to surgery, which operation will be performed?
  STN Stimulation □ STN Lesion □
  GPI Stimulation □ GPI Lesion □
If allocated to medical therapy, will apomorphine be prescribed? No □ Yes □

PART D: QUESTIONNAIRES These must be completed prior to randomisation.
Has the patient completed the following:
PDQ-39 No □ Yes □ EuroQol EQ-5D No □ Yes □
UPDRS performed in ON state: No □ Yes □ In OFF state: No □ Yes □
Has DRS2 been performed: No □ Yes □
Has the patient given written informed consent? No □ Yes □

PART E: TREATMENT ALLOCATION
Treatment: Immediate Surgery □ Medical Management □
PD SURG trial number: S □ □ □ □

PART F: CARER DETAILS
Does the patient have a regular carer? No □ Yes □
If yes, name of principal carer: ..........................................................
Has the carer given written informed consent? No □ Yes □
Has the carer completed the SF36? No □ Yes □
APPENDIX E: ENTRY FORM

PART A: PATIENT’S DETAILS

Ethnic Origin:

- Asian (Indian origin) □
- Asian (Other) □
- Black (Other) □
- Asian (Pakistani origin) □
- Black (Caribbean origin) □
- White □
- Asian (Chinese origin) □
- Black (African origin) □
- Other (Please specify) □

In which country was the patient born? ____________________________

PART B: PREVIOUS AND CURRENT DRUG THERAPY FOR PD

Please give details of the patient's previous and current medication below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Ongoing</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

If Apomorphine is being administered, please state mode.

- Intermittent subcutaneous injection □
- Prefilled pen □
- Self drawn syringe □
- Continuous subcutaneous infusion using syringe driver □

PART D PREVIOUS SURGERY FOR PD

Site _________  Technique_________________________  Left/ Right  Date_____/_____/______

Site _________  Technique_________________________  Left/ Right  Date_____/_____/______
APPENDIX F: PDQ-39

**DUE TO HAVING PARKINSON’S DISEASE**, how often have you experienced the following, during the last month?  
 *(Please tick one box for each question)*

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always or cannot do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Had difficulty doing the leisure activities which you would like to do?</td>
<td></td>
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<td>2.</td>
<td>Had difficulty looking after your home, e.g. DIY, housework, cooking?</td>
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<td>3.</td>
<td>Had difficulty carrying bags of shopping?</td>
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<td>4.</td>
<td>Had problems walking half a mile?</td>
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<td>5.</td>
<td>Had problems walking 100 yards?</td>
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<td>6.</td>
<td>Had problems getting around the house as easily as you would like?</td>
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<td>7.</td>
<td>Had difficulty getting around in public?</td>
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<td>8.</td>
<td>Needed someone else to accompany you when you went out?</td>
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<td>9.</td>
<td>Felt frightened or worried about falling over in public?</td>
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<td>10.</td>
<td>Been confined to the house more than you would like?</td>
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<td>11.</td>
<td>Had difficulty washing yourself?</td>
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<td>12</td>
<td>Had difficulty dressing yourself?</td>
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<td>13</td>
<td>Had problems doing up buttons or shoe laces?</td>
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<td>14</td>
<td>Had problems writing clearly?</td>
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<td>15</td>
<td>Had difficulty cutting up your food?</td>
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<td>16</td>
<td>Had difficulty holding a drink without spilling it?</td>
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<td>17</td>
<td>Felt depressed?</td>
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<td>18</td>
<td>Felt isolated and lonely?</td>
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<td>19</td>
<td>Felt weepy or tearful?</td>
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<td>20</td>
<td>Felt angry or bitter?</td>
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<td>21</td>
<td>Felt anxious?</td>
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<td>22</td>
<td>Felt worried about your future?</td>
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<td>23</td>
<td>Felt you had to conceal your Parkinson's from people?</td>
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<tr>
<td>24</td>
<td>Avoided situations which involve eating or drinking in public?</td>
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<tr>
<td>25</td>
<td>Felt embarrassed in public due to having Parkinson's disease?</td>
<td></td>
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<td>26</td>
<td>Felt worried by other people's reaction to you?</td>
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<tr>
<td>27</td>
<td>Had problems with your close personal relationships?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>28</td>
<td>Lacked support in the ways you need from your spouse or partner?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>29</td>
<td>Lacked support in the ways you need from your family or close friends?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>30</td>
<td>Unexpectedly fallen asleep during the day?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>31</td>
<td>Had problems with your concentration, e.g. when reading or watching TV?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>32</td>
<td>Felt your memory was bad?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>33</td>
<td>Had distressing dreams or hallucinations?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>34</td>
<td>Had difficulty with your speech?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>35</td>
<td>Felt unable to communicate with people properly?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>36</td>
<td>Felt ignored by people?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>37</td>
<td>Had painful muscle cramps or spasms?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>38</td>
<td>Had aches and pains in your joints or body?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>39</td>
<td>Felt unpleasantly hot or cold?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
</tbody>
</table>
APPENDIX G: EUROQOL EQ-5D

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.
Do not tick more than one box in each group.

MOBILITY
I have no problems walking about
I have some problems in walking about
I am confined to bed

SELF-CARE
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

PAIN/DISCOMFORT
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

ANXIETY/DEPRESSION
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.
APPENDIX H: UPDRS

I. Mentation, Behaviour and Mood

1. Intellectual Impairment

   None

   Mild. Consistent forgetfulness with particular recollection of events and no other difficulties

   Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting

   Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems

   Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all

2. Thought Disorder (Due to dementia or drug intoxication)

   None

   Vivid dreaming

   “Benign” hallucinations with insight retained

   Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities

   Persistent hallucinations, delusions, or florid psychosis. Not able to care for self

3. Depression

   Not present

   Periods of sadness or guilt greater than normal, never sustained for days or weeks

   Sustained depression (1 week or more)

   Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss interest)

   Sustained depression with vegetative symptoms and suicidal thoughts or intent

4. Motivation/Initiative

   Normal

   Less assertive than usual; more passive

   Loss of initiative or disinterest in elective (non-routine) activities

   Loss of initiative or disinterest in day to day (routine) activities

   Withdrawn, complete loss of motivation
II. Activities of Daily Living (For both “on” and “off”)

Tick boxes in left column for On and right columns for Off

5. **Speech**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>☐</td>
</tr>
<tr>
<td>Mildly affected. No difficulty being understood</td>
<td>☐</td>
</tr>
<tr>
<td>Moderately affected. Sometimes asked to repeat statements</td>
<td>☐</td>
</tr>
<tr>
<td>Severely affected. Frequently asked to repeat statements</td>
<td>☐</td>
</tr>
<tr>
<td>Unintelligible most of the time</td>
<td>☐</td>
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</table>

6. **Salivation**

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<th>ON</th>
<th>OFF</th>
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<tbody>
<tr>
<td>Normal</td>
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<tr>
<td>Slight but definite excess of saliva in mouth; may have night-time drooling</td>
<td>☐</td>
</tr>
<tr>
<td>Moderately excessive saliva; may have minimal drooling</td>
<td>☐</td>
</tr>
<tr>
<td>Marked excess of saliva with some drooling</td>
<td>☐</td>
</tr>
<tr>
<td>Marked drooling, requires constant tissue or handkerchief</td>
<td>☐</td>
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</table>

7. **Swallowing**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
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<tbody>
<tr>
<td>Normal</td>
<td>☐</td>
</tr>
<tr>
<td>Rare choking</td>
<td>☐</td>
</tr>
<tr>
<td>Occasional choking</td>
<td>☐</td>
</tr>
<tr>
<td>Requires soft food</td>
<td>☐</td>
</tr>
<tr>
<td>Requires NG tube or gastrostomy feeding</td>
<td>☐</td>
</tr>
</tbody>
</table>

8. **Handwriting**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
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<tbody>
<tr>
<td>Normal</td>
<td>☐</td>
</tr>
<tr>
<td>Slightly slow or small</td>
<td>☐</td>
</tr>
<tr>
<td>Moderately slow or small; all words are legible</td>
<td>☐</td>
</tr>
<tr>
<td>Severely affected; not all words are legible</td>
<td>☐</td>
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<tr>
<td>The majority of words are not legible</td>
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9. **Cutting food and handling utensils**

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<th>ON</th>
<th>OFF</th>
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<tbody>
<tr>
<td>Normal</td>
<td>☐</td>
</tr>
<tr>
<td>Somewhat slow and clumsy, but no help needed</td>
<td>☐</td>
</tr>
<tr>
<td>Can cut most foods, although clumsy and slow; some help needed</td>
<td>☐</td>
</tr>
<tr>
<td>Food must be cut by someone, but can still feed slowly</td>
<td>☐</td>
</tr>
<tr>
<td>Needs to be fed</td>
<td>☐</td>
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</table>
10. **Dressing**

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<th>ON</th>
<th>OFF</th>
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<tbody>
<tr>
<td>Normal</td>
<td>□</td>
</tr>
<tr>
<td>Somewhat slow but no help needed</td>
<td>□</td>
</tr>
<tr>
<td>Occasional assistance with buttoning, getting arms in sleeves</td>
<td>□</td>
</tr>
<tr>
<td>Considerable help required, but can do some things alone</td>
<td>□</td>
</tr>
<tr>
<td>Helpless</td>
<td>□</td>
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11. **Hygiene**

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<th>ON</th>
<th>OFF</th>
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<tr>
<td>Normal</td>
<td>□</td>
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<tr>
<td>Somewhat slow, but no help needed</td>
<td>□</td>
</tr>
<tr>
<td>Needs help to shower or bathe, or very slow in hygienic care</td>
<td>□</td>
</tr>
<tr>
<td>Requires assistance for washing, brushing teeth, coming hair, going to bathroom</td>
<td>□</td>
</tr>
<tr>
<td>Foley catheter or other mechanical aids</td>
<td>□</td>
</tr>
</tbody>
</table>

12. **Turning in Bed and Adjusting Bed Clothes**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>□</td>
</tr>
<tr>
<td>Somewhat slow and clumsy, but no help needed</td>
<td>□</td>
</tr>
<tr>
<td>Can turn alone or adjust sheets, but with great difficulty</td>
<td>□</td>
</tr>
<tr>
<td>Can initiate, but not turn or adjust sheets alone</td>
<td>□</td>
</tr>
<tr>
<td>Helpless</td>
<td>□</td>
</tr>
</tbody>
</table>

13. **Falling (Unrelated to freezing)**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>□</td>
</tr>
<tr>
<td>Rare falling</td>
<td>□</td>
</tr>
<tr>
<td>Occasional falls, less than once per day</td>
<td>□</td>
</tr>
<tr>
<td>Falls on average of once daily</td>
<td>□</td>
</tr>
<tr>
<td>Falls more than once daily</td>
<td>□</td>
</tr>
</tbody>
</table>

14. **Freezing when walking**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>□</td>
</tr>
<tr>
<td>Rare freezing when walking; may have start-hesitation</td>
<td>□</td>
</tr>
<tr>
<td>Occasional freezing when walking</td>
<td>□</td>
</tr>
<tr>
<td>Frequent freezing. Occasional falls from freezing</td>
<td>□</td>
</tr>
<tr>
<td>Frequent falls from freezing</td>
<td>□</td>
</tr>
</tbody>
</table>
15. **Walking**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>□</td>
</tr>
<tr>
<td>Mild difficulty. May not swing arms or may tend to drag leg</td>
<td>□</td>
</tr>
<tr>
<td>Moderate difficulty, but requires little or no assistance</td>
<td>□</td>
</tr>
<tr>
<td>Severe disturbance of walking, requiring assistance</td>
<td>□</td>
</tr>
<tr>
<td>Cannot walk at all, even with assistance</td>
<td>□</td>
</tr>
</tbody>
</table>

16. **Tremor (Symptomatic complaint of tremor in any part of body)**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>□</td>
</tr>
<tr>
<td>Slight and infrequently present</td>
<td>□</td>
</tr>
<tr>
<td>Moderate; bothersome to patient</td>
<td>□</td>
</tr>
<tr>
<td>Severe; interferes with many activities</td>
<td>□</td>
</tr>
<tr>
<td>Marked; interferes with most activities</td>
<td>□</td>
</tr>
</tbody>
</table>

17. **Sensory Complaints Related to Parkinsonism**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>□</td>
</tr>
<tr>
<td>Slight and infrequently present</td>
<td>□</td>
</tr>
<tr>
<td>Frequently has numbness, tingling or aching; not distressing</td>
<td>□</td>
</tr>
<tr>
<td>Frequent painful sensations</td>
<td>□</td>
</tr>
<tr>
<td>Excruciating pain</td>
<td>□</td>
</tr>
</tbody>
</table>

### III. Motor Examination

18. **Speech**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>□</td>
</tr>
<tr>
<td>Slight loss of expression, dictation and/or volume</td>
<td>□</td>
</tr>
<tr>
<td>Monotone, slurred but understandable; moderately impaired</td>
<td>□</td>
</tr>
<tr>
<td>Marked impairment, difficult to understand</td>
<td>□</td>
</tr>
<tr>
<td>Unintelligible</td>
<td>□</td>
</tr>
</tbody>
</table>

19. **Facial Expressions**

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>□</td>
</tr>
<tr>
<td>Minimal hypomimia, could be normal “Poker Face”</td>
<td>□</td>
</tr>
<tr>
<td>Slight but definitely abnormal diminution of facial expression</td>
<td>□</td>
</tr>
<tr>
<td>Moderate hypomimia; lips parted some of the time</td>
<td>□</td>
</tr>
<tr>
<td>Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more</td>
<td>□</td>
</tr>
</tbody>
</table>
### 20. Tremor at Rest

<table>
<thead>
<tr>
<th></th>
<th>Face</th>
<th>Left Hand</th>
<th>Right Hand</th>
<th>Left Foot</th>
<th>Right Foot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight and infrequently present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate in amplitude and present most of the time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked in amplitude and present most of the time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 21. Action or Postural Tremor of hands

<table>
<thead>
<tr>
<th></th>
<th>Left Hand</th>
<th>Right Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight; present with action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate in amplitude, present with action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate in amplitude with posture holding as well as action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked in amplitude; interferes with feeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position; ignore cog-wheeling)

<table>
<thead>
<tr>
<th></th>
<th>Neck</th>
<th>Left Arm</th>
<th>Right Arm</th>
<th>Left Leg</th>
<th>Right Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight or detectable only when activated by mirror or other movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked, but full range of motion easily achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe, range of motion achieved with difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 23. Finger Taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately)

<table>
<thead>
<tr>
<th></th>
<th>Left Hand</th>
<th>Right Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild slowing and/or reduction in amplitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can barely perform the task</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
24. **Hand Movements**  *(Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately)*

<table>
<thead>
<tr>
<th></th>
<th>Left Hand</th>
<th>Right Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td>Mild slowing and/or reduction in amplitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can barely perform the task</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25. **Rapid Alternating Movements of Hands**  *(Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, each hand separately)*

<table>
<thead>
<tr>
<th></th>
<th>Left Hand</th>
<th>Right Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td>Mild slowing and/or reduction in amplitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can barely perform the task</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

26. **Leg Agility**  *(Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3in)*

<table>
<thead>
<tr>
<th></th>
<th>Left Leg</th>
<th>Right Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td>Mild slowing and/or reduction in amplitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely impaired. Frequent hesitation initiating movements or arrests in ongoing movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can barely perform the task</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

27. **Arising From Chair**  *(Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest)*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Slow; or may need more than one attempt</td>
<td></td>
</tr>
<tr>
<td>Pushes self up from arms of seat</td>
<td></td>
</tr>
<tr>
<td>Tends to fall back and may have to try more than one time, but can get up without help</td>
<td></td>
</tr>
<tr>
<td>Unable to arise without help</td>
<td></td>
</tr>
</tbody>
</table>

38
### 28. Posture

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal erect</td>
<td></td>
</tr>
<tr>
<td>Not quite erect, slightly stooped posture; could be normal for older person</td>
<td></td>
</tr>
<tr>
<td>Moderately stooped posture, definitely abnormal; can be slightly leaning to one side</td>
<td></td>
</tr>
<tr>
<td>Severely stooped posture with kyphosis; can be moderately leaning to one side</td>
<td></td>
</tr>
<tr>
<td>Marked flexion with extreme abnormality of posture</td>
<td></td>
</tr>
</tbody>
</table>

### 29. Gait

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion</td>
<td></td>
</tr>
<tr>
<td>Walks with difficulty, but requires little or no assistance; may have some festination, short steps or propulsion</td>
<td></td>
</tr>
<tr>
<td>Severe disturbance of gait, requiring assistance</td>
<td></td>
</tr>
<tr>
<td>Cannot walk at all, even with assistance</td>
<td></td>
</tr>
</tbody>
</table>

### 30. Postural Stability  
(Response to sudden strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared, and can have had some practice runs)

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Retropulsion, but recovers unaided</td>
<td></td>
</tr>
<tr>
<td>Absence of postural response; would fall if not caught by examiner</td>
<td></td>
</tr>
<tr>
<td>Very unstable, tends to lose balance spontaneously</td>
<td></td>
</tr>
<tr>
<td>Unable to stand without assistance</td>
<td></td>
</tr>
</tbody>
</table>

### 31. Body Bradykinesia and Hypokinesia  
(Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movements in general)

<table>
<thead>
<tr>
<th>ON</th>
<th>OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Minimal slowness, giving movements a deliberate character; could be normal for some persons. Possibly reduced amplitude</td>
<td></td>
</tr>
<tr>
<td>Mild degree of slowness and poverty of movement which is definitely abnormal Alternatively, some reduced amplitude</td>
<td></td>
</tr>
<tr>
<td>Moderate slowness, poverty of small amplitude of movement</td>
<td></td>
</tr>
<tr>
<td>Marked slowness, poverty or small amplitude of movement</td>
<td></td>
</tr>
</tbody>
</table>
IV. Complications of Therapy (in the past week)

A Dyskinesias

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information)
   - None
   - 1 - 25 % of day
   - 26 - 50 % of day
   - 51 - 75 % of day
   - 76 - 100 % of day

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination)
   - Not disabling
   - Mildly disabling
   - Moderately disabling
   - Severely disabling
   - Completely disabling

34. Painful Dyskinesias: How painful are the dyskinesias?
   - No painful dyskinesias
   - Slight
   - Moderate
   - Severe
   - Marked

35. Presence of Early Morning Dystonia (Historical information)
   - No
   - Yes

B Clinical fluctuations

36. Are any “off” periods predictable as to timing after a dose of medication?
   - No
   - Yes

37. Are any “off” periods unpredictable as to timing after a dose of medication?
   - No
   - Yes

38. Do any of the “off” periods come on suddenly, e.g., over a few seconds?
   - No
   - Yes
39. **What proportion of the waking day is the patient “off” on average?**

None  
1 - 25 % of day  
26 - 50 % of day  
51 - 75 % of day  
76 - 100 % of day  

C Other complications

40. **Does the patient have anorexia, nausea or vomiting?**

No  
Yes  

41. **Does the patient have any sleep disturbances, e.g., insomnia or hypersomnolence?**

No  
Yes  

42. **Does the patient have symptomatic orthostasis?** *(Record the patient’s blood pressure, height and weight on the front page)*

No  
Yes  

**Hoehn and Yahr Stage**

Best ........................................  Worst ........................................

**Blood pressure (mmHg)**

Seated ........................................  Supine ........................................  Standing ........................................

**Pulse (bpm)**

Seated ........................................  Standing ........................................

**Height (m) ........................................**  **Weight (kg) ........................................**
APPENDIX I: HOEHN & YAHRT STAGING SYSTEM

Stage 0   No signs of Parkinson's disease
Stage 1.0  Unilateral involvement only
Stage 1.5  Unilateral and axial involvement
Stage 2.0  Bilateral involvement without impairment of balance
Stage 2.5  Mild bilateral involvement with recovery on retropulsion (pull) test
Stage 3.0  Mild to moderate bilateral involvement, some postural instability but physically independent
Stage 4.0  Severe disability, still able to walk and to stand unassisted
Stage 5.0  Wheelchair bound or bedridden unless aided
APPENDIX J: NEUROPSYCHOLOGICAL EVALUATION

1. Russell-Cairns Clinical Screen
2. Neuropsychiatric Interview (care/ relative rated)
3. Frontal Systems Behavioural Scale (FrSBe); questionnaire, patient and relative rated
4. Hospital Anxiety and Depression Scale; questionnaire
5. National Adult Reading Test (NART)
6. Weschler Abbreviated Scale of Intelligence (WASI):
   a. Vocabulary
   b. Matrices
7. California Verbal Learning Test II (CVLT-II)
8. Weschler Adult Intelligence Scale-III (WAIS-III):
   a. Digit span
   b. Symbol Search
   c. Digit symbol-coding
9. Judgement of Line Orientation (JOLO); ‘short’ form
10. Delis-Kaplan Executive Function System (D-KEFS)
    a. Verbal fluency test
    b. Trail making test
    c. Colour-Word Interference test
11. CANTAB computerised tests
    a. Intradimensional- extradimensional Set-shifting task (IED)
    b. Stockings of Cambridge (SOC)

The full battery will only be performed in selected centres by the trial psychologist.
Test/ questionnaires 4-10 inclusive form the core protocol, which can be performed in
other centres if certain criteria are met.
APPENDIX K: SF36 VERSION 2

OVERALL HEALTH

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

1. **In general**, would you say your health is:

   (Please tick one box)
   
   - Excellent [ ]
   - Very good [ ]
   - Good [ ]
   - Fair [ ]
   - Poor [ ]

2. Compared to 3 months ago, how would you rate your health in general now?

   (Please tick one box)
   
   - Much better than 3 months ago [ ]
   - Somewhat better than 3 months ago [ ]
   - About the same [ ]
   - Somewhat worse now than 3 months ago [ ]
   - Much worse now than 3 months ago [ ]

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

   (Please tick one box on each line)
   
   - Yes, limited a lot [ ]
   - Yes, limited a little [ ]
   - No, not limited at all [ ]

   a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports [ ] [ ] [ ]
   b) **Moderate activities**, such as moving a table, pushing a vacuum, bowling or playing golf [ ] [ ] [ ]
   c) Lifting or carrying groceries [ ] [ ] [ ]
   d) Climbing **several** flights of stairs [ ] [ ] [ ]
   e) Climbing **one** flight of stairs [ ] [ ] [ ]
   f) Bending, kneeling or stooping [ ] [ ] [ ]
   g) Walking **more than a mile** [ ] [ ] [ ]
   h) Walking **half a mile** [ ] [ ] [ ]
   i) Walking **100 yards** [ ] [ ] [ ]
   j) Bathing and dressing yourself [ ] [ ] [ ]
4. During the past 2 weeks, how much time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Please tick one box on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Cut down on the <strong>amount of time</strong> you spent on work or other activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) <strong>Accomplished less</strong> than you would like</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Were limited in the <strong>kind</strong> of work or other activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Had <strong>difficulty</strong> performing the work or other activities (e.g. it took more effort)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. During the past 2 weeks, how much time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Please tick one box on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Cut down on the <strong>amount of time</strong> you spent on work or other activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) <strong>Accomplished less</strong> than you would like</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Didn’t do work or other activities as <strong>carefully</strong> as usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. During the past 2 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(Please tick one box)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>
7. How much bodily pain have you had during the past 2 weeks?

(Please tick one box)

- None
- Very mild
- Mild
- Moderate
- Severe
- Very Severe

8. During the past 2 weeks how much did pain interfere with your normal work (including work both outside the home and housework)?

(Please tick one box)

- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely

9. These questions are about how you feel and how things have been with you during the past 2 weeks. For each question please give the one answer that comes closest to the way you have been feeling.

<table>
<thead>
<tr>
<th>How much time during the last 2 weeks:</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Please tick one box on each line)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Did you feel full of life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Have you been a very nervous person?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Have you felt so down in the dumps that nothing could cheer you up?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Have you felt calm and peaceful?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Did you have a lot of energy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f) Have you felt downhearted and low?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g) Did you feel worn out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h) Have you been a happy person?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Did you feel tired?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10. During the past 2 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.)?

请选择一个选项:

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

11. How TRUE or FALSE is each of the following statements for you?

请选择一个选项:

<table>
<thead>
<tr>
<th>a) I seem to get ill more easily than other people</th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Not sure</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>b) I am as healthy as anybody I know</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) I expect my health to get worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) My health is excellent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX L: POST-OPERATIVE FORM

Surgeon .............................................. Date of Admission ..............................................
Date of Surgery .................................... Date of Discharge ..............................................

PART A: PRE-OPERATIVE ASSESSMENT

Number of clinic visits prior to surgery ..............................................

Please identify the staff who were present at these visits to assess the patient (please tick all who were present)

Neurosurgeon ☐  Neurologist ☐  PD Nurse ☐
Neuropsychologist ☐  Neuropsychology assistant ☐  Other ☐ specify  ..............................................

Did the patient stay in hospital for any pre-operative assessment  Yes ☐  No ☐

If yes, how many days hospital stay was the pre-operative assessment ______ days

Please state how many tests/ procedures were used/ carried out during the pre-operative assessment

EMG ________  CT scan ________  MRI scan ________  CT-MRI fusion ________  X-ray ________

PART B: THEATRE

Was the theatre dedicated to the PD surgery for the entire day?  Yes ☐  No ☐

If no, please state the duration of theatre time required for the preparation, procedure and recovery ______ hours ______ minutes

Did you use a planning station for the planning of the operation?  Yes ☐  No ☐

If yes, which type?  Stealth ☐  Radionics ☐  Brain Lab ☐  Zeiss ☐

Please state the number of each of the following staff present in theatre for preparation, procedure and recovery

Surgeon ________  Neurosurgical technician ________  Anaesthetist ________
Registrar ________  Theatre Nurse ________ PD Nurse ________ Anaesthetist Assistant ________
ODA ________  Electrophysiologist ________  Electrophysiology Technician ________
Other, please state grade and number  ......................................................................................

Was a robotic arm used in this procedure?  Yes ☐  No ☐

What type of stereotactic frame did you use?

CRW (Radionics) ☐  Lecksell-G (Electra) ☐  Leibenger ☐  Other ☐ specify ________

PART C: PROCEDURE

Note: if staged procedure, a form needs completing for each procedure

Bilateral simultaneous ☐  Bilateral staged ☐  If staged:  First ☐  Second ☐
Unilateral ☐

Target  STN ☐  GPI ☐  Technique  Left  Stimulation ☐  Lesion ☐
Right  Stimulation ☐  Lesion ☐

Number of tracts  Left ________  Right ________

Surgery abandoned  No ☐  Yes ☐  If yes, state reason:  .................................................................
PART D: LOCALISATION
Localisation during surgery; please state number of times each test used
CT scan ………………… MRI scan …………… Visual field test ………… Ventriculography ………
ECG ………………… X-ray ………………… Other radiological (state) ………………………………
Externalisation of electrode for test period prior to implantation of pulse generator …………………
Microelectrode ………… Semi microelectrode ………… Impedance ……………………………
Microstimulation ………… Macrostimulation ……………………………
Other electrophysiological (state) ………………………………………………………………………

PART E: STIMULATOR MODEL NUMBERS
Number used Make and model number (if known) or use stickers
Implantable pulse generator …………………………………………………………………………………
DBS Electrode ………………………………………………………………………………………………
Extension Lead ……………………………………………………………………………………………
Therapy Controller ………………………………………………………………………………………
Accessory Kit ………………………………………………………………………………………………

PART F: POST OPERATIVE MANAGEMENT
Please state the number of times each test was used in the days following surgery:
CT scan ………………… MRI scan …………… Visual field test …………
ECG ………………… X-ray ………………… Other radiological (state) ………………………………
Please note MRI images may be reviewed centrally.
Following surgery and pre-discharge, which staff been involved in turning stimulator on,
testing electrode, adjusting voltage etc. Approximately how long in total have they been involved?
Neurosurgeon Yes ☐ No ☐ …………… hrs …………… mins
Neurosurgical technician Yes ☐ No ☐ …………… hrs …………… mins
Neurologist Yes ☐ No ☐ …………… hrs …………… mins
Registrar Yes ☐ No ☐ …………… hrs …………… mins
PD Nurse Yes ☐ No ☐ …………… hrs …………… mins
Theatre nurse Yes ☐ No ☐ …………… hrs …………… mins

PART F: INTRA AND POST OPERATIVE ADVERSE EVENTS
Please indicate any adverse events by ticking the appropriate box(es) below.
Death ☐ Intracerebral haematoma ☐ Hemiparesis ☐ Infection ☐
Hemiballism ☐ Dystonia ☐ Confusion ☐ Seizure ☐
Drowsiness ☐ Eyelid apraxia ☐ Diplopia ☐
Problem with Frame (specify): …………………………………………………………………………………
Anaesthetic Complications (specify): ……………………………………………………………………………
Other (specify): ………………………………………………………………………………………………
Did the adverse event prolong hospitalisation? No ☐ Yes ☐ If yes, for how long days ………
APPENDIX M: SIX MONTH POST-OP FORM

Surgeon

Date of Surgery

PART A: POST OPERATIVE ADVERSE EVENTS

Please indicate any adverse events by ticking the appropriate box(es) below. Remember to ask about admissions to other hospitals.

Device related

- Electrode malplacement
- Electrode displacement
- Electrode fracture
- Lead fracture
- Infection
- Battery malfunction
- Skin erosion
- Other (specify):

Side Effects of Stimulation (with optimum anti PD effects)

- Hemiballism
- Dystonia
- Parasthesia
- Worsening motor function
- Memory impairment
- Depression/anxiety
- Personality change
- Diplopia
- Eyelid apraxia
- Confusion
- Dysarthria
- Aphasia
- Other (specify):

Did the adverse event require hospitalisation? No [ ] Yes [ ] If yes, for how long ______ days

PART C STIMULATION PARAMETERS

<table>
<thead>
<tr>
<th>Pulse width</th>
<th>Rate</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Electrodes in use</th>
<th>LEFT Channel 1</th>
<th>RIGHT Channel 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

PART B CURRENT PD MEDICATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total daily dosage (mg)</th>
<th>Date started (if new)</th>
</tr>
</thead>
</table>

If the patient has ceased taking any PD medication since surgery, please state below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date Stopped</th>
</tr>
</thead>
</table>

Version 4
APPENDIX N: RESOURCE USAGE

Your use of health and social services due to Parkinson’s disease

We would like to know how much use you have made of the health and social services over the last 12 months because of your Parkinson’s disease. If you are not exactly sure, we would rather have your best guess than no information at all. Please answer every question, even if the answer is "0".

1. Over the last 12 months, please state how many times you have:
   - Been seen by your GP?
   - Been seen by a practice nurse?
   - Been seen by a Parkinson’s disease nurse?
   - Been seen by a health visitor?
   - Been seen by a social worker?
   - Been seen by a physiotherapist?
   - Been seen by an occupational therapist?
   - Been seen by a speech or language therapist?
   - Visited a day hospital?
   - Visited a hospital outpatient clinic?

2. If you have had any overnight hospital stays because of your Parkinson’s disease, please state the total number of nights in the last 12 months for respite or treatment.
   - Total number of nights
   - Please give the reasons:
     - Respite Care
     - Treatment

3. Over the last 12 months, have you used or received the following services? (please tick 4)
   - Home care/home help
   - Meals on wheels
   - Day centre
   - Luncheon club
   - Sitting service
   - Night Care
   - If yes, how many times per week?
4. Over the last 12 months, have you consulted a private practitioner such as an Acupuncturist or Aromatherapist as a result of your Parkinson’s disease?

   No [ ] Yes [ ] If Yes, please state how many times: __________

5. Are you currently in paid employment?  No ___ Yes ___

   If Yes, due to your Parkinson’s disease have you had to reduce the number of hours per week you work over the last 12 months? (please tick only one)

   ___ No, I work the same hours. Please state how many hours this is: __________

   ___ Yes, I have had to reduce my hours by __________ hours per week

   ___ Yes, I have had to stop work completely.

   If you are not employed: due to your Parkinson’s disease, in the last 12 months have you had to reduce the number of hours per week you spend carrying out your normal daily activities?

   No ___ Yes ___ I have had to reduce my hours by __________ hours per week.

6. Do you have regular carers who are family members or friends?  No ___ Yes ___

   If Yes, please state how many family/friend carers you have in total: _______.

   In the last 12 months, please state how many hours on average each carer has spent caring for you per week:

   Main carer: ______ hours per week  Other carer: ______ hours per week
   Other carer: ______ hours per week  Other carer: ______ hours per week

7. Are you currently receiving benefits?  No ___ Yes ___

   If Yes, please tick those you been receiving in the last 12 months?

   Statutory Sick Pay [ ] Severe Disablement Allowance [ ]
   Incapacity Benefit [ ] Disability Living Allowance [ ]
   Attendance Allowance [ ]

8. If you would like to tell us about any other costs incurred because of your Parkinson’s disease over the last 12 months, please write them here.

   ……………………………………………………………………………………………………………
   ……………………………………………………………………………………………………………

Many thanks for your help

APPENDIX O: ANNUAL FOLLOW-UP FORM

Surgeon  …………………………………………………………………………………………………………
Neurologist ………………………………………………………………………………………………………
Date of FU Clinic …………………………………………………………………………………………………
PART A: PATIENT’S CURRENT STATUS

Current Hoehn and Yahr Stage

Has patient developed dementia?  No [ ] Yes [ ]  If yes, date of diagnosis __________
Has patient suffered a stroke?  No [ ] Yes [ ]  If yes, date of stroke ______________
Has patient had any other major illness? No [ ] Yes [ ]  If yes, give date and details ________
Has patient moved to residential care? No [ ] Yes [ ]  If yes, give date and details ________
Has patient died? No [ ] Yes [ ]  If yes, give date and details ________
Has the patient been hospitalised for any other reason? ____________________________________________________________

PART B: CURRENT PD MEDICATION (ALL PATIENTS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily total dose (mg)</th>
<th>Date started (if new)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Has the medication changed since the last follow-up? No [ ] Yes [ ]
If yes, give reasons ____________________________________________________________
If Apomorphine is being administered, please state mode.
Intermittent subcutaneous injection  Prefilled pen [ ]
                          Self drawn syringe [ ]
Continuous subcutaneous infusion using syringe driver [ ]
If the patient has ceased taking any medication since last follow-up, please state below

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date Stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PART C: STIMULATION PARAMETERS (ALL PATIENTS WITH STIMULATOR)

Pulse width ...........................................
Rate ....................................................

<table>
<thead>
<tr>
<th>Electrodes in use</th>
<th>LEFT Channel 1</th>
<th>RIGHT Channel 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Amplitude (volts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range (if applicable)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PART D: INDICATION FOR SURGERY (ALL PATIENTS ALLOCATED MEDICAL MANAGEMENT)

Has surgery for PD become definitely indicated?   No [ ] Yes [ ]
If Yes, date joined waiting list for surgery: ........................................
Date surgery performed/anticipated:  ........................................
Reason (if surgery has already been performed): ........................................................................

PART E: LATE ADVERSE EVENTS (SINCE LAST FOLLOW-UP)

Please indicate any adverse events by ticking the appropriate box(es) below.

Device related
Electrode displacement [ ] Electrode fracture [ ] Battery malfunction [ ]
Lead fracture [ ] Infection [ ] Battery replacement [ ]
Skin erosion [ ] Other [ ] (specify): ........................................
Did the event require hospitalisation?   No [ ] Yes [ ] If yes, for how long ....... days

Side Effects of Stimulation (with optimum anti PD effects)
Hemiballism [ ] Dystonia [ ] Parasthesia [ ]
Worsening motor function [ ] Memory impairment [ ] Depression/ anxiety [ ]
Personality change [ ] Diplopia [ ] Eyelid apraxia [ ]
Confusion [ ] Dysarthria [ ] Aphasia [ ]
Other [ ] specify: ........................................................................
Did the event require hospitalisation?   No [ ] Yes [ ] If yes, for how long ....... days

Please use this space to continue recording current PD medication or other notes about patient.
APPENDIX P: SERIOUS ADVERSE EVENT FORM

Please report any **serious** adverse events* believed to be due to the treatments given as part of the PD SURG trial by sending or faxing the following details to the PD SURG Trial Office (fax: 0121-415 9135) within 2 weeks of the event:

Patient’s Full Name: .......................................................... PD SURG No: S [blank]
Date of Birth: ......................................................... Hospital Number: ..........................................................
Responsible doctor: ..............................................................................................................................

PD Treatment No.: ........................................... Date Treatment Started: ........................................
(if known) ..............................................................................................................................................
Date Event Started: .................................. Date Event Ceased: ........................................
Outcome (e.g. fatal, recovered, continuing): ..........................................................................................

Details of Adverse Event: .......................................................... (please attach copies of
relevant reports)
..........................................................................................................................................................
..........................................................................................................................................................
..........................................................................................................................................................

Did the event require or prolong hospitalisation? ..........................................................
Please give reasons why you consider the event to be treatment-related: ........................................
..........................................................................................................................................................
..........................................................................................................................................................

Name of Person Reporting: ..........................................................
(please print)
Telephone Number: .......................................................... Today’s Date: ..........................................................

* For the purposes of this study, “**serious**” adverse events are those which are fatal, life-threatening, disabling or require hospitalisation. It is not required to report in this way side-effects or events that might reasonably be expected, such as disease progression or death (such deaths should be reported on the standard follow-up forms).
## APPENDIX Q: TOXICITY

### Side Effects of Surgery

<table>
<thead>
<tr>
<th>Surgical</th>
<th>Device Related</th>
<th>Side Effects of Stimulation (with optimum effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Electrode malplacement</td>
<td>Hemiballism</td>
</tr>
<tr>
<td>Intracerebral haemotoma</td>
<td>Electrode displacement</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>Electrode fracture</td>
<td>Parasthesia</td>
</tr>
<tr>
<td>Hemiballism</td>
<td>Lead fracture</td>
<td>Worsening motor function</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Lead current leak</td>
<td>Memory impairment</td>
</tr>
<tr>
<td>Confusion</td>
<td>Battery malfunction</td>
<td>Depression/ anxiety</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Skin erosion</td>
<td>Personality change</td>
</tr>
<tr>
<td>Eyelid apraxia</td>
<td>Infection</td>
<td>Diplopia</td>
</tr>
<tr>
<td>Diplopia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Side Effects of Medical Therapy

<table>
<thead>
<tr>
<th>Apomorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local induration</td>
</tr>
<tr>
<td>Nodules at site of injection</td>
</tr>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td>Tenderness</td>
</tr>
<tr>
<td>Panniculitis</td>
</tr>
<tr>
<td>Ulceration</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Neuropsychiatric disturbances</td>
</tr>
<tr>
<td>Mild confusion</td>
</tr>
<tr>
<td>Visual hallucinations</td>
</tr>
<tr>
<td>Transient sedation</td>
</tr>
<tr>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Euphoria, Lightheadedness</td>
</tr>
<tr>
<td>Tremors</td>
</tr>
<tr>
<td>Restlessness</td>
</tr>
<tr>
<td>Coombs’ positive haemolytic anaemia</td>
</tr>
<tr>
<td>Eosinophilia</td>
</tr>
</tbody>
</table>
PD SURG TRIAL SCHEMA

ELIGIBILITY

◆ Any patient with PD that is not adequately controlled by current medical therapy and who is not demented.

RANDOMISATION

◆ Randomisation is based largely on the “uncertainty principle”. That is, if there is a definite contraindication against surgery then the patient is not eligible for randomisation. If, however, there is substantial uncertainty as to whether or not surgery is indicated, the patient is eligible to be randomised.

![Diagram of randomisation process]

Note A: A patient should not be entered if it is considered likely that surgery will become definitely indicated, and can be performed within 12 months of entry.

TELEPHONE RANDOMISATION

◆ Obtain patient’s consent.
◆ Prepare for telephone questions using the randomisation notepad (see Note B).
◆ Telephone the randomisation service on 0800 371 969 or 0800 731 7625 (toll-free) or +44 (0)121 4143787 from outside the UK.
◆ When all the relevant questions on the randomisation notepad have been answered, a treatment allocation and patient reference number will be given.

TREATMENT

◆ If allocated to surgery, the procedure should be performed as soon as possible (and preferably within 4 weeks).
◆ If allocated to medical therapy, the patient should receive whatever medical treatment that is considered appropriate (this may include apomorphine infusion or injection) and surgery should be avoided for as long as possible (until it becomes definitely clinically indicated).
◆ All other patient management is as considered appropriate by the responsible physicians.

FOLLOW-UP

◆ The majority of assessments will be patient (or carer) based, with questionnaires at 1, 2, 3, 5, 7 and 9 years after entry.
◆ Also at 1, 3, 5, 7 and 9 years, clinicians will be asked to assess their patients and fill in a simple form giving details of any changes in disease status, occurrence of major events and current medical therapy.

FOR RANDOMISATION TELEPHONE (TOLL FREE IN UK):
0800 953 0274 OR FAX 0121 415 9135

for RANDOMISATION from outside the UK telephone +44 (0)121 415 9129.

Also for urgent medical queries. For administrative queries and trial supplies, contact the PD Trial Office, University of Birmingham Clinical Trials Unit, Robert Aitken Institute, School of Cancer Sciences, FREEPOST RRKR-JUZR-HZHG, Birmingham B15 2TT UK. Tel: 0121 415 9129