Clinical Trial Protocol

Full title of trial
Double blind, randomised, single centre, crossover pilot trial of bilateral Nucleus Basalis of Meynert Deep Brain stimulation (as an adjunctive treatment to conventional Globus pallidum Deep Brain stimulation) to improve cognitive deficits in patients with Parkinson's disease.

Short title
DBS for thinking and memory problems in Parkinson’s.

Version and date of protocol
Version 3, 29/09/2012

Sponsor:
University College London (UCL)

Funder (if applicable):
Brain Research Trust

Trial device
Deep Brain Stimulation

Phase of trial
Phase 2

Trial sites(s)
NHNN

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Signatures

The Chief investigator and the sponsor have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing (as an urgent safety measure under section 10.3.6 requirements).

The investigator agrees to conduct the trial in compliance with the protocol, GCP, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), Research Governance Framework, (2005), the Sponsor’s SOPs and other regulatory requirements as appropriate.

Chief investigator

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Protocol Version 3.0 29/09/2012
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List of abbreviations

AE  Adverse Event
AR  Adverse Reaction
ASR Annual Safety Report
BDS Blessed Dementia Scale
CA  Competent Authority
CANTAB Cambridge Neuropsychological Test Automated Battery
CI  Chief Investigator
CPT  Continuous Performance Test
CRF Case Report Form
CRO Contract Research Organisation
CTA Clinical Trial Authorisation
CVLT-II California Verbal Learning Test-II
DBS Deep Brain Stimulation
DMC Data Monitoring Committee
DRS-2 Dementia Rating Scale-2
EC  European Commission
EMEA European Medicines Agency
EU  European Union
EudraCT European Clinical Trials Database
fMRI Functional Magnetic Resonance Imaging
GA  General Anaesthesia
GCP Good Clinical Practice
GFQ Freezing of Gait Questionnaire
GMP Good Manufacturing Practice
GPI Globus Pallidus pars Interna
<table>
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<th>Term</th>
<th>Definition</th>
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<td>HAM-D</td>
<td>Hamilton scale for Depression, Anxiety</td>
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<td>HAM-A</td>
<td>Investigator Brochure</td>
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<td>ICF</td>
<td>Informed Consent Form</td>
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<td>MEG</td>
<td>Magnetoencephalography</td>
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<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>MMSE</td>
<td>Minimental State Examination</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>NBM</td>
<td>Nucleus Basalis of Meynert</td>
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<td>NHS R&amp;D</td>
<td>National Health Service Research &amp; Development</td>
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<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
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<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
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<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PI</td>
<td>Principal Investigator</td>
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<td>PIS</td>
<td>Participant Information Sheet</td>
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<td>PRL</td>
<td>Probabilistic Reinforcement Learning</td>
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<td>QA</td>
<td>Quality Assurance</td>
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<td>RCT</td>
<td>Randomised Control Trial</td>
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<td>SAR</td>
<td>Serious Adverse Reaction</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SDR</td>
<td>Spatial Delayed response</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>SRM</td>
<td>Short Recognition Memory</td>
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<td>SSA</td>
<td>Site Specific Assessment</td>
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<td>SSAR</td>
<td>Suspected Serious Adverse Reaction</td>
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<td>STN</td>
<td>Subthalamic Nucleus</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<tr>
<td>No.</td>
<td>Abbreviation</td>
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## Summary

| Title: | Double blind, randomised, single centre, crossover pilot trial of bilateral Nucleus Basalis of Meynert Deep Brain stimulation (as an adjunctive treatment to conventional Globus Pallidum Deep Brain Stimulation) to improve cognitive deficits in patients with Parkinson's disease. |
| Short title: | DBS for thinking & memory problems in Parkinson's. |
| Trial device: | Medtronic PC Deep Brain Stimulation device |
| Phase of trial: | Phase II |
| Objectives: | **Primary Objective-**
To evaluate the effectiveness of human NBM DBS at improving a short battery of cognitive deficits (including but not restricted to deficits in attention and working memory) in PD patients referred for DBS treatment for coexisting motor impairments. **Secondary Objectives-**
To confirm the safety and tolerability of NBM DBS and its impact on activities of daily living, motor performance, broader assessments on cognitive ability, mood, behaviour, non-motor symptoms and quality of life among patients with moderate PD using standard validated tools of assessment.

To identify whether NBM DBS leads to any changes in functional imaging of cortical blood flow will be obtained using fMRI.

To identify whether NBM DBS leads to any changes in cortical activity using magnetoencephalography. |
| Type of trial: | Phase II, double blind, randomised, crossover, single site trial in Parkinson’s disease. |
| Trial design and methods: | We will perform a pilot study to evaluate the effectiveness of human NBM DBS at improving cognitive deficits in PD patients referred and eligible for conventional DBS treatment for coexisting motor impairments. Six patients with PD with both motor fluctuations and cognitive impairments (including but not restricted to deficits in attention and working memory) will have bilateral electrodes |
implanted to ensure that superficial contacts lie in the conventional motor GPi target, while the deepest electrical contacts lie in the NBM- (see figure 1). We will place electrodes using our conventional image guided, stereotactic frame-based procedure currently used in patients at NHNN. Patients will be randomised into 2 groups in a crossover trial design to have 6 week periods of NBM stimulation switched on or switched off separated by a 2 week washout period, following which the patient will cross over to have the opposite condition for a further 6 weeks- see timeline. At the end of the crossover period, all patients will be invited for continued follow up with stimulation switched on and will have neuropsychological evaluations at 6 monthly intervals. Patients will be given the option of receiving additional conventional stimulation to the motor GPi, through the higher contacts of each electrode, at the end of the crossover period.

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<th>Trial duration per participant:</th>
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<td>Total number of participants planned:</td>
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<td>Main inclusion criteria:</td>
<td>All patients will meet Queen Square brain bank criteria for the diagnosis of PD and will have motor fluctuations (off periods and/or L-dopa induced dyskinesias) in response to medications that are known to improve with GPi DBS and will be appropriate candidates for GPi DBS aside from the coexistence of cognitive impairment. Patients will be aged between 35 and 80 years. Patients will be able to give informed consent. Consent by proxy will also be obtained from the primary carer. Patients will meet criteria for PD dementia. Patients will have an MMSE score between 26 and lower cutoff of 21 to restrict the sample to those with mild dementia and cognitive impairment. This will be equivalent to an age and education adjusted scaled score of greater than 5 and lower than 9 (mildly impaired range) on the</td>
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<tr>
<td>Statistical Methodology and Analysis</td>
<td>The primary outcome measure will be the difference in performance on the selected short battery of tests of attention, working memory, executive function and processing speed (see below for details) between ON stimulation and OFF stimulation conditions. The primary outcome measure will be analysed using the Wilcoxon matched pairs signed rank test. The mean difference in the primary outcome and an estimate of its variance will be determined from our results and these data will be used for formal sample size calculations for future studies.</td>
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2 Introduction

2.1 Background

While traditionally viewed as a movement disorder, cognitive impairments are present in up to 36% of patients with Parkinson’s disease (PD) even at the time of diagnosis\(^1\). In a multicentre pooled analysis of 1346 PD patients, variable types of cognitive deficits were seen particularly in association with older age, longer disease duration and increased motor severity, and include isolated deficits in attention, executive function, memory, or visuospatial function as well as patients with deficits in multiple domains\(^2\). Cognitive deficits in attention underlie the phenomenon of dopa refractory gait freezing, a major cause of disability in PD patients\(^3\). Up to 80% of PD patients will ultimately develop dementia, and the natural history of the progression of specific cognitive impairments to dementia in PD has been the subject of detailed population based studies\(^4,5\). The patho-physiological causes of cognitive impairment in PD are diverse being influenced by neuro-degeneration occurring in subcortical dopaminergic and cholinergic neurons, non-physiological dopamine replacement and/or anti-cholinergic medications, comorbid conditions...
affecting brain function, and neuro-degeneration of cortical neurons themselves due to alpha-synuclein positive, Lewy body pathology. Cognitive processing involves the intact functioning of cortical-subcortical neuronal loops. Abnormal activity in one brain region due to its involvement in a pathological process may therefore have widespread physiological effects on other interconnected brain regions in advance of their involvement in the neurodegenerative process.

2.2 Preclinical data

The Nucleus Basalis of Meynert is the major source of cortical and limbic Acetyl-Choline (ACh) and there is extensive evidence of the importance of the NBM and ACh in cognition. When the NBM is electrically stimulated in the rodent, cortical ACh is released, there is EEG activation and facilitation of a range of cognitive tasks. Stimulation of the NBM in non-human primates (NHP) allows more sophisticated evaluation of the functions and projections of this nucleus and confirms its importance in normal cognitive function. Lesions in this area result in deficits in cognitive function in both rodent and NHP models. Furthermore, use of ACh antagonists such as scopolamine have been widely used to model age- and dementia-related cognitive deficits in human and animal models.

2.3 Clinical data

Deep Brain Stimulation surgery is an accepted treatment for the motor complications of chronic PD. Chronic stimulation of the subthalamic nucleus (STN) or globus pallidus pars interna (GPi) can lead to substantial improvements in motor function, and in the complications of chronic oral PD treatment, and the quality of life of the patient. Disturbance of the activity in functional circuits explains why stimulation of the STN (the most common target to treat the motor complications of PD) leads to deterioration in verbal fluency and executive ability, among patients with limited cognitive reserves, because of the cognitive cortical-subcortical projections that pass through the associative territory of the STN. This represents a major barrier in the application of DBS to help many patients with advanced PD.

The NBM lies beneath the GPi in each hemisphere and can be reached with a DBS electrode via the same trajectory to target the GPi, but a few millimetres deeper. The proximity of the NBM to the conventional GPi target thus makes it an appealing structure to stimulate and evaluate therapeutic effects. To date, there has been a single report of a patient with cognitive impairment in association with PD who had DBS electrodes inserted into the NBM with subsequent improvements in attention, concentration and alertness. There is therefore limited but encouraging data on the possibility of using DBS as a treatment for cognitive impairments in PD, in particular stimulation of the NBM.
2.4 Investigational device

Deep Brain stimulation device(s) to be used in this study is manufactured by Medtronic. Their PC device and 1.3mm diameter leads will be used. This can deliver a wide range of amplitude of stimulation, pulse width and frequency.

The stimulation system consists of three implantable components:

**Lead** - the lead is a thin insulated wire with four electrodes at the tip that is implanted in the brain.

**Extension** - The lead is connected to an extension, a thin, insulated wire that is threaded under the skin from the head, down the neck and into the upper chest.

**Neurostimulator** - The extension is connected to a neurostimulator, a small, sealed device similar to a cardiac pacemaker that contains a battery and electronics. The neurostimulator is implanted beneath the skin in the chest or abdominal wall. It produces the electrical pulses needed for stimulation. These electrical pulses are delivered through the extension and through the lead to the GPi in the brain.

External components of the system include a physician programmer (used to adjust neurostimulator parameters) After the trial is over the patient will be provided with a hand-held patient controller that can be held over the neurostimulator to check the battery status and to adjust the electrical parameters where necessary.

The Stimulator System is implanted by a functional neurosurgeon, a neurosurgeon who specialises in central nervous system function. Under a general anaesthetic the neurosurgeon fixes a stereotactic frame to the head and maps the brain using a magnetic resonance imaging (MRI) to localise the target within the brain. Two leads are inserted through small holes drilled through the skull and implanted in the targeted site deep within the brain. Electronic equipment that analyses the electrical properties of the brain may be used to help with this targeting process. Once the lead has been placed at the target, the extension wires and neurostimulator are implanted. Further MRI or CT scans may be obtained during or after the procedure to confirm placement of the electrodes within the desired target area.

The extension is passed under the skin of the scalp and neck, into the trunk to connect the lead to the neurostimulator. An incision of about 3 inches is made under the collar-bone or in the abdomen, a pocket is made just under the skin in which to implant the neurostimulator.

Battery longevity varies, depending on how much electrical energy is required to help improve symptoms. At the expected therapeutic settings, the battery should last an average of two to seven years. A simple surgical procedure is used to replace the neurostimulator and carries much less risk than the initial implantation of the whole device. When it needs to be changed, the old
neurostimulator is replaced by an entirely new neurostimulator that is connected to the original cables and electrode leads.

Most people will not feel the stimulation directly but may feel the effects of stimulation indirectly if it reduces some of their symptoms. Some people may feel a brief tingling sensation when the device is first turned on.

2.5 **Device marketing and current use**

The Medtronic PC device is CE marked for the use of Deep Brain stimulation of patients with Parkinson’s disease or Dystonia. The CE-marking certificate is included in Appendix 2.

2.6 **Clinical and technical Data to Date**

DBS has been in use for the treatment of patients with Movement Disorders since 1989 with many thousands of publications demonstrating its effectiveness. The devices that will be used as part of this study received their CE mark in 2010. Deep Brain Stimulation for the treatment of patients with Parkinson’s disease and Dystonia has been the subject of evaluations by the National Institute of Health and Clinical Excellence.


http://www.nice.org.uk/IPG188

This trial will not be used for commercialisation of these products and therefore does not require MHRA approval in accordance with the guidelines issued on their website-

http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm#l5

2.7 **Rationale and risks/benefits**

Hypotheses that will be tested in this study are as follows;

1. Pathological activity in the NBM is responsible for the deficits of attention and/or other cognitive impairments in PD patients.

2. Deficits in attention/other cognitive impairments in PD patients may be acutely reversed by NBM stimulation that can be achieved via the same electrodes encompassing the traditional GPi target for relief of motor symptoms.

3. NBM stimulation leads to changes in activity in a network of cortical and subcortical regions.
4. Objective clinical measures, together with objective physiological measures of local field potential recordings, magneto-encephalography and functional imaging will consistently reflect improvements in cognitive and motor performance.

5. Improvements in attention and/ or other cognitive impairments in PD patients will translate to functional benefits in day to day functioning, gait freezing, and quality of life.

Risks v benefits-

When the study stops, the DBS stimulator will still be in the participant’s brain. At that point, the participant still has a choice about whether to have it switched on or off and can discuss this with the doctors/ researchers about the level of the stimulation, and the choice or combinations of electrical contacts through which stimulation is administered to maximise benefits for both movement and cognition. We would not normally remove stimulators after a study, except in exceptional circumstances.

The complication rates of DBS surgery are roughly:
- 2% haemorrhage (this includes death)
- 5% infection
- 2% provocation of seizures

The surgical procedure itself does not differ in any way from its specified indication for which it is CE marked, namely high frequency stimulation of the Internal globus pallidum, aside from in these patients the electrodes will be advanced a few millimeters deeper along the same trajectory through the brain, so that the active contacts encompass both the GPi and the NBM.

Participation in this trial will require the patients to make additional trips to the hospital. While additional trips to hospital will be burdensome, patients will benefit from the access to experienced PD clinical advice at each visit.

In addition to undergoing a clinical examination and assessment, patients will be helped to complete all the questionnaires.

3 Objectives

Primary Objective-
To evaluate the effectiveness of human NBM DBS at improving a short battery of cognitive deficits (including but not restricted to deficits in attention and working memory) in PD patients referred for DBS treatment for coexisting motor impairments.

Secondary Objectives-

To confirm the safety and tolerability of NBM DBS and its impact on activities of daily living, motor performance, broader assessments on cognitive ability, mood, behaviour, non-motor symptoms and quality of life among patients with moderate PD using standard validated tools of assessment.

To identify whether NBM DBS leads to any changes in functional imaging of cortical blood flow will be obtained using FDG PET and/or fMRI.

To identify whether NBM DBS leads to any changes in cortical activity using magnetoencephalography.

4 Trial design

4.1 Overall design

This is a non-commercial trial of a CE marked device used to provide bilateral Deep Brain Stimulation to the Nucleus Basalis of Meynert.

We will perform a pilot study to evaluate the effectiveness of human NBM DBS at improving cognitive deficits in PD patients referred for DBS treatment for coexisting motor impairments. Six patients with PD with both motor fluctuations and cognitive impairments (including but not restricted to deficits in attention and working memory) will have bilateral electrodes implanted to ensure that superficial contacts lie in the conventional motor GPi target, while the deepest electrical contacts lie in the NBM- (see figure 1). We will place electrodes using our conventional image guided, stereotactic frame-based procedure currently used in patients at NHNN. The surgery will follow our conventional NHS practice in all ways other than the deeper insertion of the electrodes. During the 1 week between electrode insertion and implantation of the battery (IPG), recordings from the electrodes will be taken in the MEG scanner. Patients will be randomised into 2 groups in a crossover trial design to have 6 week periods of NBM stimulation switched on or switched off separated by a 2 week washout period, following which the patient will cross over to have the opposite condition for a further 6 weeks- see timeline. At the start and end of each period the patient will have a cognitive assessment to evaluate the acute and chronic effects of the stimulation in comparison to the off stimulation condition. Functional Imaging scans (fMRI) will be performed in each patient at baseline and at the end of each blinded ON or OFF stimulation period. At the end of the crossover period, all patients will be invited for continued follow up with stimulation switched on and will have neuropsychological
evaluations at 6 monthly intervals. Patients will be given the option of receiving additional conventional stimulation to the motor GPi, through the higher contacts of each electrode, at the end of the crossover period. All patients will continue to have optimal conventional PD treatment administered throughout the trial period.
Angles of 3387 electrode (10.5 mm length) can be adjusted. Both coronal and sagittal angles, to cover both ventro-posterolateral GPI and nucleus basalis Meynert.

**Figure 1**

4.2 Schematic diagram(s) of overall trial design.
Short title: DBS for memory & thinking in Parkinson's

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- Electrode implantation & Post op MRI
- MEG, LFP recording
- Baseline MRI, DTI, Detailed Neuro-psychology, Motor, NMS & Gait assessment

Derivation of DBS Parameter Session 1/52

6 weeks NBM stimulation ON/OFF

Washout

Condition 1 Detailed Neuropsychology, Motor, NMS & Gait assessment

Condition 2 Detailed Neuropsychology, Motor, NMS & Gait assessment

fMRI

IPG implantation

Weeks 1, 4, 6, 12, 14, 20

Open label GPi DBS +/- NBM DBS

fMRI

Cognitive subtests to assess acute change in performance
5 Selection of Subjects

5.1 Inclusion criteria

All patients will meet Queen Square brain bank criteria for the diagnosis of PD and will have motor fluctuations (off periods and/or L-dopa induced dyskinesias) in response to medications that are known to improve with GPi DBS \(^{24}\), and will be appropriate candidates for GPi DBS aside from the coexistence of cognitive impairment.

Patients will be aged between 35 and 80 years.

Patients will be able to give informed consent. Consent by proxy will also be obtained from the primary carer.

Patients will meet criteria for PD dementia\(^{25}\). Patients will have a MMSE score between 26 and lower cutoff of 21 to restrict the sample to those with mild dementia and cognitive impairment. This will be equivalent to an age and education adjusted scaled score of greater than 5 and lower than 9 (mildly impaired range) on the Mattis Dementia Rating Scale-2.

Patients will have only minimal atrophy on pre-operative brain MRI scans.

Patients will be living at home and will have a carer living with them e.g. their spouse

Able to comply with trial protocol and willing to attend clinic necessary visits

5.2 Exclusion criteria

Diagnosis or suspicion of other cause for parkinsonism or dementia.

Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol.

Prior intra-cerebral surgical intervention for Parkinson’s disease including Deep Brain stimulation, lesional surgery, growth factor administration, gene therapy or cell transplant.

5.3 Concomitant medication

Trial participants will be permitted to use any licensed PD medication throughout the course of the trial that is recommended by their referring Neurologist. Patients will be given advice in any necessary minor adjustments to their pre-existing PD drug therapy at each of their visits and note made of L-dopa equivalent doses at each visit.
6 Recruitment

Patient contact will only be made once the study receives documented main REC approval, any relevant regulatory approval, Local Trust R&D approval, signed site agreement and the site has been initiated by the Sponsor.

Patients will be recruited from the National Hospital for Neurology & Neurosurgery, London.

Patients attending their routine follow up appointments will be informed about the trial by their Neurologist and given a Patient Information sheet. Each potential patient will be pre-screened according to the inclusion/exclusion criteria. At the individual’s request, their contact details will be passed to the trial Investigator.

7 Study procedures and schedule of assessments

7.1 Informed consent procedure

All patients will have had greater than 24 hours between the Patient Information sheet being given and Informed Consent being sought. All potential participants will be assessed for their capacity to provide informed consent by an experienced neuropsychologist independent from the trial group. Providing the patient has been judged to have capacity to provide consent following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study, the chief Investigator, or a person delegated by the Investigator will obtain written informed consent from each subject prior to participation in the trial.

All potential patients/subjects will be properly informed as to the purpose of the trial and the potential risks and benefits known, or that can be reasonably predicted or expected. All personnel obtaining consent from patients will have up to date GCP training. The Investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site and a third copy will be filed in the patients hospital notes. Only the consent form approved by the relevant trial ethics committee will be used.

Each patient wishing to participate in the trial and who provides informed consent will be evaluated with the inclusion/exclusion criteria for eligibility. A thorough review of medical records for each patient will be necessary to review treatment history and ensure the patient meets all the inclusion/exclusion criteria. This review will take place after the patient signs the informed consent.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, given a copy of the revised form and will give their consent to continue in the study.
7.2 Screening and eligibility assessment

As part of their informed consent, the contact details of the research team will be given to each patient. Each patient will have a review of their demographics and data regarding their PD history, medication history, family history, previous imaging, previous genetic tests, and previous drug compliance issues. The Queen Square Brain Bank criteria will thus be applied and their current PD medication regime will be noted. Each patient will be aware that, if eligible, they will have DBS electrodes surgically implanted and that they will then have a 50% chance of being allocated randomly to active stimulation during the first or second 3 month period. They will then be invited for an in-person evaluation to confirm eligibility.

7.3 Screening assessments

Each patient will have an up to date structural MRI brain scan and a Levodopa challenge, (including the Unified Parkinson’s disease rating scale (MDS-UPDRS) identical to the routine NHS assessment of DBS eligibility. The patient will undergo brief cognitive assessment with the mini-mental state examination (MMSE), and the Mattis Dementia Rating scale-2. The results of these tests will be discussed with the patient during a multidisciplinary appointment including the patient, their carer, their Neurologist and a member of the neurosurgical team, and a decision taken on their eligibility for recruitment.

7.4 Baseline Assessments

The patient will be given the Parkinson’s disease quality of life questionnaire (PDQ39), SCOPA Sleep, SCOPA AUT, Non Motor symptoms questionnaire (NMS quest) & Smell Identification test self-assessment forms to complete and bring with them to their baseline evaluation. This will comprise a detailed neuropsychological battery to be completed within one month prior to surgery and will consist of the following;

- MMSE
- Mattis Dementia Rating Scale-2
- National Adult Reading Test
- Wechsler Abbreviated Scale of Intelligence (Vocabulary, Matrices)
- Episodic memory measures (California Verbal Learning Test-II, Short Recognition Memory for Faces)
- Working memory index of WAIS-III (Letter number sequencing, Digit Span, Arithmetic)
- Attention (Continuous Performance Test, Spatial Delayed response, Posner’s covert attention test)
- Executive function (Verbal fluency, Trail Making Test, Probabilistic Reinforcement Learning)
**Processing speed** (Symbol Search and Digit Symbol coding of WAIS-III; simple and choice RT of CANTAB)

Florida Apraxia Screening test

EQ5D

Neuropsychiatric Inventory (an interview schedule for use with the carer)

The Blessed Dementia Scale (an interview schedule for use with the carer)

Clinician rated measures of mood (HAM-D and HAM-A, Starkstein Apathy Scale).

In addition to cognitive assessments, standard PD gait evaluations -quantitative gait analysis, Gait & Falls Questionnaire, will be performed by fully trained individuals.

Pre-operative structural MR imaging will be performed including DTI to allow connectivity analysis according to our standard current practice for DBS. Functional Imaging using fMRI will also be performed at baseline and at the end of each 6 week stimulation period. (FMRI will only be used if the patient is judged to have the motor and cognitive ability to control head movement while lying in the scanner in accordance with our existing research policy).

This will allow an in vivo evaluation of the widespread cortical effects resulting from NBM Stimulation, and represents a vital aspect of the clinical research.

### 7.5 Surgical procedure

The surgery will be performed according to NHS standard clinical practice. The surgery will be performed in general anaesthesia using MR imaging to visualise and target the NBM. The NBM lies just below the GPi and electrodes will be implanted (one in each hemisphere) to include the deepest electrical contacts in NBM and more superficial contacts in GPi using Medtronic wide spaced electrodes- see figure 1. The accuracy of electrode implantation will be confirmed with a post operative MRI scan. The implanted electrodes will be externalised for a period of 1 week during which the patient will undergo a short period of simultaneous local field potential (LFP) recording and magneto- encephalographic (MEG) recording at rest and during a brief period of cognitive testing. The implantable pulse generator will be placed 1 week after electrode implantation in general anaesthesia.

### 7.6 Derivation of DBS parameters

DBS will be switched on only 4 weeks after surgery to ensure all surgical swelling has resolved. Each DBS contact will be tested in turn individually and all subjective patient reports and objective observations of positive and negative effects will be noted for each contact at a range of stimulation frequencies (20-130 Hz). The contacts/ frequencies with the highest ratio between positive and negative effects will be selected for future stimulation at an amplitude threshold just below that associated with patient awareness of the effects of stimulation. In the absence of a clear advantage of one contact, then the post operative
imaging will be used to select the contacts with the optimal anatomical location. In the absence of a clear advantage of any specific frequency, then 130Hz will be used. The stimulation pulse width will be kept at 60 microseconds in all patients.

7.7 Randomisation procedures

Each patient will be randomised to have stimulation ON first or OFF first using previously created randomisation lists. The patient will not be aware of the order of their stimulation allocation. Randomisation lists will be created by the JRO and held independently from the DBS team. All randomisation procedures will take place during working hours.

7.8 Blinding

All the clinical scores done after 6 weeks on-stimulation and 6 weeks off-stimulation will be double-blind, the patient and the clinician directly involved in the scoring will not be aware of the condition of stimulation. The clinician doing the programming will spend the same time adjusting the stimulator of the patient at the start of the on or off-stimulation period. The electrical parameters will be selected in a way that does not induce any lasting side-effect perceived by the patient.

7.9 Emergency unblinding

All participants will have contact details for the DBS team, which is the standard practice for all patients undergoing DBS therapy for any indication. In the event that unblinding of the state of stimulation becomes clinically relevant, the CI will be asked to reveal the stimulation status. All adverse events reported by patients will be recorded. Adverse reactions (likely related to the stimulation) will lead to unblinding of the stimulation status, and open label adjustment of the stimulation to alleviate the adverse event will be performed.

7.10 Subsequent assessments

An abbreviated cognitive assessment comprising the;
- CVLT-II
- Verbal Fluency
- Simple & Choice RT (CANTAB)
- Digit span
- Posner’s covert attention test

will be performed during the first week after surgery, 1 day after each change in condition and at the end of each washout period. This shorter battery of selected tests is amenable to repeated administration (possibility of parallel versions and less affected by practice) will be
used to assess cognition before and after each cross-over phase of the study to identify acute stimulation effects. This short battery includes tests of attention, working memory, episodic memory, executive function and processing speed.

At the end of each 6 week period of stimulation, a battery of assessments identical to the baseline assessments (aside from measures of IQ) will be repeated by individuals unaware of stimulation condition namely;

The patient will be sent the Parkinson’s disease quality of life questionnaire (PDQ39), SCOPA Sleep, SCOPA AUT, & Smell Identification test self-assessment forms to complete and bring with them to their follow up evaluations.

MMSE
Mattis Dementia Rating Scale-2
Episodic memory measures (California Verbal Learning Test-II, Short Recognition Memory for Faces)
Working memory index of WAIS-III (Letter number sequencing, Digit Span, Arithmetic)
Attention (Continuous Performance Test, Spatial Delayed response, Posner’s covert attention test)
Executive function (verbal fluency, Trail Making Test, Probabilistic Reinforcement Learning)
Processing speed (Symbol Search and Digit Symbol coding of WAIS-III; simple and choice RT of CANTAB)
Florida Apraxia Screening test
EQ5D
Neuropsychiatric Inventory (an interview schedule for use with the carer)
The Blessed Dementia Scale (an interview schedule for use with the carer)
Clinician rated measures of mood (HAM-D and HAM-A, Starkstein Apathy Scale).

In addition to cognitive assessments, standard PD evaluations - The Unified Parkinson’s disease rating scale (MDS-UPDRS), Non Motor symptoms questionnaire (NMS quest), quantitative gait analysis, Gait & Falls Questionnaire, will be performed by fully trained individuals.

Functional Imaging using fMRI will again be performed at the end of each 6 week stimulation period. (FMRI will only be used if the patient is judged to have the motor and cognitive ability to control head movement while lying in the scanner in accordance with our existing research policy).

Adverse events and concomitant medications will be recorded at each visit.
### 7.11 Flowchart of study assessments

<table>
<thead>
<tr>
<th>Timing of assessment</th>
<th>Activities during assessment</th>
<th>Forms to be completed</th>
</tr>
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<tr>
<td>Initial discussion during Outpatient clinic visit</td>
<td>Participant education re trial. Patient Information sheet given. Research team contact details given</td>
<td>Consent Form Patient Demographics PD background Information Inclusion/Exclusion criteria MDS-UPDRS On/Off meds MMSE DRS-2</td>
</tr>
<tr>
<td>DBS Eligibility</td>
<td>Patient questions answered &amp; formal assessment of capacity. Patient signs Informed consent - Demographic data re PD - medication history - L-dopa response - Family history - Imaging - Previous genetic tests Structural MRI Brain scan L-dopa challenge MDS-UPDRS MMSE DRS-2</td>
<td>PDQ39, SCOPA Sleep, SCOPA AUT Standard NHS blood tests reviewed prior to baseline evaluation to ensure patient eligibility. MMSE DRS-2 NART WASI CVLT-II SRM (Faces) WAIS-III CPT, SDR, PCAT Verbal fluency, TMT, PRL FAST EQ5D NPI BDS BDS HAM-D, HAM-A, SAS.</td>
</tr>
<tr>
<td>Baseline Assessments</td>
<td>PDQ39, SCOPA Sleep, SCOPA AUT Smell Identification test (to be given to patient and brought to baseline evaluation)</td>
<td>PDQ39, SCOPA Sleep, SCOPA AUT Standard NHS blood tests reviewed prior to baseline evaluation to ensure patient eligibility. MMSE DRS-2 NART WASI CVLT-II SRM (Faces) WAIS-III CPT, SDR, PCAT Verbal fluency, TMT, PRL FAST EQ5D NPI BDS BDS HAM-D, HAM-A, SAS.</td>
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<tr>
<td>Timepoint</td>
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<tr>
<td>Post electrode insertion</td>
<td>WAIS-III Symbol Search and Digit Symbol coding</td>
<td>MDS-UPDRS, NMS quest, GFQ, fMRI datasheet</td>
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<td></td>
<td>Simple and choice RT of CANTAB)</td>
<td>AE</td>
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<td></td>
<td>FAST</td>
<td>Con Meds</td>
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<td></td>
<td>EQ5D</td>
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<td>NPI</td>
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<td>BDS</td>
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<td>HAM-D, HAM-A, SAS</td>
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<td></td>
<td>MDS- UPDRS, NMS quest, Quantitative gait analysis, GFQ.</td>
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<td>fMRI</td>
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<tr>
<td>First week Post IPG surgery</td>
<td>MEG, LFP recording</td>
<td>AE</td>
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<td>CVLT-II</td>
<td>CVLT-II</td>
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<td>Verbal Fluency</td>
<td>Verbal fluency form</td>
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<td>Simple &amp; Choice RT (CANTAB)</td>
<td>Digit span form</td>
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<td></td>
<td>Digit span</td>
<td>PCAT form</td>
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<td></td>
<td>Posner’s covert attention test</td>
<td>AE</td>
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<tr>
<td>4 weeks post electrode insertion</td>
<td>DBS parameter evaluation</td>
<td>DBS parameters to be used</td>
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<td></td>
<td>Randomisation</td>
<td>Randomisation outcome</td>
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<tr>
<td>6 weeks post electrode insertion</td>
<td>CVLT-II</td>
<td>CVLT-II</td>
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<td>Verbal Fluency</td>
<td>Verbal fluency form</td>
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<td>Simple &amp; Choice RT (CANTAB)</td>
<td>Digit span form</td>
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<td>Digit span</td>
<td>PCAT form</td>
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<td></td>
<td>Posner’s covert attention test</td>
<td>AE</td>
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<tr>
<td></td>
<td>to be completed before and 1 day after stimulation set to condition 1</td>
<td>Con Meds</td>
</tr>
<tr>
<td>End of condition 1 Assessments</td>
<td>PDQ39, EQ5D, SCOPA Sleep, SCOPA AUT, Smell Identification test (to be given to patient and brought to baseline evaluation)</td>
<td>PDQ39, SCOPA Sleep, SCOPA AUT, MMSE</td>
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<tr>
<td>(12 weeks post electrode insertion)</td>
<td>MMSE</td>
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<td><strong>14 weeks post electrode insertion</strong></td>
<td><strong>CVLT-II</strong></td>
<td><strong>Verbal Fluency</strong></td>
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<tr>
<td><strong>End of condition 2 Assessments (20 weeks post electrode insertion)</strong></td>
<td><strong>PDQ39, EQ5D, SCOPA Sleep, SCOPA AUT, Smell Identification test (to be given to patient and brought to baseline evaluation)</strong></td>
<td><strong>PDQ39, SCOPA Sleep, SCOPA AUT</strong></td>
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<tr>
<td>MMSE</td>
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<td>DRS-2</td>
<td>DRS-2</td>
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<td>CVLT-II</td>
<td>CVLT-II</td>
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<td>SRM (Faces)</td>
<td>SRM (Faces)</td>
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<tr>
<td>WAIS-III (Letter number sequencing, Digit Span, Arithmetic)</td>
<td>WAIS-III</td>
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<tr>
<td>CPT, SDR, Posner’s covert attention test</td>
<td>CPT, SDR, PCAT</td>
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<td>Verbal fluency, TMT, PRL</td>
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<td>WAIS-III Symbol Search and Digit Symbol coding</td>
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<td>BDS</td>
<td>HAM-D, HAM-A, SAS.</td>
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<td>HAM-D, HAM-A, SAS.</td>
<td>MDS-UPDRS, NMS quest, GFQ</td>
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<tr>
<td>MDS-UPDRS, NMS quest, Quantitative gait analysis, GFQ.</td>
<td>fMRI datasheet</td>
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<td>fMRI</td>
<td>AE</td>
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<tr>
<td>AE</td>
<td>Con Meds</td>
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</tbody>
</table>

### 7.12 Methods

#### 7.12.1 Laboratory procedures

All patient blood samples will be analysed by the standard accredited hospital routine laboratories of the National Hospital for Neurology and Neurosurgery and UCLH.
7.12.2 Radiology or other procedures

All patients will have structural MRI scans performed to assess eligibility, and as part of their DBS surgery according to standard NHS practice at NHNN. DTI scans will also be performed according to our ongoing research protocol- REC approval number 10/H0706/68. fMRI scans will be performed at baseline and at the end of each condition according to our ongoing research protocol 09/H0716/51.

All imaging will take place at the NHNN under the supervision of the CI or delegated members of the DBS clinical team. Analysis of scans will be performed by an experienced trained individual.

7.13 Definition of end of trial

The end of the trial will be the date of the last visit by the last participant.

7.14 Discontinuation/withdrawal of participants and ‘stopping rules’

Appropriate symptomatic treatment for common adverse effects of DBS surgery, and or general anaesthesia will be provided, including nausea, vomiting, pain, transient confusion. Rare adverse effects of DBS surgery including intracerebral haemorrhage, infection, or provocation of seizures will also be treated symptomatically using standard NHS care.

Patients wishing to discontinue participation with the trial will be free to do so. The reasons for withdrawal will be sought from all individuals and recorded. Adverse events will be recorded systematically throughout the trial and from all patients wishing to withdraw. Appropriate medical advice and treatment will be made available to any individuals experiencing adverse events from trial participation.

The trial will be stopped prematurely if there are doubts regarding the safety or scientific validity of its continuation, in accordance with the principles of Good Clinical Practice and the Medicines for Human Use (Clinical Trials) Regulations 2004 Part 4.

8 Assessment of compliance

The patients will not have the facility to turn the DBS system on or off. Adverse reactions (considered by the CI to be related to the DBS) will lead to unblinding of the patients. Open label adjustments to DBS parameters will be made by the trial team to allow continued open label participation.
9 Recording and reporting of adverse events and reactions

9.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product or device has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a device or Investigational Medicinal Product (IMP), whether or not considered related to the device.

Adverse Reaction (AR)

An AR is any untoward and unintended response in a subject to a device, which is related to any administration of the device. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a device qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse event (SAE) or Serious Adverse Reaction (SAR)

Serious Adverse Event (SAE)

An SAE/ SAR fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Suspected unexpected Serious Adverse Reaction (SUSAR)

The definition of a SUSAR is any suspected unexpected adverse reaction related to a device that is both unexpected and serious. In this case the event is not outlined in the manufacturer guide to the device or in the protocol.
9.2 Notification and reporting Adverse Events or Reactions

AEs and ARs will be recorded in the CRF of each patient and the AE/AR log.

9.3 Notification and Reporting of Serious Adverse Events/SUSAR

As the device used in this project are licensed in the UK and used within their marketing authorization, the EXPECTED SARs will be RECORDED in the subjects’ notes/CRF. No SAE forms will be completed and sent to the sponsor. Trust reporting requirements for events and incidents will be followed.

UNEXPECTED Serious Adverse Event (SAE’s) will be recorded in the subjects’ notes/CRF, the sponsor SAE form and reported to the UCL/UCLH/RF Joint Biomedical Research (JRO) Unit as soon as possible. The co-investigators listed in this protocol will be authorized to sign the SAE forms in the absence of the PI. Suspected Unexpected Serious Adverse Reactions (SUSAR’s) during the trial will be reported to the JRO and the main REC within one working day of the PI or co-investigator becoming aware of the event. NHS Trust reporting requirements for events and incidents will be followed.

9.4 Identification of SAE’s/SUSARs

Expected SAEs include:

- Infection of surgical wounds and/or DBS hardware
- Epileptic seizures
- Intra-cranial haemorrhage

SAEs may be related to the surgery (e.g. bleeding in the brain, which 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). Although these events are rare (e.g. infection: 1%; bleeding <1%; lead fracture <1% in specialised centres across UK), they may be serious when they do occur. There is also a risk of epilepsy or having a convulsive fit with any brain operation (estimated at 0.6% for DBS surgery). The risk of death from surgery is again below 1 in a hundred.

9.4.1 Notification of deaths

All deaths will be immediately (within one working day of the CI becoming aware of the death) reported to the sponsor irrespective of whether the death is related to disease progression, the implantation of the device, or an unrelated event.
10 Data management and quality assurance

10.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 1998. The Case Report Forms (CRFs) will not bear the subject’s name. The subject’s initials, date of birth and trial identification number, will be used for identification.

10.2 Data collection tools and source document identification

Case report forms will be designed and produced by the investigator, according to the sponsor’s CRF template. The final version will be approved by the sponsor. All data will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted.

10.3 Data handling and analysis

A Microsoft Access database will be specifically designed for data entry and storage. Numerical limits (e.g. valid values 0-4) will be put in place to prevent erroneous data being entered. This database will be stored on a single UCL computer with secure server backup to prevent data loss in case of hardware failure. This computer will have restricted access, will be username and password protected, and will be kept in a secure University research facility. The CI will delegate responsibility for data entry and quality to a named individual who will be part of the trial team. The CI will be responsible for data analysis which will be done independently of data entry.

11 Record keeping and archiving

The Chief Investigator is responsible for the secure archiving of trial documents and the trial database. The site files, CRFs and consent forms, and the trial database will be retained for 10 years after completion of the study. Data will be stored to enable additional retrospective subgroup analyses to be performed or to look at long term follow up outcomes, should future data indicate that this may be of interest or importance.

These data will be stored in a secure University Research facility.
12 Statistical Considerations

Dr Foltynie has been formally trained in Epidemiology and Biostatistics at the University of Cambridge (MPhil 2000), and has taken the statistical decisions in the design of the protocol. Additional statistical advice has been sought through the UCL JRBU.

12.1 Endpoints

12.1.1 Primary endpoints

Differences between each item of the abbreviated cognitive battery scores between patients after 6 weeks ON stimulation and 6 weeks OFF stimulation.

- CVLT-II
- Verbal Fluency
- Simple & Choice RT (CANTAB)
- Digit span
- Posner’s covert attention test

12.1.2 Secondary endpoints

Difference between the following assessments between patients ON stimulation and OFF stimulation in:

- MMSE
- DRS-2
- SRM (Faces)
- WAIS-III (Letter number sequencing, Arithmetic)
- CPT, SDR
- TMT, PRL
- WAIS-III Symbol Search and Digit Symbol coding
- FAST
- EQ5D
- NPI
- BDS
- HAM-D, HAM-A, SAS.
- MDS-UPDRS, NMS quest,
12.2 Sample size and recruitment

12.2.1 Sample size calculation

Six patients will be recruited to this pilot study. There has only been a single case report of NBM DBS in humans and therefore there is not sufficient prior data to perform sample size calculations. Following completion of this trial, a refined estimate of the potential efficacy of NBM DBS can then be used in the design and sample size calculation in a future larger trial. This pilot data will also provide evidence of safety of NBM DBS in this patient group.

12.3 Statistical analysis plan

12.3.1 Primary endpoint analysis

Every effort will be made to ensure that missing data for the primary outcomes is kept to a minimum. In view of the small sample size, a non-parametric test e.g the Wilcoxon matched pairs signed rank test will be used to assess differences between scores ON and OFF stimulation. No subgroup analyses are planned. The mean difference in the primary outcome and an estimate of its variance will be determined from our results and these data will be used for formal sample size calculations for future studies.

12.3.2 Secondary endpoint analysis

Each of the secondary outcome measures will be analysed using the Wilcoxon matched pairs signed rank test. Every effort will be made to ensure that missing data is kept to a minimum for all secondary endpoints. However the tests will be arranged such that missing data due to fatigue will have minimal impact on the scientific interpretation of the data.
13 Name of Committees involved in trial

A Trial Management Group (TMG) will be created to supervise the conduct of the trial. This will comprise the chief investigator, two collaborating senior principal investigators, and the research fellow coordinating data collection and data entry.

14 Ethics

This trial will be conducted in accordance with the Seoul revision of the Declaration of Helsinki (2008), the principles of Good Clinical Practice according to the EU directive 2005/28/EC (GCP Directive) and The Medicines for Human Use (Clinical Trials) Regulations Statutory Instruments 2004/1031 and 2006/1938 in the UK.

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by main REC prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical approval prior to implementation.

15 Finance

All patients participating in this trial will be eligible and appropriate for pallidal (GPi) DBS for the treatment of the motor aspects of the Parkinson’s disease. The DBS systems will therefore be funded by the patient’s PCT as this indication is NICE approved.

All other aspects of the trial will be funded by the Brain Research Trust- ref-PAR11141

16 Insurance

Standard NHS Indemnity arrangements apply for providing indemnity and/or compensation in the event of a claim by, or on behalf of participants for negligent harm.

UCL will provide non-negligent insurance cover.
17 Publication policy

The results of this pilot trial will be submitted for publication in a peer reviewed journal, in addition to reports at appropriate specialist conferences.

18 Statement of compliance

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

19 References

Reference List


