The INVEST study

Treatment in advanced Parkinson's disease: continuous intrajejunal levodopa INfusion VErsus deep brain STimulation.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
aPTT	**activated partial thromboplastin time**
AE	**Adverse Event**
ALDS	**AMC Linear Disability Score**
AMC	**Academic Medical Center**
AR	**Adverse Reaction**
CA	**Competent Authority**
CAI	**Continuous subcutaneous Apomorphine Infusion**
CBO	**Centraal BegeleidingsOrgaan**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CDRS	**Clinical Dyskinesia Rating Scale**
CEA	**Cost Effectiveness analysis (CEA)**
CLI	**Continuous intrajejunal Levodopa Infusion**
CRF	**Case Report Form**
CRU	**AMC Clinic Research Unit**
CT	**Computed Tomography**
CV	**Curriculum Vitae**
DBS	**Deep Brain Stimulation**
DSMB	**Data Safety Monitoring Board**
EKG	**Electocardiogram**
EQ-5D	**Euro-Qol 5D**
EU	**European Union**
FDA 21CFR	**US Food and Drug Administration Code of Federal Regulations Title 21**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICH	**International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use**
iMCQ	**Institute for Medical Technology Assessment Medical Consumption Questionnaire**
IMP	**Investigational Medicinal Product**

IMPD	**Investigational Medicinal Product Dossier**
INVEST	**Infusion Versus Stimulation**
iPCQ	**Institute for Medical Technology Assessment Productivity Cost Questionnaire**
MDS-UPDRS	**Movement Disorder Society's Unified Parkinson's Disease Rating Scale**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MINI	**Mini-International Neuropsychiatric Interview**
MRI	**Magnetic Resonance Imaging**
NFU	**Nederlandse Federatie van Universitaire Medische Centra**
NSTAPS	**The Netherlands SubThalamic and Pallidal Stimulation**
PD	**Parkinson's Disease**
PD-CRS	**Parkinson's Disease Cognitive Rating Scale**
PDQ-39	**The 39-Item Parkinson's Disease Questionnaire**
PEG	**Percutaneous Endoscopic Gastrostomy**
PIN	**Patient Identification Number**
PT	**Prothrombin Time**
PROAPD	**Patient-reported outcome tool for advanced Parkinson's disease**
QALY	**Quality Adjusted Life Year**
RCT	**Randomized Controlled Trail**
RvZ	**Raad voor de Volksgezondheid**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
STN	**Subthalamic Nucleus**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WTP	**Willingness-to-pay**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Both Continuous intrajejunal Levodopa Infusion (CLI) and Deep Brain Stimulation (DBS) are accepted therapies for the treatment of advanced Parkinson's disease (PD). Neurologists and patients tend to prefer the more expensive CLI although a scientific rationale is lacking. To determine the optimal treatment in advanced PD, a comparative study of CLI and DBS is warranted.

Hypothesis: We hypothesize that CLI is a more expensive therapy in advanced PD than DBS and that the surplus in costs is not cost-effective with regard to benefits for the patient and caregivers in quality of life, PD symptoms and adverse events.

Objective: To realize a cost-effective treatment strategy in advanced PD.

Study design: Prospective, randomized, open label multicentre trial, with two additional observational patient preference treatment arms ("patient preference randomized trial").

Study population: Patients with PD who, despite optimal pharmacological treatment, have severe response fluctuations, dyskinesias, painful dystonia, or bradykinesia. A total of 66 patients will be randomized, at least120 patients will be included in the patient preference arms.

Intervention: Patients will be randomized to DBS or CLI. For DBS treatment, 2 electrodes will be implanted in the brain. The electrodes are connected to an implanted pulse generator, which will be placed subcutaneously in the subclavian area. For CLI treatment, a tube will be placed in the jejunum via a percutaneous endoscopic gastrostomy (PEG). This tube is connected to an external pump that delivers the levodopa-gel.

Main study parameters: There are 8 specified assessment visits for the patients in the randomized trial: at baseline, and 1 week, 3, 6, 9, 12, 24 and 36 months after start of the study treatment. The primary health economic outcomes are the costs per unit on the PDQ-39 and the costs per QALY for the cost-effectiveness and cost-utility analyses, respectively. The EQ-5D will be applied as the utility measure. Among the secondary outcomes are neurological impairments, functional health, care use and perceptions of patients and neurologists regarding both treatments.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The study investigates the cost-effectiveness and cost-utility comparing CLI and DBS. Both treatments are currently available for advanced PD and both have a small risk of severe side effects. The surplus in burden of study participation compared to the regular treatment consists of a more detailed assessment procedure. The additional time for these extra assessments — consisting of questionnaires and motor symptom assessments — is approximately 15 hours, including time to travel. Besides this small burden the study has no additional risk compared to standard practice, which constitutes a negligible risk

according to the NFU (Nederlandse Federatie van Universitaire Medische Centra) criteria for human research.

1. INTRODUCTION AND RATIONALE

Parkinson's disease (PD) is a neurodegenerative disease affecting the motor, autonomic, cognitive, and sensory systems. It is a disease of the elderly: above the age of 55 years, the prevalence of PD is 1.4%.[1] In 2011, almost 60.000 patients in the Netherlands were estimated to have PD and due to ageing of the population an increase of at least 50% is expected in the following years.[2] PD is one of the diseases causing the largest reduction in quality of life and social functioning and the ability to work are impaired.
The core symptoms of PD are caused by the degeneration of dopamine producing neurons. At present there is no cure for PD, but several symptomatic therapies are available that mainly act upon the motor symptoms. Most of these (i.e., tremor, rigidity and bradykinesia) initially respond well to oral dopamine replacement although dyskinesias frequently occur after a variable period. Patients with advanced PD frequently show rapid and seemingly unpredictable swings between mobility, often with dyskinesias (ON-phase), and immobility (OFF-phase).[3] In the Netherlands, the prevailing treatment options for these patients are Deep Brain Stimulation (DBS) and Continuous intrajejunal Levodopa Infusion (CLI).[4] Continuous apomorphine infusion (CAI) is gaining more ground as another treatment option, since this treatment was researched in a recent double blind randomised controlled trial.[5]

For DBS, a neurosurgeon places two electrodes in the brain. These are connected to an implantable pulse generator. Patients continue with PD medications, though often at a lower dose.
For CLI, a gastroenterologist places a tube in the jejunum, which is connected to a portable pump. A levodopa-gel is continuously administered through the tube. In general, patients with CLI may stop other PD medications. Similar to DBS treatment, patients are hospitalized for placement of the tube and for the start of the levodopa-gel treatment. In both treatments, patients regularly visit the outpatient clinic to adjust the treatment.
Another treatment option for patients with advanced PD is Continuous subcutaneous Apomorphine Infusion (CAI). In the Netherlands CAI is used in a smaller number of patients. CAI is not included in this research protocol, because at start of this trial, the evidence for effectiveness of CAI was of poor quality. Besides, CAI is slightly more expensive than DBS. A study that directly compares all three treatments is not feasible because of the large sample size needed.
Both treatment with DBS and CLI is expensive. We estimate that DBS equipment and batteries cost €10,000 per patient/year and CLI equipment and infusion solutions cost

€45,000 per patient/year. In addition, patients need surgery and they frequently visit the clinic. In a recent Spanish study the mean cumulative 5-year cost per patient (including the surgery) was estimated € 88,014 for DBS and € 233,986 for CLI. [6]

Several level I studies have shown that DBS is efficacious for the treatment of PD motor symptoms: it reduces dyskinesias and motor fluctuations.[7] CLI reduces off-time and is effective for the treatment of motor fluctuations and dyskinesias as was shown in a few small and one larger level I trial. Both therapies significantly improve quality of life.[7-13] No head-to-head comparison of DBS and CLI has been performed, but when comparing individual studies, the effects on quality of life are similar.[8, 13] Little is known about comparative adverse-effects profiles of the therapies. One retrospective study suggests a higher rate of complications in CLI.[14]

The lack of comparative knowledge is reflected in the current CBO-guideline for PD (2010), which states no preference for one of the therapies.[4] Both DBS and CLI are available in the Netherlands and both are covered by the basic health insurance. After the introduction of CLI in 2007, the number of patients with PD receiving the traditionally standard treatment DBS initially slightly decreased, while the number of patients receiving CLI has increased, resulting in an approximately equal number of yearly DBS and CLI procedures in the Netherlands at the moment (80 each). [15] Currently, an estimated 600 PD patients have DBS and 300 patients are treated with CLI in the Netherlands. At present, there is unwanted variation in medical practice. Surveys we performed showed that out of 287 Dutch neurologists (response 50.5%), 45% prefers CLI and 35% prefers DBS. In 62 PD patients from a regional branch of the Dutch Parkinson Association only treated with oral medication, 40% prefers CLI, against 9% preferring DBS and 51% without preference.
That both patients and neurologists tend to prefer CLI over the traditionally standard treatment DBS, is of interest considering the lower level of evidence of CLI, but also given the fact that CLI probably is much more expensive than DBS.

In this comparative study between DBS and CLI we will assess the cost-effectiveness of both treatment options in advanced PD. Results of the INVEST study will probably lead to an unambiguous practice guideline. The resulting more efficient care may facilitate treatment with DBS in the more early stage of the disease process.[12]

2. OBJECTIVES

2.1 Primary Objective

To realize an efficient allocation of resources to the available treatment options in advanced PD, while guaranteeing the highest standard of care.

For the primary objective the following research questions will be answered:
1. What are, in the Netherlands, the direct and indirect costs and benefits of CLI and DBS as the two prevailing treatment options for advanced PD?
2. Is CLI cost-effective in advanced PD when compared to DBS?
3. With regard to the implementation, what are the perceptions about the two therapies in advanced PD in patients and neurologists and do they correspond to the actual figures on burden of the procedure and care, the effects, adverse events and costs?

2.2 Secondary Objectives

Secondary objectives are to compare motor and non-motor symptoms, quality of life, and daily functioning, adverse effects and complications between treatment with DBS and CLI.

3. STUDY DESIGN

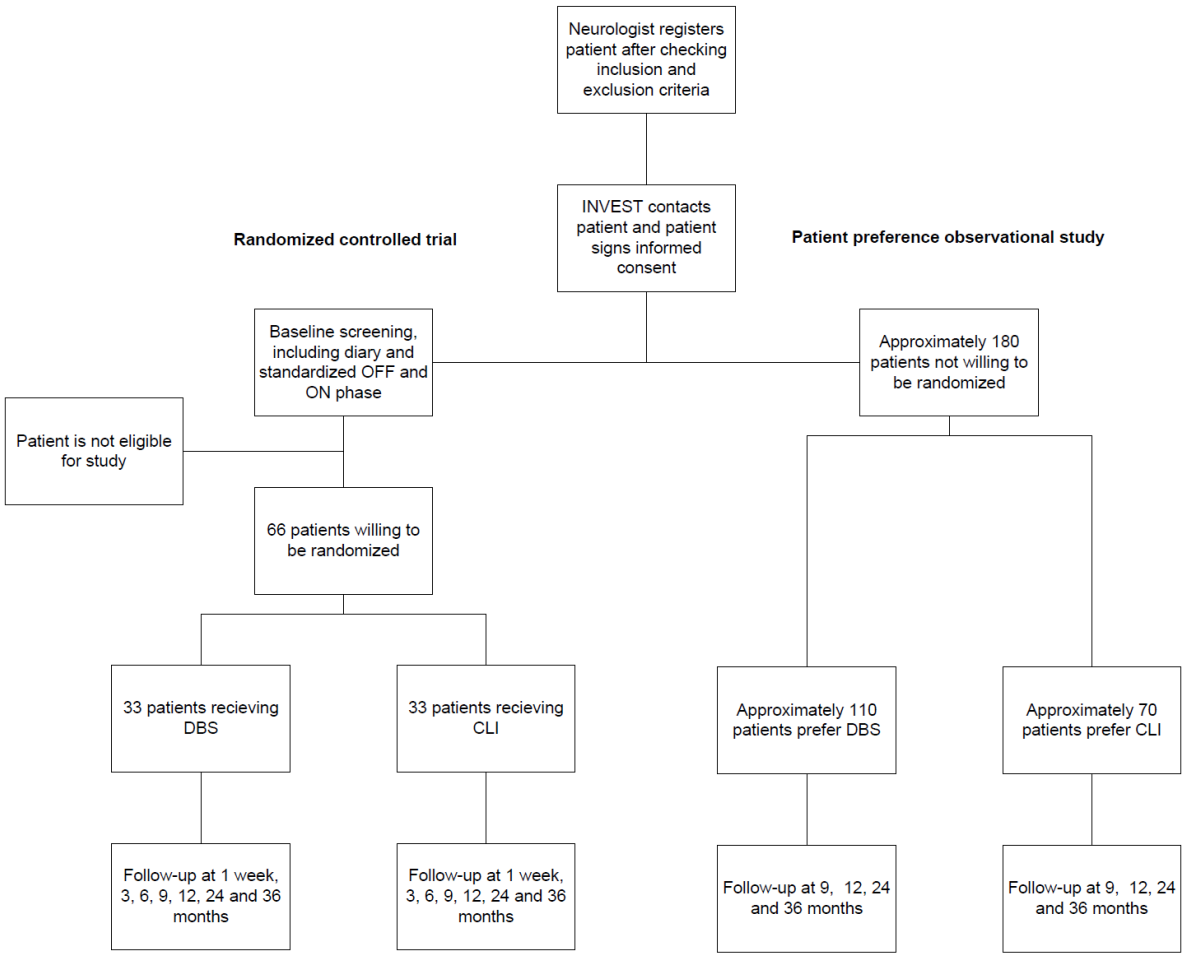
A prospective open label multi-centre randomized controlled trail (RCT) will be performed, with two additional patient preference arms (“patient preference randomized trial”).
Patients who do not want to be randomized for treatment with one of the available therapies, will be asked to participate in the patient preference observational study. All patients will undergo a baseline evaluation and an assessment at the end of the 12-month follow-up (see figure 1 on page 15). A prolonged follow-up of 24 and 36 months will be evaluated too. A total of 66 patients will be included in the RCT and at least 120 patients are expected to take part in the patient preference part of the study.
For patients that do not want to take part in the patient preference randomized trial, the treating neurologist will be asked to fill in an anonymous questionnaire assessing general information in terms of age, sex, medication, age of onset PD, duration of PD, comorbidities and therapy of choice.

Because DBS and CLI are invasive treatments and both procedures have a (small) risk for irreversible and severe adverse events, it is not ethical to perform additional sham procedures. Therefore it is not possible to blind the patient for treatment assignment. As the primary health economic outcome and the primary clinical outcome are both based on patient-reported perceived quality of life measure (PDQ-39), a blinded endpoint assessment (PROBE-design) is not possible.

Rationale for the design

The RCT design in combination with an observational patient preference study was chosen because the studied therapies are available and differ largely. Currently, patients and neurologists together decide on what therapy to choose. Both patients and treating neurologists seem to have specific perceptions about the therapies. Consequently, the proportion of patients that is willing to be randomized between the two available treatments may be relatively small. This patient selection may restrict the generalization of the RCT results. Therefore, patients who are not willing to be randomized will be asked to take part in the patient preference observational study. These patients are allowed to receive their desired treatment without randomization and will be studied with respect to their baseline characteristics, primary clinical outcome and adverse events of the treatment. If the randomized patients resemble the non-randomized patients the RCT-results reflect a more accurate estimate of the treatment benefits and greater evidence of its external validity.

Figure 1, flowchart



4. STUDY POPULATION

4.1 Population (base)

Research population and source population

Patients with advanced PD who are eligible for treatment with both DBS and CLI. Adult patients will be recruited from academic and non-academic hospitals.

Feasibility

Currently, in the Netherlands, each year approximately 140 patients are eligible for treatment with DBS and CLI (all 80 patients yearly treated with DBS and approximately 80% of 80 patients yearly treated with CLI).
Approximately 160 are treated with DBS or CLI in the Netherlands yearly. We estimate that 140 patients will be eligible for the study and that 110 are initially treated in one of the participating centres. With a study duration of 33 months 302 patients will be eligible. This implies that a total of 66 patients (22% of eligible patients) will need to be randomized to assess cost-effectiveness of the treatments. This is a realistic goal because in the latest study in the same patient population, 58% of the eligible patients were recruited.[11]

For the two patient preference arms, we estimate that up to 180 patients will take part (i.e. 60% of the eligible population). It is our experience, from discussions with representatives of the Parkinson's disease association and in the outpatient clinic, that patients consider it important that more information on treatment of advanced PD becomes available. Therefore, we think this is a realistic estimation. The burden of cooperation is low for the patient, especially since visits for the study will be combined with visits to the outpatient clinic for regular care or will be performed at home.

Characteristics of study population

PD is a disease of the elderly. We expect the population will be similar to the NSTAPS study, a study that was recently performed in the Academic Medical Center, comparing treatment with DBS in two different targets in the brain. In this study, the mean age was approximately 60 years, with a mean age of onset of PD of 49 years. In the NSTAPS study about 69% of the patients was male.[11]

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
Age > 18 years

• idiopathic PD with bradykinesia and at least two of the following signs; resting tremor, rigidity, and asymmetry;
• despite optimal pharmacological treatment, at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonia or bradykinesia;
• a life expectancy of at least two years.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• legally incompetent adults
• previous PD-neurosurgery (e.g., DBS, pallidotomy, thalamotomy);
• previous CLI (through a PEG-tube or Nasal Jejunal tube);
• contraindications for DBS surgery, such as a physical disorder making surgery hazardous;
• contraindications for PEG surgery such as interposed organs, ascites and oesophagogastric varices, or for Duodopa;
• Hoehn and Yahr stage 5 at the best moment during the day;
• other, severely disabling condition
• dementia or indication for severe cognitive impairment, such as PD-CRS <65
• psychosis;
• current depression;
• pregnancy, breastfeeding, and women of child bearing age not using a reliable method of contraception;
• no written informed consent;
• age below 18 years;

4.4 Sample size calculation

RCT

The primary objective of the study is to realize an efficient allocation of resources to the available treatment options in advanced PD. For this, primarily an economic evaluation will be carried out and the sample size has been calculated accordingly. Society's willingness-to-pay (WTP) per Quality Adjusted Life Year (QALY) may be indicative of whether or not CLI is affordable compared to DBS. The Dutch Raad voor de Volksgezondheid (RvZ) reported a value of €80,000 per additional QALY in 2006 as a potential upper limit of affordability. Explicitly, the figure is reported by the RvZ as a potential, but also unofficial limit: it should

not be taken as a definite one. Other arguments based on patient preference or access to health care should be taken into account as well. Considering that CLI may be a less invasive intervention and access to health care is easier to facilitate when two interventions can be provided, a more lenient upper limit for the extra societal costs per additional QALY may be appropriate here. We propose a sample size calculation based on a WTP per additional QALY of €120,000 (50% above the RvZ figure). Based on the net health benefit formula suggesting that differences in QALYs between the interventions should be larger than the difference in costs (i.e., €34,174 a year) divided by the maximum WTP (i.e., €120,000 per QALY) in order for one intervention to be accepted as more efficient than another intervention, CLI treatment should at least outperform DBS treatment by 0.2847 QALY per year. Based on literature data with comparable costs estimates, [6] we anticipate standard deviations (SD) for QALYs up to 0.35 and for total costs up to €10,000 (factoring in a 12-month follow-up and non-responders).
To achieve 80% power and given a two-sided significance level of 0.05, up to 26 patients per group (or 52 in total) are needed to detect a difference of at least 0.2847 QALY for WTP-values up to €120,000 and a worst case scenario of zero correlation between costs and clinical effect, using a two-group t-test. Accounting for a possible dropout of 20%, we will randomize 66 patients (33 per group). With this sample size and given the same test conditions (power, type-I error rate, test chosen, drop-out rate) we are also able to detect a difference in mean PDQ-39 scores between both groups of 11.9, assuming an expected mean score of 32 in the DBS group and a standard deviation of 15.

Motivation for standard deviations for QALY
Literature data [8-10] show that the standard deviation for PDQ-39 scores from operated PD patients equals 15 points and that a 4 to 5 points difference is associated with a QALY difference of approximately 0.1,[16] suggesting a standard deviation for QALYs of up to 0.35.

Patient preference trial
We (conservatively) estimate that during the inclusion period a total of 180 patients (60% of the eligible patients) may decline to participate in the RCT, but are willing to take part in the preference observational study. Based on our clinical experience it is expected that 60% of these patients (n=108) prefers DBS, against 40% (n=72) preferring CLI.

When comparing the effect of DBS treatment of patients who express a preference for that treatment with the effect of DBS treatment in the randomised patients, and given the same test conditions (power, type-I error rate, two group t-test) we are able to detect a difference in

mean PDQ-39 scores between both groups of 8,4, assuming an expected mean score of 32 in the randomized DBS group and a standard deviation of 15.
In case only 120 patients (40% of the eligible patients) agree to take part in the preference observational study, we are able to detect a difference in mean PDQ-39 scores between both DBS groups of 8,9.

When comparing the effect of CLI treatment for patients who express a preference for that treatment with the effect of CLI treatment in the randomised patients, and given the same test conditions (power, type-I error rate, chosen test) we are able to detect a difference in mean PDQ-39 scores between both groups of 8,9, assuming an expected mean score of 43,9 in the randomized CLI group and a standard deviation of 15. In case only 120 patients (40% of the eligible patients) agree to take part in the preference observational study, we are able to detect a difference in mean PDQ-39 scores between both CLI groups of 9,6.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

CLI and DBS are both complex treatments and are therefore performed by teams that consist of various specialties (e.g. neurologist, neurosurgeon, gastroenterologist, and specialized nurses). In the Netherlands, 6 centres are permitted to perform DBS. Three of these also offer CLI, but in a much smaller number. CLI is performed in approximately 45 centres. For the study, CLI and DBS treatments should be optimally performed, i.e. by the best-trained teams. It is inevitable that the centres that perform the treatments at present perform the study-treatments as well. This implies that CLI and DBS will be carried-out in different centres. An advantage of this (Dutch) situation is that the study design closely resembles the current clinical practice, and as such the study results will be highly externally valid.

DBS treatment (Medtronic, Minneapolis, MN, USA)

Treatment is in accordance with the usual care regarding this procedure. For DBS, a neurosurgeon places two electrodes in the brain. These are connected to an implantable pulse generator. Patients are on average 4 days hospitalized. Patients do not receive PD drugs on the day of surgery until the end of the procedure. A stereotactic technique will be employed for implantation with the Leksell stereotactic frame (Elekta, Stockholm, Sweden) and guided by MRI. For this part of the surgery, patients will have local or general anaesthesia, both methods are possible in usual care and the surgeon will decide the method with the patient. The decision for electrode placement is based on MRI, microelectrode recordings and macro-electrode stimulation effects. A four contact electrode will be implanted in the subthalamic nucleus (STN). Subsequently, patients will have a second surgery under general anaesthesia to implant the pulse generator (ActivaPC or ActivaSC), subcutaneously in the subclavian area. The electrodes are connected to the pulse generator. During the course of the study, changes in drug treatment are allowed. Patients will regularly visit the outpatient clinic to adjust stimulation parameters and PD medication while assessing the interaction between both treatments.

CLI treatment (Duodopa, Abbott, Abbott Park, IL, USA)

Treatment is in accordance with the usual care regarding this procedure. In CLI, a levodopa-gel is continuously administered through a tube in the jejunum. The CLI-gel is dispensed into cassettes connected to an ambulatory programmable pump that delivers the suspension. One cassette supplies 100 ml gel containing 2000 mg levodopa and 500 mg carbidopa that lasts — depending on the individual needs — on an average 16 hours.

The pump and cassette weight approximately 0.5 kg. The initiation and dose adjustments of CLI require 5 to 12 days of hospitalization. In some centres, a temporary nasoduodenal tube is used to find out if the patient responds favourably to continuous levodopa infusion on day 1 to 3. On day 1 or 4 (depending on whether a temporary nasoduodenal tube is used first), a gastroenterologist endoscopically places a PEG tube in the stomach with an extension tube clipped in the jejunum using local anaesthetic and sedation with a short acting benzodiazepine. The tube is subsequently connected to the pump. Thereafter, CLI will immediately be continued and subsequently adjusted within the following days of inpatient stay. On day 5 to 12, the patient will be discharged. Patients will regularly visit the outpatient clinic to adjust the dose. Most patients use the pump only during daytime.

5.2 Use of co-intervention

The use of oral co-medication is allowed, as in regular daily practice. The treating neurologist supervises any changes in medication. The main motivation for this approach is to stay close to regular daily practice routines for reason of generalizability.

6. INVESTIGATIONAL PRODUCT

The medicinal product under investigation in this study is Duodopa, an intestinal gel containing levodopa and carbidopa, produced by Abbott pharmaceuticals. The information being referred to in the next section is derived from the Summary of Product Characteristics (SPC) of Duodopa, which is available in appendix 13.2 and D2 SPC Duodopa. The product will be used according to market authorization. The study does not contain any investigation of unauthorized use of Duodopa.

6.1 Name and description of investigational product(s)

For a description of Duodopa intestinal gel, see page 1-3, section 1 to 4.2 of the SPC (appendix 13.2).

6.2 Summary of findings from non-clinical studies

For a summary of findings from non-clinical studies on Duodopa intestinal gel, see page 15, section 5.3 of the SPC (appendix 13.2).

6.3 Summary of findings from clinical studies

Four RCTs [13, 17-19] and a number of lower quality studies evaluated CLI by comparison with best oral medical treatment. Overall, CLI showed improvements regarding PD motor symptoms (UPDRS motor examination), ON-phase time, and functional health. Two CLI RCT's also assessed patient-reported perceived quality of life with the PDQ-39, which improved in correlation with motor symptoms and functional health. [13, 18]

6.4 Summary of known and potential risks and benefits

For a summary of potential undesirable effects of Duodopa intestinal gel, we refer to page 3-11, section 4.3 to 4.9 of the SPC (appendix 13.2).

6.5 Description and justification of route of administration and dosage

For a description of the pharmacological properties both pharmacodynamics and pharmacokinetics see page 8 and 9, section 5.1 and 5.2 of the SPC (appendix 13.2).

6.6 Dosages, dosage modifications and method of administration

For a description of posology and the method of administration see page 2 to 3, section 4.2, of the SPC (appendix 13.2).

The total dose/day of Duodopa is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses.
Morning dose: The morning bolus dose is administered by the pump to rapidly achieve the therapeutic dose level (within 10-30 minutes). The dose is based on the patient's previous morning intake of levodopa and the volume to fill the tubing. The total morning dose is usually 5-10 ml, corresponding to 100-200 mg levodopa. The total morning dose should not exceed 15 ml (300 mg levodopa).
Continuous maintenance dose: The maintenance dose is adjustable in steps of 2 mg/hour (0.1 ml/hour). The dose is calculated according to the patient's previous daily intake of levodopa. When supplementary medicines are discontinued the Duodopa dose should be adjusted. The continuous maintenance dose is adjusted individually. It should be kept within a range of 1-10 ml/hour (20-200 mg levodopa/hour) and is usually 2-6 ml/hour (40-120 mg levodopa/hour). In exceptional cases a higher dose may be needed.
Extra bolus doses: To be given as required if the patient becomes hypokinetic during the day. The extra dose has to be adjusted individually, normally 0.5-2.0 ml. In rare cases a higher dose may be needed. If the need for extra bolus doses exceeds 5 per day the maintenance dose should be increased.
After the initial dose setting, fine adjustments of the morning bolus dose, the maintenance dose and extra bolus doses should be carried out over a few weeks.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

Outcome parameters

The primary health economic outcomes of the randomized trial are the costs per unit on the PDQ-39 and the costs per QALY for the cost-effectiveness and cost-utility analyses respectively. The EQ-5D will be applied as the utility measure.

For a detailed motivation for outcome measures see appendix 13.3.

7.1.2 Secondary study parameters/endpoints

The main clinical outcome is quality of life (PDQ-39), Other secondary parameters are:

PD motor symptoms (Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Clinical Dyskinesia Rating Scale (CDRS), 3-day motor symptom diary), non-motor symptoms such as autonomic functions and sleep (Non Motor Symptom Checklist, Rotterdam Symptom Checklist), neuropsychological and psychiatric assessment, possible cognitive decline on PD_CRS, Hoehn & Yahr stage, functional health status (ALDS), PD-medication, patient and physician preferences, Satisfaction with Life Scale, treatment satisfaction, adverse effects and complications, treatment failure, stopping treatment, starting with the alternative than initially started treatment, caregiver burden, (informal) care use and medical and non-medical care costs evaluated with the Institute for Medical Technology Assessment Productivity Cost Questionnaire (iMCQ) and Institute for Medical Technology Assessment Productivity Cost Questionnaire **(**iPCQ).

7.1.3 Other study parameters

When possible, a few baseline values will be collected from all patients, if possible including those not willing to be included in the patient preference trial study (anonymously), such as age, sex, medication, age of onset of PD, duration of PD, comorbidities, preference for treatment and possible reasons not to participate in the study.

7.2 Randomisation, blinding and treatment allocation

The randomization procedure will be website-based, using random blocks and stratified by:

level of experience of the including centre with DBS and CLI therapy (experienced DBS centres have treated at least 5 patients with DBS in the last two years and an experienced CLI centre has treated at least 5 patients with CLI each year in the last two years);

7.3 Study procedures

See also figure 1 and appendix 13.4 (assessment schedules). A patient can participate in the RCT after inclusion by the treating neurologist of a centre registered as a study site. Patients not willing to be randomized can participate in the patient prerefence trial in which only telephonic assessments will be executed either through 1. inclusion by the treating neurololgist in a centre registered as a study site; 2. providing contact information of the patient to the study team (approved by the patient) by a neurologist not registered as a study site whereafter the patient will be additionally informed by the team and informe consent will be signed; 3. direct registration by the patient with the INVEST study team, whereafter, if approved by the patient, the treating neurologist will be asked whether the patients fulfills the in- and exclusion criteria This procedure is described in 9.2, Recruitment and consent.

RCT

If the patient agrees to be randomized, a trial nurse will make an appointment for the first visit. There are eight specified assessment visits: at baseline and 1 week, 3 months, 6 months, 9 months, 12 months, 24 months and 36 months after start of the study treatment (visits 1, 2, 3, 4, 5,6, 7 and 8). The last two assessments were added after the start of the trial. Additional follow-up might provide very relevant data on long term costs, side-effect and cross-over. Regarding visits 2, 3, 4, and 5, the visits for standard care in both CLI and DBS are extended with the questionnaires for the study or the patients will be interviewed. For the assessment schedule please see appendix 13.4, document F1 “Vragenlijsten” will give an outline of all used scales and questionnaires.

At baseline (visit 1), age, sex, educational level, medication, age at onset of PD, duration of PD, Hoehn and Yahr stage, and comorbidities will be recorded. In addition, he or she will have an electrocardiogram (EKG), CT/MRI-scan of the head, and fasting blood analysis for sodium, potassium, creatinine, glucose, prothrombin time (PT), activated partial thromboplastin time (aPTT), leukocytes, erythrocytes, platelets. Vitamin B6, B12 and folic acid will be analysed.
Former participation in medical research and reason(s) to participate in this study will be evaluated. Patients will keep a motor symptom diary (3 days; including ON/ OFF phases,

dyskinesias, and sleep states). The patients will have an assessment containing the MDS-UPDRS and the AMC Linear Disability Score (ALDS) in standardized OFF and ON phases. The OFF phase is defined as the condition of the patient after withholding PD medication for 12 h and being awake for at least 1 h. The ON phase is the condition 1 h after a supra-threshold levodopa dose. The supra-threshold levodopa dose is based on the patient's usual first morning dose of PD drugs. To calculate the supra-threshold levodopa dose, different drugs will be pooled in Levodopa Equivalent Doses.
The standardized OFF and ON phases examination will be videotaped. In the ON phase the patient will also undergo documentation of the Non Motor Symptom Checklist, Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire, Hoehn and Yahr stage, ALDS, Rotterdam Symptom Checklist, Clinical Diskinesias Rating Scale (CDRS), patient-reported perceived quality of life (PDQ-39), EuroQol-5D (EQ-5D), iMTA Medical Consumption Questionnaire (iMCQ), iMTA Productivity Cost Questionnaire (iPCQ), use of (informal) care, apathy assessed by researcher and caregiver, caregiver burden and preference for treatment. The trial nurse will also administer the Mini-International Neuropsychiatric Interview (MINI) [20] and the Columbia Suicide Severity Rating Scale to screen psychiatric morbidity. The patients will undergo a neuropsychological examination including the Mattis Dementia Rating Scale and the Parkinson's Disease Cognitive Rating Scale (PD-CRS) and Patient-reported outcome tool for advanced Parkinson’s disease (PROAPD) and a standardized psychiatric assessment.

After baseline screening, patients eligibility for both treatments will be discussed with the appropriate disciplines (neurology, neuropsychology, neurosurgery, and gastroenterology) in the treating centre, or the centre that will provide the treatment. If any possible contra-indications for one of the treatments is found, the patient will be excluded from the study. Possible contra-indications are a non-dopamine responsive tremor as main complaint or if the effect of dopaminergic medication on motor symptoms is too small. Subsequently, the patient is randomized using a web-based application. Dependent on the result of randomization, the patient will be treated in the own hospital or he or she will be referred to one of the cooperating DBS centres. Within 3 months after the baseline assessment the study-treatment — DBS or CLI — will be started. The treatment will be performed as described in section 5.1

At visits 2, 3, 4, 5, 6, 7 and 8 patients will undergo documentation of PD-medication, adverse events (through a standardized questionnaire), treatment failure and cross-over. The iMCQ, iPCQ, use of (informal) care and caregiver burden are assessed at visit 3, 4, 5, 6, 7 and 8. At visits 5, 6, 7 and 8 we will record the PDQ-39. At visit 6, 7 and 8 the patients

will keep a motor symptom diary (3 days; including ON/ OFF phases, dyskinesias, and sleep states) and the Non Motor Symptom Checklist, ALDS and patient satisfaction with the treatment. At visit 6 we will record the MDS-UPDRS, the CDRS and blood analysis as described above will be repeated. Also, patients will undergo a short neuropsychological examination and standardized psychiatric assessment at visit 6 and 8. The first year of follow-up, a margin of one month is deemed acceptable in planning a visit, for the second and third year of follow-up, the visits will be completed within two months of the defined follow-up date.

Patient preference trial

Patients that are not willing to participate in the RCT, but do take part in the ancillary patient preference observational study, will have a baseline visit with a limited set of evaluations. At the baseline visit, age, sex, medication, age at onset of PD, duration of PD, Hoehn and Yahr stage, and comorbidities will be recorded. The patients will have an assessment of the patient-reported perceived quality of life (PDQ-39) and will fill in a questionnaire on preference for treatment and expectations (PROADP). Follow-up visits are planned at 9 months, 12 months, 24 months and 36 months after the study treatment. In these visits, the PDQ-39 and patient satisfaction with the treatment will be assessed (PROADP), complications and adverse events will be evaluated using a questionnaire and the medical charts will be reviewed for complications and adverse events. If necessary, based on complications and adverse events questionnaire, the medical information from other hospitals will be requested and reviewed. The first year of follow-up, a margin of one month is deemed acceptable in planning a visit, for the second and third year of follow-up, the visits will be completed within two months of the defined follow-up date.

Furthermore, during the study current preferences regarding treatment of advanced PD amongst treating physicians will be evaluated.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Follow-up of subjects withdrawn from treatment

The analysis of the study will be based on the intention-to-treat principle. In case a patient stops the study-treatment (CLI or DBS), the authors will strive to continue the follow-up assessments. In other words, a patient that stops the study-treatment is not considered to be a dropout. We will record the number of patients that stop the assigned study-treatment, the number of patients that crossover to the “other” study-treatment, and the number of patients that eventually need the “other” treatment in addition to the initially assigned study-treatment. Hence, these protocol violations are considered to be important secondary outcomes parameters of the study.

7.6 Premature termination of the study

There are no predefined reasons for termination of any of the study parts (randomized trial or patient preference observational study), as both DBS and CLI is regular care.

8. SAFETY REPORTING

8.1 Temporary half for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention or the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded in patients participating in the randomised controlled trial, from the moment patients undergo visit 1: screening until end of study. Since the patient preference study is observational, adverse events and SAEs will be reported using line listing.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

1. results in death;
2. is life threatening (at the time of the event);
3. requires hospitalisation or prolongation of existing inpatients' hospitalisation;
4. results in persistent or significant disability or incapacity;
5. is a congenital anomaly or birth defect;
6. Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

If a SAE occurred in a patient randomised to one of the therapies, the principal investigator in the centre where the SAE occurred will notify the principal investigator in the coordinating centre by email or telephone within 24 hours.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

Both procedures require a form of surgery and sedation. The procedures are performed in mainly elderly patients with a neurodegenerative disease. In these circumstances transient adverse effects like delirium or infections commonly cause prolonged hospitalization. Therefore, the categories concerning (prolongation of) hospitalization and “any other important medical event” will be reported to the accredited METC that approved the protocol in a twice-yearly line listing until the follow-up of the last patient is completed (categories 3 and 5).

Furthermore, the following situations do not need to be reported as SAEs:

- Any admission unrelated to an AE, e.g. cosmetic surgery, social and/or convenience admissions to a hospital;
- Elective hospitalisation (planned before the subject consented for study participation) for pre-existing conditions that have not been exacerbated by study treatment as judged by the clinical investigator and where admission did not take longer than anticipated.
- Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical investigator.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present at the start of the study that do not worsen.
- Protocol-specified admission, e.g., for a procedure required by the study protocol;

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 8.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in Summary of Product Characteristics (SPC) for an authorised medicinal product.

If a SUSAR occurred, the principal investigator in the centre where the SUSAR occurred will notify the principal investigator in the coordinating centre by email or telephone within 24 hours.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Pregnancy

To ensure patient safety, each pregnancy must be reported to the Coordinating PI within 24 hours of learning of its occurrence. As pregnancy is an exclusion criterion, the participant should be withdrawn from the trial. The pregnancy should be followed up for an appropriate period to determine outcome, including spontaneous or voluntary termination, details of the birth and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications. Pregnancy should be recorded on a Clinical Trial Pregnancy Form. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to investigational medicinal product of any pregnancy outcome. Any SAE experienced during pregnancy must be reported compliant with reporting procedures for a SAE.

8.6 Data Safety Monitoring Board (DSMB) / Safety Committee]

Since this open label trial consists of two routine treatments applied in regular daily practice, and participation in this study does not contain additional risks for patients (see chapter 12 for risk analysis) we consider this RCT, including the patient preference trial, as a negligible risk study. Therefore, no DSMB will be established.

STATISTICAL ANALYSIS

8.7 Primary study parameter(s)

Statistical analyses will be based on the intention-to-treat principle. Baseline assessments and outcome parameters will be summarized using simple descriptive statistics. The main health economic analyses are a cost-effectiveness analysis based on costs and quality of life measured with the PDQ-39 and a cost-utility analysis, using the EQ-5D utility measure. (see also appendix 13.5 “Cost effectiveness analysis” and 13.6 “Patient Outcome Analysis”).

8.8 Secondary study parameter(s)

RCT

The main clinical analysis of the study consists of a comparison between the trial treatment groups (DBS versus CLI) of the primary clinical outcome (PDQ-39) 12 months after the start of the study treatment. First, the follow-up difference between PDQ-39 scores will be analysed using a two-group t-test. Second, the PDQ-39 follow-up scores will be further investigated using multiple linear regression taking into account patients' PDQ-39 baseline values, the stratifying variables (experience of the including centre with DBS and CLI; response to Levodopa) and (if necessary) for clinically relevant baseline imbalances. Additionally, the repeated data structure will be investigated with a linear mixed model. The same analyses will be performed for the 24 and 36 month outcomes. With regard to the comparisons of the other secondary outcomes PD motor symptoms (MDS-UPDRS, CDRS, 3-day motor symptom diary), non-motor symptoms such as autonomic functions and sleep (Non Motor Symptom Checklist, Rotterdam Symptom Checklist), PD-medication, neuropsychological and psychiatric assessment, disability, functional health status (ALDS), patient and physician preferences, patient satisfaction, adverse effects and complications, treatment failure, stopping treatment, starting with the alternative than initially started treatment, caregiver burden and medical and non-medical care costs (iMCQ, iPCQ) we will use the appropriate parametric and non-parametric statistics. In all analyses, statistical uncertainties will be expressed in 95% confidence intervals.

Patient preference trial

As mentioned before a patient preference observational study will be conducted to asses external validity of the randomized controlled trial results. The primary clinical outcome of the non-randomized group and randomized group will be compared using the two-group t-test and linear regression, whereas baseline characteristics will be compared with the

two-group t-test and Chi-square test, when appropriate. Finally, the impact of the treatment on the PDQ-39 follow-up scores of the randomized and non-randomized group will be analysed using multiple linear regression, adjusting for relevant imbalanced baseline variables and randomized status (agreeing to randomization or not).

8.9 Interim analysis (if applicable)

. No interim analysis is planned. If patient recruitment shows to be falling behind, an interim analysis may become necessary, to evaluate if preliminary completion of the study is deemed feasible.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version of 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. Study monitoring will be performed in accordance with the ICH GCP guidelines.

9.2 Recruitment and consent

Patients will be approached to participate in this study by their treating neurologist. The neurologist will check the inclusion and exclusion criteria in possible eligible patients. If the patient is eligible according to the criteria, the neurologist will inform the patient about the two treatment options and introduce the study. The patient will be asked permission to be contacted by members of the INVEST research team. Written information about the study will be provided to the patient, containing information on the 36 month follow-up period. (see E1-2, patient information). Patients will be given as much time needed to decide if they want to participate. Then, the neurologist or a member of the research team will ask the patient to participate in the randomized trial. The following 3 scenarios may then take place:

- The patient wants to participate and agrees to be randomized. The patient signs the informed consent form in presence of a member of the research team and subsequently study Visit 1 is planned
- The patient declines randomization, but agrees to participate in the patient preference observational arm of the study. The participant will receive the informed consent form with the first CRF by mail if not already signed during an outpatient visit. A member of the research team will call the participant to aid with the CRF, and asks the participant to send the signed consent form along with the first CRF.
- The patient declines randomization. The neurologist records the patient characteristics.

Furthermore, neurologists working in other hospitals in the Netherlands, that are not currently active INVEST study sites, may refer patients for the observational study. A member of the INVEST research team will contact the patient and supply patient information. The written consent will be acquired as described above at the second bullet point. Patients are allowed to contact the research team independently. With their permission, the research team will verify with their treating neurologist if the individual patient is eligible for the observational study. Subsequently, written consent will be acquired as described above.

9.2.1 Recruitment and consent for additional 24 and 36 month follow-up for participants already enrolled

During the consent procedure for the 12 month follow-up, participants did or did not give permission to be contacted for further research. They have been informed about a pending additional follow-up period in the “Informatiebrief verlenging onderzoek” they received.

The participants of the RCT, and the observational study who agreed to be contacted, will be asked by phone or mail to participate in the 24 and 36 month follow-up study. If interested, the patient is offered an optional informational meeting either in the hospital the patient was included in or at the home of the patient. If the patient want to participate in the extended follow-up, informed consent can be signed during this visit. If a patient wants to participate, but considers an informational meeting unnecessary, he or she will receive a separate 24 and 36 month follow-up informed consent form by mail. A member of the research team will call the participant to aid with said CRF, and asks the participant to send the signed consent form along with the first CRF.

9.3 Benefits and risks assessment, group relatedness

If patient agree to participate in the randomized controlled trial, patients will undergo regular treatment without additional risks. There is a small added burden of more and more detailed assessment procedures. We estimate these extra procedures — consisting of explanation of the research, questionnaires and motor symptom assessments — take approximately 15 hours for the 3 year follow-up, including time to travel to the hospital. This is a negligible risk according to the NFU (Nederlandse Federatie van Universitaire Medische Centra) criteria for human research. If patients do not agree to be randomized, but participate in the patient preference arms of the study, they will undergo regular treatment of their choice without any additional risks. The study related assessments take approximately 5 hours for patients participating in the patient preference observational study.

9.4 Compensation for injury

Since participation in this study does not entail additional risks because two regular treatments are compared, the METC has granted exemption to the obligation to take out liability insurance for the study subjects in accordance with article 7, subsection 9 of the WMO.

9.5 Incentives (if applicable)

Patients will not receive incentives or privileges to participate in this study. Most DBS-centres have a waiting list for treatment with DBS whereas treatment with CLI can be initiated at a relatively short notice (within 3 months). For optimal comparison of the therapies, in patients who participate in the study, start of treatment will be within three months of the baseline screening. This may be a motivation for patients to participate in the study. We do not expect that the waiting list for treatment with DBS will grow for patients not taking part in the study, as a proportion of patients that would otherwise be treated with DBS, will now be randomized for treatment with CLI.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

The investigator will set up a Trial Master File at the beginning of the study. The list of essential documents will be in accordance with the GCP-guidelines. The essential documents that make up the file will be stored in a secure but accessible manner. All essential documents will be legible and accurate. The participating centres will keep copies of relevant documents, including essential centre-specific documents in their Investigator Files.

After inclusion, the patient will be web-based randomized (TENALEA Clinical Trial Data Management System). This application will be made available by the Clinical Research Unit (CRU) of the AMC.

For each randomized patient a digital Case Record Form (CRF) will be completed. The CRF consists of a sequential set of instructions with provision for data recording. All randomized patients are identified by a Patient Identification Number (PIN) in combination with a centre number. Trial personnel will not pass names outside the local hospital. The local investigator will ensure that patients' anonymity is maintained. On screening forms, digital or paper CRF’s or other documents submitted to the coordinating centre, patients will only be identified by a PIN in combination with a centre number. The subject identification code list will be safeguarded by the investigator. Data will be stored for 15 years. Collected anonymised data may be used for future studies.

10.2 Monitoring

Academic Medical Center’s Clinical Research Unit (CRU) will provide independent monitoring according to the crafted monitorplan. After an initiation visit, monitoring will take place after 10 randomized patients at the principal site, and after 3 randomized patients at other sites. For more details, please consult the INVEST monitor plan.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient’s last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

10.6 Public disclosure and publication policy

The study is registered at the EudraCT trial register under number 2014-004501-32. The authors aim to publish the results in high-impact peer-to-peer reviewed journals.

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

Not applicable, both treatment options are standard care. For further explanation see 12.2.

11.2 Synthesis

The proposed research project involves treatment options that are standard care in daily practice in advanced PD. The therapies will not be combined with other investigational products. Both therapies have a small risk of severe complications and a larger risk of modest side-effects. There is a small-added burden of a more detailed assessment procedure. We estimate these extra assessments —consisting of health(-economic) questionnaires and motor symptom assessments — to take approximately 10 hours, including time to travel to the hospital. Besides this small burden, the study has no additional risk. Participation in the INVEST study constitutes a negligible risk according to the NFU-criteria for human research.

12. APPENDICES

12.1 Contributing centres

Centre	Investigator on site
Academisch Medisch Centrum	Dr. J.M. Dijk
Vrije Universiteit Medisch Centrum	Dr. E.M.J. Foncke
Spaarne Gasthuis Haarlem	Dr. A.G. Munts
Spaarne Gasthuis Hoofddorp	Dr. M. Eurelings
Canisius Wilhelmina Ziekenhuis	Dr. C.C.P. Verstappen
Onze Lieve Vrouwe Gasthuis	Dr. A.M.M. Vlaar
Flevoziekenhuis	J.P. Blankevoort
Maastricht UMC+	Dr. M.L. Kuijf
Radboud Medisch Centrum	Dr. R.A.J. Esselink
Zuwe Hofpoort Ziekenhuis	H. Hesselmans
Zuyderland Medisch Centrum locatie Sittard	Dr. P.H.M.F. van Domburg
Zuyderland Medisch Centrum locatie Heerlen	Dr. G. Tissingh
Bronovo Ziekenhuis	N. Weerkamp
Hagaziekenhuis	Dr. F. Contarino

12.2 Summary of Product Characteristics (SPC) of Duodopa

The Duodopa SPC is attached to this application in Adobe .pdf format and is also available online on the site of the College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board) through the following link: http://www.cbg-meb.nl/, or via the following direct link: http://db.cbg-meb.nl/IB-teksten/h30589.pdf

12.3 Motivation for outcome measures

To date, in most studies evaluating invasive treatments in advanced PD, the outcome is based on the recording of PD symptoms with the MDS-UPDRS, the time being in ON-phase, the level of physical disability or perceived quality of life as measured with the PDQ-39. The mechanisms of action and procedures of both therapies are very different. For example, DBS treatment includes neurosurgery, implantation of stimulation equipment, and tuning of DBS-parameters in combination with gradual adjustments of the medication-schedule. In DBS, OFF-phase symptoms improve; and patients may experience this as more ON-phase time. DBS may influence behaviour and mood. In case of CLI, patients have a percutaneous endoscopic gastrostomy (PEG). During chronic CLI treatment, the pump has to be started every morning, it has to be removed every night, the PEG-stoma needs continuous care, and there is no change regarding OFF-phase symptoms, but OFF-phase time decreases and ON-phase time increases. The pump weights 0.5 kg. Considering all these aspects and patients' preferences, using OFF-phase parkinsonism, time being in ON-phase, or physical disability as a primary outcome would be inadequate. Therefore we have chosen to use patient-reported perceived quality of life -- measured with the PDQ-39 -- as a primary clinical outcome and as the effect measure to be linked with costs in the cost-effectiveness analysis. In addition, the cost per QALY was chosen as the outcome measure of the cost-utility analysis to allow for comparisons of results from economic evaluations of different interventions within and across different disease populations and different health sectors. The EQ-5D will be applied as the utility measure.

12.4 Assessment schedules

	Visit 1 Baseline	Visit 2 1wk	Visit 3 3mo	Visit 4 6mo	Visit 5 9mo	Visit 6 12mo	Visit 7 24mo	Visit 8 36mo
Baseline characteristics	X							
EKG, CT/MRI brain	X							
blood analysis	X					X		
Medication	X	X	X	X	X	X	X	X
MDS-UPDRS motor score	X					X		
Clinical Dyskinesia Rating Scale (CDRS)	X					X		
Motor symptom diary (3 days)	X					X	X	X
Non-motor symptom checklist	X					X	X	X
Impulsive compulsive (QUIP)	X					X		
Apathy scale Starkstein (AS)	X					X		
Neuropsychological examination (incl. Mattis Dementia rating scale)	X					X		X
Mini-International Neuropsychiatric Interview	X					X		
Psychiatric assessment	X					X		
Hoehn and Yahr stage	X					X	X	X
AMC disability scale (ALDS)	X					X	X	X
PDQ-39	X				X	X	X	X
EQ-5D	X	X	X	X	X	X	X	X
Treatment preference	X							
Treatment satisfaction						X	X	X
Satisfaction with life scale	X					X	X	X
Treatment failures		X	X	X	X	X	X	X
Side effects/adverse events/complications		X	X	X	X	X	X	X
Crossover to other treatment			X	X	X	X	X	X
iMTA Medical Consumption Questionnaire (iMCQ)	X		X	X	X	X	X	X
iMTA Productivity Cost Questionnaire (iPCQ)	X		X	X	X	X	X	X
Use of (informal) care	X		X	X	X	X	X	X
Caregiver burden	X		X	X	X	X	X	X

Table 2: assessment schedule patient preference trial

	Visit 1 Baseline	Visit 2 9mo	Visit 3 12mo	Visit 4 24mo	Visit 5 36 mo
Baseline characteristics	X				
Medication	X	X	X	X	X
Hoehn and Yahr stage	X				
PDQ-39	X		X	X	X
Treatment preference	X				
Treatment satisfaction			X	X	X
Side effects/adverse events/complications		X	X	X	X
Treatment failures and cross-over		X	X	X	X

12.5 Cost Effectiveness analysis (CEA)

The economic evaluation of CLI against DBS treatment will be performed based on intention-to-treat as a cost-effectiveness and cost-utility analysis from a societal perspective with the costs per unit on the PDQ-39 and the costs per quality adjusted life-year (QALY) as the primary outcomes respectively. The primary outcome of the cost-effectiveness analysis is closely related to the primary clinical outcome, the PDQ-39. The cost-utility analysis is considered mandatory to enable health policy makers allocating scarce health care resources across disease populations, across interventions, and across health sectors, based on explicit efficiency criteria. It is expected that CLI generates higher costs than DBS during the year of follow-up and should therefore sufficiently pay off compared with DBS in terms of increased effectiveness in order to be affordable for patient populations that might benefit from both treatments. It is yet unclear whether CLI actually pays off sufficiently.

Incremental cost-effectiveness and cost-utility analyses will be performed for a willingness-to-pay value of €120,000 (for rationale, see sample size calculation) based on the net health benefit transformations of the respective incremental cost-effectiveness ratios and assuming reasonably normally distributed cost data. The time horizon in the study equals 1 year. With this time frame no discount rate will be applied for effects and costs to account for time preference. However, given the 5-year life-cycle of the studied devices (neurostimulator, tube, and pump) and the marked contrast of costs in the first year of treatment compared to subsequent years within the life-cycle period, we will depreciate the initial add-on intervention costs (placement of neurostimulator for DBS and tube and pump placement for CLI) over five years.
One-way and multi-way probabilistic sensitivity analyses will be performed for the length of the friction period (3-6 months), and choice of UK rather than Dutch tariffs of time trade-off ratings of health states.
Additional analyses will be performed with the assessments 24 and 36 months after start of treatment, to assess the longer term costs and benefits of both treatments more precisely.

Cost analysis
From the societal perspective the economic evaluation will include the direct medical as well as the direct and indirect non-medical costs of care. Indirect medical costs are not included as both treatments do not affect survival. All costs made by providers (index intervention and subsequent inpatient and outpatient health care), employers (loss of productivity due to absence from and impaired presence at work), patients (out-of-pocket

expenses due to health care related travel, household assistance, over-the-counter medication) and their primary caregivers (non-reimbursable expenditures) will be quantified.

Unit costing will be in accordance with the most recent update of existing national guideline as much as possible.[21]. Costs will be price-indexed for the base year 2014. Yearly consumer price indices will be used to standardize unit costs estimated in different calendar years. Mean costs per patient over the period of the trial will be calculated.

12.6 Patient outcome analysis

Parkinson's disease may seriously affect a person's quality of life due to the physical symptoms and the psychological impact of having to cope with a chronic progressive condition. Adverse events of treatment too may affect how patients perceive their quality of life. To assess the health burden in the study population, the disease specific PDQ-39 will be used. In addition, the EQ-5D will be applied as the utility measure in the cost-utility analysis. The EQ-5D has been validated in PD patients, strongly correlates with clinical scales, and is more sensitive in this patient group than the well-known, also generic Short Form-36 (SF-36).[16] The EQ-5D scoring profile can be converted into a utility score based on general population based tariffs of time trade-off ratings of health states. Initially, available Dutch tariffs [22] will be applied, while widely used UK tariffs [23] will be applied in the sensitivity analysis (see 13.5). For measurement frequency, see the paragraph concerning outcome parameters. Whereas patient preferences for the target interventions DBS or CLI matter, they have been incorporated into our patient preference trial design. If the health care efficiency results from the RCT turn out as indecisive, outcome analyses in the preference group become of further interest.

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