Protocol and data analysis plan of manuscript

Title: Deep Brain Stimulation of the ventral anterior limb of the internal capsule for treatment resistant depression: A randomized, crossover trial.

This supplement contains the following items:

1. a) Original protocol, b) Final protocol, c) Summary of changes
2. a) Original statistical analysis plan, b) Final statistical analysis plan, c) Summary of changes
1A. INITIAL PROTOCOL

Academisch Medisch Centrum
Amsterdam

Deep Brain Stimulation in Treatment-refractory patients with Major Depressive Disorder

A pilot study

Version: (3) November 2008

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1. INTRODUCTION

In any given 1-year period, 5.8 percent of the Dutch population suffer from Major Depressive Disorder (MDD). The economic cost for this disorder is high, but the cost in human suffering cannot be estimated. MDD often interferes with normal functioning and causes pain and suffering not only to those who have a disorder, but also to those who care about them. Serious MDD can destroy family life as well as the life of the ill person. A recent World Health Organization report predicts that MDD will be the leading cause of disability and premature death in the industrial world by the year 2020. Without treatment, ten percent of people suffering from severe MDD commit suicide. With adequate treatment, the majority of patients with this illness recover.

1.1 What is depressive disorder?

MDD is manifested by a combination of symptoms (see symptom list) that interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Such a disabling episode of depression may occur only once, but more commonly occurs several times in a lifetime. In adults, MDD affects twice as many women as men. For both genders it is most common in those who are 25-44 years of age, but over the age of 65 incidence-rates increase again. Within an entire lifetime, MDD will affect 10%-25% of women and 5%-12% of men. Those with a parent or sibling who has had MDD may be 1.5 to 3 times more likely to develop the condition than those who do not.

<table>
<thead>
<tr>
<th>Diagnosis of Major Depressive Disorder, Single Episode</th>
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<td>Summarized from the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition.</td>
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A. The person experiences a single major depressive episode:

1. For a major depressive episode a person must have experienced at least five of the nine symptoms below for the same two weeks or more, for most of the time almost every day, and this is a change from his/her prior level of functioning. One of the symptoms must be either (a) depressed mood, or (b) loss of interest.

   a. Depressed mood. For children and adolescents, this may be irritable mood.

   b. A significantly reduced level of interest or pleasure in most or all activities.

   c. A considerable loss or gain of weight (e.g., 5% or more change of weight in a month when not dieting). This may also be an increase or decrease in appetite.
For children, they may not gain an expected amount of weight.

d. Difficulty falling or staying asleep (insomnia), or sleeping more than usual (hypersomnia).

e. Behavior that is agitated or slowed down. Others should be able to observe this.

f. Feeling fatigued, or diminished energy.

g. Thoughts of worthlessness or extreme guilt (not about being ill).

h. Ability to think, concentrate, or make decisions is reduced.

i. Frequent thoughts of death or suicide (with or without a specific plan), or attempt of suicide.

2. The persons’ symptoms do not indicate a mixed episode.

3. The person's symptoms are a cause of great distress or difficulty in functioning at home, work, or other important areas.

4. The person's symptoms are not caused by substance use (e.g., alcohol, drugs, medication), or a medical disorder.

5. The person's symptoms are not due to normal grief or bereavement over the death of a loved one, they continue for more than two months, or they include great difficulty in functioning, frequent thoughts of worthlessness, thoughts of suicide, symptoms that are psychotic, or behavior that is slowed down (psychomotor retardation).

B. Another disorder does not better explain the major depressive episode.

C. The person has never had a manic, mixed, or a hypomanic Episode (unless an episode was due to a medical disorder or use of a substance).

**Major Depressive Disorder, Recurrent:**
All of the above criteria apply, except with regard to criteria A there have been two or more major depressive episodes with at least two months in between in which no major depressive episode was present.

 **1.2 What is refractory depressive disorder?**

Although the therapeutic armamentarium available for clinicians treating MDD patients has expanded substantially over the last decades, treatment resistant or 'refractory' MDD in its broadest sense still characterizes a significant number of patients in therapy. Refractory MDD is a term used in clinical psychiatry to describe cases of MDD that do not respond to typical modes of treatment, such as psychotherapy and common antidepressants such as SSRIs and tricyclic antidepressants (TCAs). Furthermore, most of the refractory MDD patients do not respond to classical Monoamine Oxidase A
Inhibitors (MAO-I) and/or Electroconvulsive therapy (ECT; see below). About 50% of the patients treated for MDD do not respond satisfactorily to the first antidepressant prescribed. There are individuals (up to 15% of patients) for whom multiple interventions will be unhelpful and who will have significant depression despite aggressive pharmacologic and psychotherapeutic approaches.

1.3 What are treatment options for refractory depressive disorder?

Treatment of refractory MDD most commonly involves ECT and use of non-standard medications, but may also involve more intrusive interventions such as vagus nerve stimulation. ECT is useful, particularly for individuals whose depression is severe or life-threatening, or complicated with psychotic features, nevertheless, between 10-40% of patients do not fully recover after ECT. Furthermore, ECT has a high relapse-rate, especially when not followed by maintenance pharmacological therapy. In case of response to acute ECT, followed by relapse (despite adequate pharmacotherapy), continuation or maintenance ECT is performed, with biweekly to monthly ECT-sessions, sometimes lifelong.

1.4 Neurosurgery for refractory depressive disorder

For a small proportion of the refractory DD patients, neurosurgery is a last resort. Physicians familiar with neurosurgery are convinced that, drawing on their clinical experience, highly selective and stereotactically produced lesions in the brain can benefit a number of carefully selected, chronically ill psychiatric patients. A clinically significant response after neurosurgery is reported in about 30-50% of the patients. The highest response is seen in patients with lesions in the anterior limb of the internal capsule. Lesions are either made by thermocoagulation of by radiosurgical means using the Leksell Gamma Knife. Controlled studies of these procedures have not been conducted, but Sakas et al (2007) has reviewed the results of 213 cases and found satisfactory results in 63% of the cases. [1] Other stereotactic surgical interventions include subcaudate tractomy, cingulotomy and limbic leukotomy. Although the methods may vary, all these ablative procedures create a lesion in the brain by various methods. Besides the risks of any intracranial surgery, these lesions have a low occurrence rate of unwanted mental side effects, but the great disadvantage of lesioning parts of the brain
is its irreversible nature. Therefore, for a small proportion of the refractory MDD patients, neurosurgery is a last resort.

1.5 What is Deep brain stimulation?

Recently, a potentially ‘non-destructive’ alternative to ablative neurosurgery has emerged: deep brain stimulation (DBS). DBS uses a lead just larger than 1 mm in diameter implanted stereotactically into specific brain targets. The stimulating leads are connected to pulse generators typically placed in the chest. The leads themselves have several independently programmable electrode contact sites, which means that the anatomical extent of the stimulation is adjustable. The frequency, intensity, and pulse width are also programmable. DBS does not damage brain tissue and the stimulation itself can be modified or discontinued in the event of side effects. The device can even be removed if necessary. The major risks of device implantation are hemorrhage and infections. Experience with DBS for movement disorders, however, indicates that the incidence of these risks is low: approximately 1%. Therefore, DBS is accepted as a safer, more advantageous alternative to a permanent brain lesion. The adjustability of the stimulation parameters over time, to maximize clinical benefit while minimizing adverse side effects, and the reversibility of this procedure, with the potential to benefit from drugs developed in the future, are potential advantages of DBS.

1.6 Deep brain stimulation for refractory depressive disorder

Presently there is anecdotal evidence that DBS is effective in patients with refractory MDD. Interestingly, signs and symptoms of severe depression can be (reversibly) induced in PD patients undergoing DBS [2], likely because of inadvertent stimulation of limbic portions of the STN, the adjacent ZI, or SNr. The insight that focal brain stimulation can profoundly alter limbic function suggests that DBS of the limbic circuitry (at other targets) could be used to treat MDD in patients who suffer from intractable forms of the disease. Although earlier single case studies have reported that DBS of mesothalamic targets or of the inferior thalamic peduncle is effective against reactive MDD in patients with chronic pain [3], or single MDD [4], respectively, the precise target has not been well defined. In a recent study involving six patients with refractory depression, it has been shown that DBS of the white matter in the subgenual cingulate region (area 25) can produce very significant clinical benefits [5]. This target was chosen
after a series of neuroimaging studies, which showed that area 25 is overactive in
depression, and remains overactive in refractory MDD patients. A region in the rostral
cingulate gyrus has also been proposed as a possible target for DBS in depression [6]. In
addition, a recent preliminary report of 3 patients showed DBS of the nucleus
accumbens to be effective as well [7]

1.7 Bilateral accumbens stimulation for refractory depressive disorder
The target of the current study will be the nucleus accumbens. The nucleus accumbens is
an important part of what is known as the "reward system". It ensures that we remember
good experiences and puts us in a state of pleasurable anticipation. Without the reward
system we would not make plans for the future, simply because we could not enjoy the
fruits of these plans. Inactivity and inability to enjoy things are two important signs of
MDD. The conclusion is therefore obvious that the nucleus accumbens plays a key role in
the genesis of the disease. Preliminary data in three patients has shown efficacy of DBS
in three MDD patients [8] , and experience in our current study stimulating the
accumbens for obsessive-compulsive disorder (OCD) patients shows improved mood in
14 out of 16 cases as well.

1.8 Ethical considerations regarding DBS in neuropsychiatry
The previous era of psychosurgery ended in the 1970s because of severe condemnation
of the excessive and indiscriminate use of these procedures, their disappointing
outcomes, and the lack of patient protection. It may seem surprising, then, that
neurologists, neurosurgeons, and psychiatrists are again exploring such surgical
procedures for severe psychiatric disorders, such as OCD, Tourette syndrome (TS), and
MDD. The acceptance of DBS is due to several facts, including (1) the failure of existing
drugs to deal effectively with the psychiatric condition in a subset of treatment refractory
patients, (2) the remarkable success of DBS procedures in treating movement disorders,
(3) the relatively less invasive and reversible nature of DBS, (4) the greater public
awareness of the enormous lifelong burden of these disorders on patients and their
caregivers, and (5) the greater scrutiny and protection of patient rights. DBS procedures
for neuropsychiatric conditions remain strictly experimental at this point. Use of DBS in
neuropsychiatric diseases is based on findings suggesting that these conditions are, at
least partly, due to abnormalities within the nonmotor basal ganglia circuits, most
prominently the limbic circuitry.
2. OBJECTIVES

The primary objective of the present study is to assess efficacy of DBS in the nucleus accumbens for patients with refractory MDD. Secondary objectives are the evaluation of long term efficacy and tolerability of DBS for patients with therapy refractory MDD.

3. PROCEDURE

The study comprises 5 sequential phases

|-----------------------|-----------------|-----------------------|----------------------|---------------------|

3.1 Preoperative phase

Six weeks prior to surgery, any existing medication is tapered off to the minimum effective dosage regimen and maintained at this level throughout the entire study. Psychometric assessments will be conducted twice, four weeks apart, when the stable dosage regimen has been implemented. Baseline neuropsychological tests and tasks will also be performed during this period (see study schedule). Standard psychiatric care will be available to all patients throughout this period and if necessary patients may be hospitalized at the psychiatric department of the AMC.

Neuro imaging, psychometric assessments, neuropsychological tests and affective information processing tasks will be conducted during this period which will be described in an amendment.

3.2 Surgery

The implantation of the electrodes will be performed according to standard procedures using the stereotactic method. Under local anaesthesia, a stereotactic frame is attached to the skull, providing a Cartesian coordinate system for all points within the stereotactic space (i.e. the skull and all of its contents). Thereafter, a MRI-scan is made. The anterior and posterior commissures, as well as the anterior part of the internal capsule are identified on the 3-dimensional reconstruction of the MRI. The stereotactic coordinates
of the position of the nucleus accumbens (NAc) on both sides of the brain are calculated, using the spatial relationship between the NAc and the commissures as obtained from a standard stereotactic atlas. The planning software of the 3-dimensional imaging program is used to determine the optimal trajectories for electrode implantation through the brain, in such a way that the deepest of the four electrical contacts of the electrodes is positioned in the NAc, with the preceding three electrode contacts positioned in the anterior part of the internal capsule. Thus, a path is obtained for each electrode with both an entry point in the skull and a target point in the NAc.

The patient is transported to the Operation Room (OR), where the stereotactic arc is attached to the frame, after which the location of the burr hole for electrode implantation can be identified. After a small incision in the skin is made bilaterally, two frontal burr holes are made and the dura is opened. The electrodes are inserted, after which brief exploratory trial stimulation can be performed to confirm the absence of side effects of stimulation at the target site. The electrodes are then fixed to the skull and the incisions are closed. Under general anaesthesia the distal part of the electrodes are connected to extension cables. These cables are tunnelled under the skin to the infraclavicular region, where they are connected to the stimulators, which are placed in a subcutaneous pocket bilaterally. Directly after surgery, a CT-scan is made which is used to verify the correct position of the electrode. To this end, the CT is fused with the stereotactic 3-D volumetric MRI using standard image fusion techniques.

Electrodes (Model 3389, Medtronics Inc. Mineapolis, MN, USA) will be implanted bilaterally and connected to Soletra DBS stimulators (Medtronics, Inc. Mineapolis, MN, USA).

### 3.3 Optimization period

After recovery from surgery, testing for optimal stimulation parameters will be performed during a variable period ranging from 1-3 months. Stimulation parameters (principally stimulation site by choosing the best contacts, frequency, amplitude, pulse width and stimulation mode, viz multipolar, bipolar or monopolar) will be optimized by the psychiatrist during this period. Stimulation parameters include a frequency of 2-128 Hz, a voltage range of 0-10 V and pulse widths ranging from 60-450 µseconds. The stimulators are programmed via a portable device that communicates with the implanted generators via telemetry. Optimization will be based on the changes in
severity assessed with the Hamilton Depression rating scale (HDRS) and the
Montgomery-Asberg depression rating scale (MADRS). If necessary, adjustment will be
made every week for a period of up to 3 months. Contact combinations with the best
treatment outcome will be used in the subsequent double-blind phase. Optimization will
be performed on an outpatient basis, but if necessary patients may be hospitalized for a
short period at the psychiatric department of the participating centers.

Patients enter the next phase of the study after the optimization period is completed,
which is (1) after three months of trial stimulation during which the stimulation
parameter settings are determined that give the best clinical improvement, or (2) earlier
when a >50% reduction of the HDRS (primary outcome measure) has been reached.

3.4 Double blind assessment period

The efficacy of DBS is evaluated in a randomized double blind, two-phase cross-over
design. Patients are randomly allocated to two periods of two weeks with the stimulators
in the ‘on’ position in one period and in the ‘off’ position in the other. The order of these
periods is randomly assigned. The psychiatrist responsible for the treatment will turn
the stimulator ‘on’ or ‘off’ according to a computer generated randomization table, but
the investigators responsible for assessments are blind to the position of the stimulator.
The stimulation parameters are kept constant if possible during the treatment phases,
but readjustment is possible between the treatment phases if the impedance has
changed. The randomization code can be broken in case of unexpected events by the
investigator. If necessary, patients may be hospitalized for a short period at the
psychiatric department of the AMC.

Neuro imaging, psychometric assessments (including assessment of life-events),
neuropsychological tests and affective information processing tasks will be conducted
during this period at regular intervals as indicated in the study schedule which will be
described in an amendment.

3.5 Maintenance period

The maintenance phase consists of a period of 1 year following the blind assessment
phase. This period will commence, if necessary, with a further optimization of
stimulation parameters. The stimulators are ‘on’ for all patients, but can be switched off
for a certain period if necessary, and optimization of the parameters during this period is possible on demand. During the maintenance period patients will be invited to join a (cognitive) behavioural therapy (BT) program individually designed for post operative DBS treatment. In general, cognitive behavioral therapy is one of the most promising types of psychotherapy for MDD. In cognitive behavioral therapy the therapist seeks to correct negative thoughts or dysfunctional attitudes in order to overcome pessimism and hopelessness. Furthermore, we will focus on reactivation and rehabilitation of these patients. Because these patients have been depressed for many years before entering the study, their illness presumably caused them to retract from normal life and social functioning. Even when they fully respond to DBS, they will suffer from isolation and loss of daily activities, for which rehabilitation techniques are required.

Psychometric, psychiatric and neuropsychological tests will be conducted at regular intervals as indicated in the study schedule.

4. PATIENTS AND METHODS

A total of 16 treatment-refractory (see below) patients with MDD will be selected to participate in the study after written informed consent has been obtained. Patients will be recruited from the program for mood disorders of the AMC Amsterdam.

4.1 Inclusion criteria

- Primary diagnosis: MDD (single episode or recurrent; 296.2 or 296.3) according to the DSM-IV criteria based on a psychiatric interview and the SCID as diagnostic instrument
- Illness duration > 2 years, chronic MDD
- HAM-D total $\geq 18$ (measured twice, at least two weeks apart with the last assessment just before surgery)
- Disabling severity with substantial functional impairment according to the DSM-IV criterion C and a Global Assessment of Function (GAF) score of 45 or less
- The level of impairment must have been persistent for at least 2 years
- Age: 18-65 years old
- Written informed consent
- Able to fully understand the consequences of the procedure (IQ > 80)
• Dutch or English speaking and able to answer the study questions
• Capable to make his or her own choice without coercion
• Treatment refractory defined as failure of:
  - At least 2 adequate treatments of at least two distinctly different classes of 2nd generation antidepressants (SSRI, SNRI, NaSSA) for a period of 6-8 weeks
  and
  - An adequate trial of a TCA 6-8 weeks (at therapeutic drug levels)
  and
  - TCA + addition of lithium when tolerable at least 6 weeks at therapeutic drug levels (>0.6 mmol/L))
  and
  - An adequate trial of a MAOI
  and
  - ≥1 session of ECT, for which the series of ECT was terminated either due to adverse effects or insufficient response (including at least 6 sessions of bilateral ECT).
  or
  - Patients who are kept stable with maintenance ECT, but who relapse after discontinuation of this maintenance ECT are also eligible, but need to fulfill the above inclusion criteria

4.2 Exclusion criteria

• Unstable physical condition
• Organic cause
• Parkinson’s disease, dementia, epilepsy
• Schizophrenia /history of psychosis unrelated to MDD
• Alcohol or substance abuse (including benzodiazepines) during last 6 months
• Current Tic disorder
• Antisocial personality disorder
• Bipolar Disorder
• Pregnancy
• Mental retardation

Caveat Neurosurgery:
no anticoagulants

4.3 Efficacy measures

Primary efficacy measure:
The Hamilton depression rating scale (HDRS; Hamilton, 1960) and the Montgomery Åsberg depression rating scale (MADRS; Montgomery, 1979).
- Improvement is defined as a drop in HDRS or MADRS of 25–49%
- Response is defined as ≥50% from baseline in HDRS or MADRS
- Remission as HDRS ≤7 or MADRS ≤7.

Secondary efficacy measures

- Inventory for Depressive Symptoms (IDS-SR; Rush et al., 1986)
- Hamilton Anxiety Scale (HAM-A)
- Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995)
- Symptom Checklist 90 (SCL-90)
- Quality of life enjoyment and satisfaction Questionnaire and MOS SF36
- Sheehan Disability Scale (SDS)
- The Clinical Global Impression (CGI)

4.4. Personality assessments
Personality changes will be evaluated with Minnesota Multiphasic Personality Inventory (MMPI-2)

4.5. Neuropsychological Investigations (NPI):
The neuropsychological tests before and after treatment will be described in a separate protocol.

4.6. Neuroimaging:
Neuro imaging procedures before and after treatment will be described in a separate protocol.

4.7. Biochemical measures:

The determination of various biochemical parameters from blood before and after treatment will be described in a separate protocol. For all patients 14 cc of blood will be collected for future genetic research.

5. DATA COLLECTION, STATISTICAL ANALYSES AND SAMPLE SIZE

5.1 Data collection

Date will be collected in a case record form (CRF), containing the clinical characteristics of the patient, the rating scales, adverse event forms and information on the stimulation parameters.

All data collected from each subject will be entered legibly and accurately into the subject file. The files will be kept current to reflect the present status at each phase during the course of the study. After completion of the study the completed subject files will be stored in the hospital archives and maintained for a minimum of 15 years.

5.2 Statistics

The primary outcome is the change on the HAM-D or MADRS and the number of responders to treatment. Patients are classified as responders to treatment if the HAM-D or MADRS score decreases 50% or more.

Analyses will be primarily based on the change score of all measures obtained during the double-blind crossover treatment period comparing the ‘on’ and ‘off’ period. Treatment, treatment by period and period effects will be analyzed in this period using one-way ANOVA in completers.

The number of responders in the ‘on’ and ‘off’ period will be calculated and tested with the Fisher exact test.
Data of the optimisation and maintenance phase will be presented descriptively as change from baseline and as the number of patients with a sustained response.

Effects on the MMPI-2, SDS and QoL scales will be analysed with multivariate analysis of variance on an Intent-to-treat basis.

Statistical analyses will be performed in collaboration with the department of Clinical Epidemiology and Biostatistics of the AMC in Amsterdam.

5.3 Sample size

This an explorative trial using a new procedure, which does not permit exact power calculations. However, we performed a power calculation for the continuous treatment outcome: taking a reduction of 9 points on the Ham-D as a clinically relevant response and assuming that the placebo response in this treatment refractory group is almost zero and assuming (based on drug studies) a standard deviation of 6 points, 16 patients should be sufficient to assess the potential efficacy of this procedure with a type I error of 0.01 and a type II error of 0.1. The total study population is enlarged to 26 as crossover trials are vulnerable to the effects of patient withdrawal, which can be anticipated if the perceived effects of stimulation are particularly large in the first period of the crossover.

6. ADVERSE EVENTS AND DISCONTINUATION

6.1 Patient withdrawal

Subjects may be withdrawn from the study for the following reasons:

(a) On request of the subject, at any time.
(b) When a subject does not comply with the directives of the procedures.
(c) When a subject needs other than the allowed medication.
(d) When the investigator or the treating psychiatrist decides this is in the best interest of the subject.
6.2 Reporting of adverse events

Questioning the subjects in general terms, by questionnaire and by spontaneous reports of the subjects and by observation will derive information on adverse events. The investigators will describe any adverse events whether or not related to the study procedure in the CRF. Medical and scientific judgment should be exercised in deciding whether other important medical events should be considered serious.

6.3 Safety committee

The Department of Epidemiology and Biostatistics at the AMC Amsterdam will serve as an independent safety committee. This committee shall be composed of at least one clinician with expertise in MDD and one neurosurgeon and has the following function and mandates:

1. Monitoring of (severe) adverse events
2. Monitoring (lack of) efficacy during the study.
3. Judgment whether continuation of the study is ethically justified based on adverse events and efficacy.

The final decision to terminate the study will be made by the safety committee after consultation of the investigators.

6.4 Premature termination of the study

In case of premature termination, the investigator will provide a written statement as to why the termination has taken place. This statement will be documented in the subject files. The investigator will notify the ethics committee.

7. ETHICAL CONSIDERATIONS
As previously mentioned, DBS is now a conventional therapeutic option for patients with intractable movement disorders. DBS has therefore become an attractive therapeutic option in an otherwise untreatable group of patients who experience tremendous suffering and functional impairment. The interest in DBS for patient with severe neuropsychiatric illness is now growing rapidly. Such patients likewise experience extreme distress and inability to participate in social and occupational life. And, as is true for movement disorders, lesions procedures as a treatment option have led to the identification of potential anatomic targets for DBS in MDD. In current practice, patients with extreme severe MDD can only be offered neurosurgery as last resort. DBS can be a non-ablative, reversible and adjustable alternative for these patients.

All patients fulfilling the inclusion criteria in this study will be reviewed by an independent review board, consisting of one psychiatrist, a neurosurgeon and a psychiatric nurse, not involved in the study and not appointed as independent physician to the study. Based on all information gathered during the screening phase, this review board will decide whether inclusion of the patients is ethically justified. The investigators will comply with their judgment.

This protocol is also in accordance with the principles laid down by the Declaration of Helsinki. The study will be conducted in accordance to the requirements of ICH Good Clinical Practice and the recommendations of the World Health Organization.

7.1 Informed Consent

Before enrollment into the study the investigator will inform every participant about the nature of the study, its purpose, procedures, expected duration and the benefits and risks involved in study participation. Each subject will be given the opportunity to ask questions and will be informed about the right to withdraw from the study at any time without prejudice. Trial subjects will be given adequate opportunity to read the information and inquire about details of the study before consent is given. Subjects will have to voluntary sign and date a written informed consent statement before participation. The informed consent statement will be signed and dated by an investigator. The subject will receive a copy of the consent statement.

7.2 Ethics Review Committee
The protocol, any protocol amendment, the consent form and the information sheet will be submitted to the medical ethics committee (MEC) of the AMC Amsterdam for review and approval. On the approval sheet the trial (title, protocol number and version) the documents studied (protocol, informed consent material and other material where applicable) and the date of the review will be clearly stated. After approval by the MEC of the AMC, the protocol will be subsequently submitted to the MEC of the St Elisabeth Hospital and the University Hospital Maastricht in order to judge local feasibility and endorsement of the AMC MEC approval in these centers. The study will not start until the investigators have received a copy of this written approval. Complementary information or requirements will be described in an appendix, where applicable.

8. REGULATORY REQUIREMENTS AND OBLIGATIONS OF THE INVESTIGATORS

For the purpose of ensuring compliance with Good Clinical Practice and regulatory guidelines, Health Authorities may conduct a site audit or an inspection. By signing this protocol the investigator agrees to allow regulatory agencies to have direct access to the study records for review.

8.1 Confidentiality

All persons involved in the study agree to keep confidential any information pertaining to the subject's identity, which becomes known to them in the course of the study.

8.2 Clinical study report and publication of the study results

The investigators will provide a final clinical study report. Any publication of the study results will be considered as a collaborative effort between the all investigators. Authorship shall be determined by mutual consent.

8.3 Compensation for medicine-induced injury

Investigators and appropriate staff will be indemnified by the treatment center for liability for medicine-induced injury. Injury resulting from participation in this study will be covered by an insurance taken out by the hospital for this purpose.
8.4 Protocol amendments

The investigator may make no changes or amendments to this protocol after the protocol has been agreed to and signed by all parties. If an amendment to the protocol is required a formal amendment procedure will be followed to receive approval from all authorities who approved of the original protocol. Unless there are overriding safety-reasons the investigator will wait for signed approval of the amendment from the ethics committee before proceeding with the clinical study. In case an amendment may require a change to a consent form, the investigator must receive approval of the ethics committee of the revised consent prior to implementation of the change.

Reference List


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# PROTOCOL SIGNATURE SHEET

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In any given 1-year period, 5.8 percent of the Dutch population suffers from Major Depressive Disorder (MDD). The economic cost for this disorder is high, but the cost in human suffering cannot be estimated. MDD often interferes with normal functioning and causes pain and suffering not only to those who have a disorder, but also to those who care about them. Serious MDD can destroy family life as well as the life of the ill person. A recent World Health Organization report predicts that MDD will be the leading cause of disability and premature death in the industrial world by the year 2020. Without treatment, ten percent of people suffering from severe MDD commit suicide. With adequate treatment, the majority of patients with this illness recover.

1.1 What is depressive disorder?

MDD is manifested by a combination of symptoms (see symptom list) that interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Such a disabling episode of depression may occur only once, but more commonly occurs several times in a lifetime. In adults, MDD affects twice as many women as men. For both genders it is most common in those who are 25-44 years of age, but over the age of 65 incidence-rates increase again. Within an entire lifetime, MDD will affect 10%-25% of women and 5%-12% of men. Those with a parent or sibling who has had MDD may be 1.5 to 3 times more likely to develop the condition than those who do not.

### Diagnosis of Major Depressive Disorder, Single Episode

Summarized from the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition.

A. The person experiences a single major depressive episode:

6. For a major depressive episode a person must have experienced at least five of the nine symptoms below for the same two weeks or more, for most of the time almost every day, and this is a change from his/her prior level of functioning. One of the symptoms must be either (a) depressed mood, or (b) loss of interest.

   a. Depressed mood. For children and adolescents, this may be irritable mood.

   b. A significantly reduced level of interest or pleasure in most or all activities.

   c. A considerable loss or gain of weight (e.g., 5% or more change of weight in a month when not dieting). This may also be an increase or decrease in appetite.
For children, they may not gain an expected amount of weight.

d. Difficulty falling or staying asleep (insomnia), or sleeping more than usual (hypersomnia).

e. Behavior that is agitated or slowed down. Others should be able to observe this.

f. Feeling fatigued, or diminished energy.

g. Thoughts of worthlessness or extreme guilt (not about being ill).

h. Ability to think, concentrate, or make decisions is reduced.

i. Frequent thoughts of death or suicide (with or without a specific plan), or attempt of suicide.

7. The persons’ symptoms do not indicate a mixed episode.

8. The person's symptoms are a cause of great distress or difficulty in functioning at home, work, or other important areas.

9. The person's symptoms are not caused by substance use (e.g., alcohol, drugs, medication), or a medical disorder.

10. The person's symptoms are not due to normal grief or bereavement over the death of a loved one, they continue for more than two months, or they include great difficulty in functioning, frequent thoughts of worthlessness, thoughts of suicide, symptoms that are psychotic, or behavior that is slowed down (psychomotor retardation).

B. Another disorder does not better explain the major depressive episode.

C. The person has never had a manic, mixed, or a hypomanic Episode (unless an episode was due to a medical disorder or use of a substance).

**Major Depressive Disorder, Recurrent:**
All of the above criteria apply, except with regard to criteria A there have been two or more major depressive episodes with at least two months in between in which no major depressive episode was present.

### 1.2 What is refractory depressive disorder?

Although the therapeutic armamentarium available for clinicians treating MDD patients has expanded substantially over the last decades, treatment resistant or ‘refractory’ MDD in its broadest sense still characterizes a significant number of patients in therapy. Refractory MDD is a term used in clinical psychiatry to describe cases of MDD that do not respond to typical modes of treatment, such as psychotherapy and common antidepressants such as SSRIs and tricyclic antidepressants (TCAs). Furthermore, most of the refractory MDD patients do not respond to classical Monoamine Oxidase A
Inhibitors (MAO-I) and/or Electroconvulsive therapy (ECT; see below). About 50% of the patients treated for MDD do not respond satisfactorily to the first antidepressant prescribed. There are individuals (up to 15% of patients) for whom multiple interventions will be unhelpful and who will have significant depression despite aggressive pharmacologic and psychotherapeutic approaches.

1.3 What are treatment options for refractory depressive disorder?

Treatment of refractory MDD most commonly involves ECT and use of non-standard medications, but may also involve more intrusive interventions such as vagus nerve stimulation. ECT is useful, particularly for individuals whose depression is severe or life-threatening, or complicated with psychotic features, nevertheless, between 10-40% of patients do not fully recover after ECT. Furthermore, ECT has a high relapse-rate, especially when not followed by maintenance pharmacological therapy. In case of response to acute ECT, followed by relapse (despite adequate pharmacotherapy), continuation or maintenance ECT is performed, with biweekly to monthly ECT-sessions, sometimes lifelong.

1.4 Neurosurgery for refractory depressive disorder

For a small proportion of the refractory DD patients, neurosurgery is a last resort. Physicians familiar with neurosurgery are convinced that, drawing on their clinical experience, highly selective and stereotactically produced lesions in the brain can benefit a number of carefully selected, chronically ill psychiatric patients. A clinically significant response after neurosurgery is reported in about 30-50% of the patients. The highest response is seen in patients with lesions in the anterior limb of the internal capsule. Lesions are either made by thermocoagulation of by radiosurgical means using the Leksell Gamma Knife. Controlled studies of these procedures have not been conducted, but Sakas et al (2007) has reviewed the results of 213 cases and found satisfactory results in 63% of the cases. [1] Other stereotactic surgical interventions include subcaudate tractomy, cingulotomy and limbic leukotomy. Although the methods may vary, all these ablative procedures create a lesion in the brain by various methods. Besides the risks of any intracranial surgery, these lesions have a low occurrence rate of unwanted mental side effects, but the great disadvantage of lesioning parts of the brain
is its irreversible nature. Therefore, for a small proportion of the refractory MDD patients, neurosurgery is a last resort.

1.5 What is Deep brain stimulation?

Recently, a potentially ‘non-destructive’ alternative to ablative neurosurgery has emerged: deep brain stimulation (DBS). DBS uses a lead just larger than 1 mm in diameter implanted stereotactically into specific brain targets. The stimulating leads are connected to pulse generators typically placed in the chest. The leads themselves have several independently programmable electrode contact sites, which means that the anatomical extent of the stimulation is adjustable. The frequency, intensity, and pulse width are also programmable. DBS does not damage brain tissue and the stimulation itself can be modified or discontinued in the event of side effects. The device can even be removed if necessary. The major risks of device implantation are hemorrhage and infections. Experience with DBS for movement disorders, however, indicates that the incidence of these risks is low: approximately 1%. Therefore, DBS is accepted as a safer, more advantageous alternative to a permanent brain lesion. The adjustability of the stimulation parameters over time, to maximize clinical benefit while minimizing adverse side effects, and the reversibility of this procedure, with the potential to benefit from drugs developed in the future, are potential advantages of DBS.

1.6 Deep brain stimulation for refractory depressive disorder

Presently there is anecdotal evidence that DBS is effective in patients with refractory MDD. Interestingly, signs and symptoms of severe depression can be (reversibly) induced in PD patients undergoing DBS [2], likely because of inadvertent stimulation of limbic portions of the STN, the adjacent ZI, or SNr. The insight that focal brain stimulation can profoundly alter limbic function suggests that DBS of the limbic circuitry (at other targets) could be used to treat MDD in patients who suffer from intractable forms of the disease. Although earlier single case studies have reported that DBS of mesothalamic targets or of the inferior thalamic peduncle is effective against reactive MDD in patients with chronic pain [3], or single MDD [4], respectively, the precise target has not been well defined. In a recent study involving six patients with refractory depression, it has been shown that DBS of the white matter in the subgenual cingulate
region (area 25) can produce very significant clinical benefits [5]. This target was chosen after a series of neuroimaging studies, which showed that area 25 is overactive in depression, and remains overactive in refractory MDD patients. A region in the rostral cingulate gyrus has also been proposed as a possible target for DBS in depression ([6]. In addition, a recent preliminary report of 3 patients showed DBS of the nucleus accumbens to be effective as well [7].

1.7 Bilateral accumbens stimulation for refractory depressive disorder

The target of the current study will be the nucleus accumbens. The nucleus accumbens is an important part of what is known as the "reward system". It ensures that we remember good experiences and puts us in a state of pleasurable anticipation. Without the reward system we would not make plans for the future, simply because we could not enjoy the fruits of these plans. Inactivity and inability to enjoy things are two important signs of MDD. The conclusion is therefore obvious that the nucleus accumbens plays a key role in the genesis of the disease. Preliminary data in three patients has shown efficacy of DBS in three MDD patients [8], and experience in our current study stimulating the accumbens for obsessive-compulsive disorder (OCD) patients shows improved mood in 14 out of 16 cases as well.

1.8 Ethical considerations regarding DBS in neuropsychiatry

The previous era of psychosurgery ended in the 1970s because of severe condemnation of the excessive and indiscriminate use of these procedures, their disappointing outcomes, and the lack of patient protection. It may seem surprising, then, that neurologists, neurosurgeons, and psychiatrists are again exploring such surgical procedures for severe psychiatric disorders, such as OCD, Tourette syndrome (TS), and MDD. The acceptance of DBS is due to several facts, including (1) the failure of existing drugs to deal effectively with the psychiatric condition in a subset of treatment refractory patients, (2) the remarkable success of DBS procedures in treating movement disorders, (3) the relatively less invasive and reversible nature of DBS, (4) the greater public awareness of the enormous lifelong burden of these disorders on patients and their caregivers, and (5) the greater scrutiny and protection of patient rights. DBS procedures for neuropsychiatric conditions remain strictly experimental at this point. Use of DBS in neuropsychiatric diseases is based on findings suggesting that these conditions are, at
least partly, due to abnormalities within the nonmotor basal ganglia circuits, most prominently the limbic circuitry.

2. OBJECTIVES

The primary objective of the present study is to assess efficacy of DBS in the nucleus accumbens for patients with refractory MDD. Secondary objectives are the evaluation of long term efficacy and tolerability of DBS for patients with therapy refractory MDD.

3. PROCEDURE

The study comprises 5 sequential phases.


3.1 Preoperative phase

If a patient is a possible candidate for DBS, this patient will undergo an extended diagnostic intake by the research team to assess whether all in- and exclusion criteria are met. The diagnostic intake consists of psychiatric interviews, (neuro)psychological assessments, and a structural MRI scan. This diagnostic intake is a standard extended diagnostic intake, which is done in complex diagnostic cases. Because of this, no written informed consent (IC) will be asked of the patients before this intake. Moreover, some therapy-resistant psychiatric patients might be given false hope by signing an IC for the DBS study before the diagnostic intake, because it is not certain whether they will be eligible for DBS. A contra-indication after the intake might result in an increase of mental stress in these patients. Therefore, only an oral consent for the diagnostic intake is asked of the patient.

If the patient is indicated for DBS surgery, the patient will be asked for written informed consent for surgery and research as specified in this protocol. At the same time patients are also asked to participate in an additional neuropsychological and neuro-imaging
study as described in protocol 2009/220 (see paragraph 4.4 and 4.5). Six weeks prior to surgery, the treating psychiatrist assesses all prescribed psychoactive medication and tapers them off to the minimum effective dosage regimen, if clinically justified and after the patient has signed the informed consent. The medication regimens will be kept stable if possible, but may be changed during the study by the treating psychiatrist on indication. Psychometric assessments will be conducted when the stable dosage regimen has been implemented. Baseline psychometric assessments and tasks (depression and quality of life scales) will be performed 1-3 weeks prior to surgery (see study schedule). If patients gave their consent, neuro imaging, psychometric assessments, neuropsychological tests and affective information processing tasks will be conducted during this period, which are described in protocol 2009/220. Standard psychiatric care will be available to all patients throughout this period and if necessary patients may be hospitalized at the psychiatric department of the AMC.

### 3.2 Surgery

The implantation of the electrodes will be performed according to standard procedures using the stereotactic method. Under general anaesthesia, a stereotactic frame is attached to the skull, providing a Cartesian coordinate system for all points within the stereotactic space (i.e. the skull and all of its contents). Thereafter, a MRI-scan is made. The anterior and posterior commissures, as well as the anterior part of the internal capsule are identified on the 3-dimensional reconstruction of the MRI. The stereotactic coordinates of the position of the nucleus accumbens (NAc) on both sides of the brain are calculated, using the spatial relationship between the NAc and the commissures as obtained from a standard stereotactic atlas. The planning software of the 3-dimensional imaging program is used to determine the optimal trajectories for electrode implantation through the brain, in such a way that the deepest of the four electrical contacts of the electrodes is positioned in the NAc, with the preceding three electrode contacts positioned in the anterior part of the internal capsule. Thus, a path is obtained for each electrode with both an entry point in the skull and a target point in the NAc. The patient is transported to the Operation Room (OR), where the stereotactic arc is attached to the frame, after which the location of the burr hole for electrode implantation can be identified. After a small incision in the skin is made bilaterally, two frontal burr holes are made and the dura is opened. The electrodes are inserted, after which brief exploratory trial stimulation can be performed to confirm the absence of side
effects of stimulation at the target site. The electrodes are then fixed to the skull and the
incisions are closed. Under general anaesthesia the distal part of the electrodes are
connected to extension cables. Theses cables are tunnelled under the skin to the
infraclavicular region, where they are connected to the stimulators, which are placed in a
subcutaneous pocket bilaterally. Directly after surgery, a CT-scan is made which is used
to verify the correct position of the electrode. To this end, the CT is fused with the
stereotactic 3-D volumetric MRI using standard image fusion techniques.
Electrodes (Model 3389, Medtronics Inc. Mineapolis, MN, USA) will be implanted
bilaterally and connected to Activa PC DBS stimulators (Medtronics, Inc. Mineapolis,
MN, USA).

3.3 Optimization period

After recovery from surgery, the stimulation device will stay in off mode during three
weeks in order to overcome direct effects from surgery, which might interfere with
optimization. After these three weeks, psychometric assessments are repeated, and
optimization of the stimulation device will be started immediately. Optimization will be
performed during at least 3 months (12 weeks). If thereafter clinical improvement is still
expected with additional changes in device settings a continuation of the optimization-
phase is possible for 9 more months, with assessments of improvement every 2 weeks
until a plateau of effectiveness is reached. If necessary, patients may start additional
behavioural therapy during the optimization period, aimed at re-activation and
improvement of social functioning. Patients enter the next phase of the study after the
optimization period is completed, which is (1) after at least three months of trial
stimulation during which the stimulation parameter settings are determined that give
the best clinical improvement, or (2) when after an elongation of the optimization phase
no (further) clinical improvement can be achieved.

3.4 Double blind assessment period

The efficacy of DBS is evaluated in a 12 week randomized double blind, two-phase cross-
over design. Patients are randomly allocated to two periods of maximal six weeks with
the stimulators in the ‘on’ position in one period and in the ‘off’ position in the other.
The order of these periods is randomly assigned. An independent psychiatrist or
psychologist will turn the stimulator ‘on’ or ‘off’ according to a computer generated
randomization table. The treating psychiatrists and investigators responsible for assessments are blind to the setting of the stimulator. The stimulation parameters are kept constant if possible during the treatment phases, but readjustment is possible between the treatment phases if the impedance has changed. During the double-blind phase the patients will be monitored weekly by telephone calls of one of the investigators. The full 6 weeks of the double-blind phases can be ended prematurely after a minimal period of 1 week, if 1) a relapse of depressive symptoms occurs in responders (defined by an increase in HDRS by $\geq 50\%$ and absolute HDRS $\geq 15$), 2) treating psychiatrists or investigators judge the suffering related to symptom increase to be too high to continue the current phase (e.g. suicidal ideation increases), or 3) the patient requests a discontinuation of the phase. In case of premature ending of the first cross-over phase, the patient will cross-over to the second phase immediately. In case of premature ending of the second phase, the patient will start the maintenance period immediately. Treating psychiatrists, investigators and patients will be kept blind, whether cross-over phases are ended prematurely or not. The randomization code can only be broken in case of unexpected events by the investigator. If necessary, patients may be hospitalized for a short period at the psychiatric department of the AMC.

Psychometric assessments (including assessment of life-events) will be conducted during this period at three times: before the start of the first cross-over phase, and at the end of both cross-over phases. If the patient has given written consent for protocol 2009/220, neuro-imaging and neuropsychological tests will be performed at the same times.

### 3.5 Maintenance period

The maintenance phase consists of a period of 12 months following the blind assessment phase. This period will commence, if necessary, with a further optimization of stimulation parameters. The stimulators are ‘on’ for all patients, but can be switched off for a certain period if necessary, and optimization of the parameters during this period is possible on demand. During the maintenance period patients will continue their behavioural therapy (BT) program individually designed for post-operative DBS treatment. If necessary, additional cognitive therapy will be added to address persistent negative thoughts and/or dysfunctional attitudes. In general, (cognitive) behavioral therapy is one of the most promising types of psychotherapy for MDD. In cognitive
behavioral therapy the therapist seeks to correct negative thoughts or dysfunctional attitudes in order to overcome pessimism and hopelessness. Furthermore, we will focus on reactivation and rehabilitation of these patients. Because these patients have been depressed for many years before entering the study, their illness presumably caused them to retract from normal life and social functioning. Even when they fully respond to DBS, they will suffer from isolation and loss of daily activities, for which rehabilitation techniques are required.

Psychometric, psychiatric and neuropsychological tests will be conducted at regular intervals as indicated in the study schedule.

4. PATIENTS AND METHODS

A total of 26 treatment-refractory (see below) patients with MDD will be selected to participate in the study after written informed consent has been obtained. Patients will be recruited from the program for mood disorders of the AMC Amsterdam.

4.1 Inclusion criteria

- Primary diagnosis: MDD (single episode or recurrent; 296.2 or 296.3) according to the DSM-IV criteria based on a psychiatric interview and the SCID as diagnostic instrument
- Illness duration > 2 years, chronic MDD
- HAM-D total ≥ 18 (measured twice, at least two weeks apart with the last assessment just before surgery)
- Disabling severity with substantial functional impairment according to the DSM-IV criterion C and a Global Assessment of Function (GAF) score of 45 or less
- The level of impairment must have been persistent for at least 2 years
- Age: 18-65 years old
- Written informed consent
- Able to fully understand the consequences of the procedure (IQ > 80)
- Dutch or English speaking and able to answer the study questions
- Capable to make his or her own choice without coercion
- Treatment refractory defined as failure of:
- At least 2 adequate treatments of at least two distinctly different classes of 2nd generation antidepressants (SSRI, SNRI, NaSSA) for a period of 6-8 weeks

  and

- An adequate trial of a TCA 6-8 weeks (at therapeutic drug levels)

  and

- TCA + addition of lithium when tolerable at least 6 weeks at therapeutic drug levels (>0.6 mmol/L))

  and

- An adequate trial of a MAOI

  and

- ≥1 session of ECT, for which the series of ECT was terminated either due to adverse effects or insufficient response (including at least 6 sessions of bilateral ECT).

  or

- Patients who are kept stable with maintenance ECT, but who relapse after discontinuation of this maintenance ECT are also eligible, but need to fulfill the above inclusion criteria

### 4.2 Exclusion criteria

- Unstable physical condition
- Organic cause
- Parkinson’s disease, dementia, epilepsy
- Schizophrenia /history of psychosis unrelated to MDD
- Alcohol or substance abuse (including benzodiazepines) during last 6 months
- Current Tic disorder
- Antisocial personality disorder
- Bipolar Disorder
- Pregnancy
- Mental retardation
Caveat Neurosurgery:
no anticoagulants

4.3 Efficacy measures

Primary efficacy measure:
The Hamilton depression rating scale (HDRS; Hamilton, 1960) and the Montgomery Åsberg depression rating scale (MADRS; Montgomery, 1979).
- Improvement is defined as a drop in HDRS or MADRS of 25–49%
- Response is defined as ≥50% from baseline in HDRS or MADRS
- Remission as HDRS \leq 7 or MADRS \leq 7.

Secondary efficacy measures
- Inventory for Depressive Symptoms (IDS-SR; Rush et al., 1986)
- Quality of life enjoyment and satisfaction Questionnaire and MOS SF36
- Sheehan Disability Scale (SDS)

4.4. Neuropsychological Investigations (NPI):
The neuropsychological tests before and after treatment are described in protocol 2009/220.

4.5. Neuroimaging:
Neuro imaging procedures before and after treatment are described in protocol 2009/220.

5. DATA COLLECTION, STATISTICAL ANALYSES AND SAMPLE SIZE

5.1 Data collection
Date will be collected in a case record form (CRF), containing the clinical characteristics of the patient, the rating scales, adverse event forms and information on the stimulation parameters.
All data collected from each subject will be entered legibly and accurately into the subject file. The files will be kept current to reflect the present status at each phase.
during the course of the study. After completion of the study the completed subject files will be stored in the hospital archives and maintained for a minimum of 15 years.

5.2 Statistics

The primary outcome is the change on the HAM-D or MADRS and the number of responders to treatment. Patients are classified as responders to treatment if the HAM-D or MADRS score decreases 50% or more.

Analyses will be primarily based on the change score of all measures obtained during the double-blind crossover treatment period comparing the ‘on’ and ‘off’ period. Treatment, treatment by period and period effects will be analyzed in this period using one-way ANOVA in completers.

The number of responders in the ‘on’ and ‘off’ period will be calculated and tested with the Fisher exact test.

Data of the optimisation and maintenance phase will be presented descriptively as change from baseline and as the number of patients with a sustained response.

Effects on the MMPI-2, SDS and QoL scales will be analysed with multivariate analysis of variance on an Intent-to-treat basis.

Statistical analyses will be performed in collaboration with the department of Clinical Epidemiology and Biostatistics of the AMC in Amsterdam.

5.3 Sample size

This an explorative trial using a new procedure, which does not permit exact power calculations. However, we performed a power calculation for the continuous treatment outcome: taking a reduction of 9 points on the Ham-D as a clinically relevant response and assuming that the placebo response in this treatment refractory group is almost zero and assuming (based on drug studies) a standard deviation of 6 points, 16 patients should be sufficient to assess the potential efficacy of this procedure with a type I error of 0.01 and a type II error of 0.1. The total study population is enlarged to 26 as crossover trials are vulnerable to the effects of patient withdrawal, which can be
anticipated if the perceived effects of stimulation are particularly large in the first period of the crossover.

6. ADVERSE EVENTS AND DISCONTINUATION

6.1 Patient withdrawal

Subjects may be withdrawn from the study for the following reasons:

(a) On request of the subject, at any time.
(b) When a subject does not comply with the directives of the procedures.
(c) When a subject needs other than the allowed medication.
(d) When the investigator or the treating psychiatrist decides this is in the best interest of the subject.

6.2 Reporting of adverse events

Questioning the subjects in general terms, by questionnaire and by spontaneous reports of the subjects and by observation will derive information on adverse events. The investigators will describe any adverse events whether or not related to the study procedure in the CRF. Medical and scientific judgment should be exercised in deciding whether other important medical events should be considered serious.

6.3 Safety committee

An independent data safety monitoring board (DSMB) shall monitor efficacy and safety issues of the study. The DSMB consists of prof. dr. J. Swinkels (Department of Psychiatry) and dr. R. de Bie (Departement of Neurology). The DSMB has the following functions and mandates:

1. Monitoring of (severe) adverse events
2. Monitoring (lack of) efficacy during the study.
3. Judgment whether continuation of the study is ethically justified based on adverse events and efficacy.

The final decision to terminate the study will be made by the safety committee after consultation of the investigators.
6.4 Premature termination of the study

In case of premature termination, the investigator will provide a written statement as to why the termination has taken place. This statement will be documented in the subject files. The investigator will notify the ethics committee.

7. ETHICAL CONSIDERATIONS

As previously mentioned, DBS is now a conventional therapeutic option for patients with intractable movement disorders. DBS has therefore become an attractive therapeutic option in an otherwise untreatable group of patients who experience tremendous suffering and functional impairment. The interest in DBS for patient with severe neuropsychiatric illness is now growing rapidly. Such patients likewise experience extreme distress and inability to participate in social and occupational life. And, as is true for movement disorders, lesions procedures as a treatment option have led to the identification of potential anatomic targets for DBS in MDD. In current practice, patients with extreme severe MDD can only be offered neurosurgery as last resort. DBS can be a non-ablative, reversible and adjustable alternative for these patients.

All patients fulfilling the inclusion criteria in this study will be reviewed by an independent review board, consisting of one psychiatrist, a neurosurgeon and a psychiatric nurse, not involved in the study and not appointed as independent physician to the study. Based on all information gathered during the screening phase, this review board will decide whether inclusion of the patients is ethically justified. The investigators will comply with their judgment.

This protocol is also in accordance with the principles laid down by the Declaration of Helsinki. The study will be conducted in accordance to the requirements of ICH Good Clinical Practice and the recommendations of the World Health Organization.

7.1 Informed Consent

Before enrollment into the study the investigator will inform every participant about the nature of the study, its purpose, procedures, expected duration and the benefits and risks involved in study participation. Each subject will be given the opportunity to ask questions and will be informed about the right to withdraw from the study at any time without prejudice. Trial subjects will be given adequate opportunity to read the
information and inquire about details of the study before consent is given. Subjects will have to voluntary sign and date a written informed consent statement before participation. The informed consent statement will be signed and dated by an investigator. The subject will receive a copy of the consent statement.

7.2 Ethics Review Committee
The protocol, any protocol amendment, the consent form and the information sheet will be submitted to the medical ethics committee (MEC) of the AMC Amsterdam for review and approval. On the approval sheet the trial (title, protocol number and version) the documents studied (protocol, informed consent material and other material where applicable) and the date of the review will be clearly stated. After approval by the MEC of the AMC, the protocol will be subsequently submitted to the MEC of the St Elisabeth Hospital in order to judge local feasibility and endorsement of the AMC MEC approval in these centers. The study will not start until the investigators have received a copy of this written approval. Complementary information or requirements will be described in an appendix, where applicable.

8. REGULATORY REQUIREMENTS AND OBLIGATIONS OF THE INVESTIGATORS

For the purpose of ensuring compliance with Good Clinical Practice and regulatory guidelines, Health Authorities may conduct a site audit or an inspection. By signing this protocol the investigator agrees to allow regulatory agencies to have direct access to the study records for review.

8.1 Confidentiality
All persons involved in the study agree to keep confidential any information pertaining to the subject's identity, which becomes known to them in the course of the study.

8.2 Clinical study report and publication of the study results
The investigators will provide a final clinical study report. Any publication of the study results will be considered as a collaborative effort between the all investigators. Authorship shall be determined by mutual consent.
8.3 Compensation for medicine-induced injury

Investigators and appropriate staff will be indemnified by the treatment center for liability for medicine-induced injury. Injury resulting from participation in this study will be covered by an insurance taken out by the hospital for this purpose.

8.4 Protocol amendments

The investigator may make no changes or amendments to this protocol after the protocol has been agreed to and signed by all parties. If an amendment to the protocol is required a formal amendment procedure will be followed to receive approval from all authorities who approved of the original protocol. Unless there are overriding safety-reasons the investigator will wait for signed approval of the amendment from the ethics committee before proceeding with the clinical study. In case an amendment may require a change to a consent form, the investigator must receive approval of the ethics committee of the revised consent prior to implementation of the change.

Reference List


1C. SUMMARY OF CHANGES

Minor changes (e.g. typos or inclarities for the Medical Ethical Committee) are not listed in this summary. Below is a list of changes effecting the DBS treatment and design of the study:

1. The sample size was increased from 16 to 26 patients from v3 to v4 in order to increase power to detect changes and compensate for dropouts.

2. Maximum duration of optimization phase was extended from 3 to 6 months in v4 of the protocol, which was the protocol in effect when the first patient was included. The duration was further extended to 12 months in v5 on basis of clinical experience with OCD patients treated by DBS in our center and the first depression patients included in this study protocol.

3. The double blind crossover phases were extended from 2 periods of 2 weeks to 2 periods of 2-6 weeks from v3 to v4. This was done on basis of the first published case series of Mayberg et al. (Neuron 2005; 45(5): 651-660). In this study DBS targeted at the Subcallosal Gyrus was deactivated in 1 of the 6 patients and this patient relapsed after 4 weeks of continued effectiveness. As a consequence, a sham period of 2 weeks might not have been long enough to detect changes of depressive symptoms. We changed the duration of the double blind phases to 1-6 weeks from v4 to v5, since it was clinically and ethically not feasible to keep some patients in (one of) the crossover phases for a minimum of 2 weeks.

4. Part of the DBS surgery (implanting the DBS electrodes) was done under local anesthesia, but this was changed to general anesthesia from v4 to v5. We learned by expanded clinical experience it was no longer necessary to implant electrodes under local anesthesia.
5. In v3 it is stated that the treating psychiatrist randomized the patients to active or sham stimulation in the double blind phase (see p.11 of this document). Since the actual procedure during the entire study was that an independent psychologist randomized patients, we changed this sentence in the protocol in v5.

6. From the start of the study we did not perform some of the secondary outcome measures to prevent overload of this severely ill patient group. This concerned the following measures: Hamilton Anxiety Scale, Snaith-Hamilton Pleasure Scale, Symptom Check List-90, Minnesota Multiphasic Personality Inventory, and blood tests. These tests were formally deleted from the protocol from v4 to v5.

NB: no changes from v5 to v6, or from v6 to v7 are described in this summary, since these changes concerned minor adaptations only (e.g. procedures were clarified in more detail on request of the Medical Ethical Committee). These changes did not affect the DBS treatment protocol or design of the study.
2A. INITIAL STATISTICAL ANALYSIS PLAN

The initial statistical analysis plan was part of the initial protocol in paragraph 5.2 (see also page 15 of this document):

The primary outcome is the change on the HAM-D or MADRS and the number of responders to treatment. Patients are classified as responders to treatment if the HAM-D or MADRS score decreases 50% or more.

Analyses will be primarily based on the change score of all measures obtained during the double-blind crossover treatment period comparing the ‘on’ and ‘off’ period. Treatment, treatment by period and period effects will be analyzed in this period using one-way ANOVA in completers.

The number of responders in the ‘on’ and ‘off’ period will be calculated and tested with the Fisher exact test.
2B. FINAL STATISTICAL ANALYSIS PLAN

Data analysis optimization phase

Results of the optimization phase are analyzed by change of HAM-D, MADRS and IDS-SR score. This is modeled with 3 linear mixed models, one for every depression scale (HAM-D, MADRS and IDS). The depression scale is taken as dependent variable, while Intercept and Days from baseline (BL) are included as independent variable. Both Intercept and Days from BL are included as random variables with individual subjects as grouping variable. In case change of depression score over days might not have a linear relationship, the 3 mixed models are also executed with a log transformation of days from BL.

Assumptions of mixed models are: 1) normal distribution of the residuals and random effects, and 2) a linear relationship between intercept and change over days exists. For each mixed model, normality assumptions are checked visually through QQ plots and formally through Shapiro tests. Second, a linear relationship between intercept and change over days is visually checked by inspection of individual growth plots.

In addition, the optimization phase is analysed by describing the count of responders, partial responders and non-responders. The definition of responder status is defined on basis of percentage reduction of HAM-D score at T2 compared to baseline. In case patients have dropped out of the study before T2 or refused to participate at T2, the last observation before 1 year of DBS optimization is carried forward to T2. Patients are classified as responders if the reduction of HAM-D score is at least 50% compared to baseline, and as non-responders if the reduction is less than 50%. In a separate analysis patients were classified as partial responders if the reduction lies between 25% and 50%.
Data analysis active / sham crossover phase

Analyses are primarily based on the change score of all measures obtained during the double-blind crossover treatment period comparing the ‘on’ and ‘off’ period. Treatment, treatment by period and period effects will be analyzed in this period. Three mixed models are executed in order to test for differences of stimulation phase with HAM-D, MADRS or IDS score as dependent variable. Independent variables are Intercept, Period as factor (levels: T3 / T4), Treatment as factor (levels: Active / Sham), and Period X Treatment interaction (to correct for carryover effects). Depression score at T2 is included as a covariate, in order to correct for possible differences in depression score at the start of the crossover phase between patients randomized to ‘first active, then sham’ and patients randomized to ‘first sham, then active’.
2C. SUMMARY OF CHANGES

The final statistical analysis plan is essentially a more detailed and updated description of the analyses as described in the initial protocol. The final data analysis plan is part of our Data Management Plan. This is a list of the changes:

1. In the initial analysis plan changes of depression scores is stated as one of the primary outcomes, but no model is specified. In the final plan this model was specified in more detail (i.e. the mixed models described on p. 45).

2. In the final analysis we added ‘partial responders’ as an extra classification next to ‘responders’ and ‘non-responders’, which were mentioned in the initial plan. This was done in order to gain more insight in possible partial improvement in some non-responders.

3. In our initial analysis plan a one-way ANOVA was planned to model differences between active and sham stimulation. Following the of advice of the expert statistician at our department and the literature, we modified this analysis to a more appropriate model accounting for correlated measures of repeated testing (i.e. the mixed models described on p. 46).

4. In the final analysis plan we deleted the Fisher exact test mentioned in the initial analysis plan, since Fisher exact tests with a sample of this size can only detect differences of large effect sizes and are therefore susceptible to Type II errors.