Statistical analysis plan for the DBS-ITAP trial: a randomized controlled trial comparing imaging-based programming with threshold assessment-based programming of deep brain stimulation for Parkinson's disease

Version of this SAP: 1, 19-10-2026

Full title of the study: Randomized Controlled Trial comparing imaging-based programming with threshold assessment-based programming of Deep Brain Stimulation for Parkinson's disease
Short title of the study/acronym: DBS-ITAP
ABR number: 84601
Research protocol: ID/number: NL84601.018.23 Protocol version: 9, 10-05-2024
Trial registration number: NCT06223399 (Study Details | NCT06223399 | DBS Imaging-based vs. Threshold Assessment-based Programming | ClinicalTrials.gov)

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Section 1. Administrative information.

1.1. NAMES AND SIGNATURES			
Role of contributor	**Name and full affiliation**	**Signature**	**Date of signature**
Principal investigator	Rob M.A. de Bie		
Researcher who will perform the statistical analysis	Annabel van der Weide		
Senior statistician consulted	Jeroen Hoogland		

1.2. REVISION HISTORY				
Updated statistical analysis plan version	**Protocol version**	**Section number(s) changed**	**Description of and reason for changes**	**Date of approval**
1.0	9.0	-	-	19 October 2026

1.3. How is the trial registered?

This study is registered at ClinicalTrials.gov:
NCT06223399 (Study Details | NCT06223399 | DBS Imaging-based vs. Threshold Assessment-based Programming | ClinicalTrials.gov)

1.4. What is the planned period of observation?

The expected date of the inclusion of the first patient is 03-JAN-2024.
The expected date of the completion of follow-up for the last patient is 19-OCT-2026.

Section 2. Introduction.

2.1. What is the background and rationale for the study?
Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for disabling motor fluctuations in Parkinson's disease. Correct programming of DBS settings to provide optimal stimulation within the target region is crucial for a successful clinical outcome. To date, programming DBS settings is based on the selection of contact point(s) and stimulation parameters using standardized threshold assessments: for each contact point, the current is increased in small steps, while the severity of motor symptoms and the occurrence of possible adverse effects are assessed at each step. This process is challenging and time consuming because of the vast number of possible parameter combinations. Furthermore, individual variation in patient anatomy and placement of DBS leads must be considered. This results in long programming sessions that can be exhausting for patients and often leads to inconclusive results due to fatigue. Imaging techniques have been improved greatly over the years and could be useful for programming of DBS settings based on patient-specific anatomy.
2.2. What are the objectives of the study?
This study investigates whether the effectiveness of STN DBS for the treatment of Parkinson motor symptoms using imaging-based DBS programming is non-inferior compared to the current standard practice of clinical threshold assessment-based DBS programming.

Section 3. Study Methods.

3.1. What is the study design?

The study is a single centre prospective, randomized, open-label, blinded endpoint (PROBE design) non-inferiority clinical trial.

3.2. Will randomization be performed in this study?

Following DBS implantation, in total 132 patients will be randomized in a 1:1 ratio to initial imaging-based DBS programming (Imaging group) or to DBS programming based on initial threshold assessment (Threshold group). Randomization is done in Castor v2026.1.0.3 (Castor, Amsterdam, the Netherlands). No stratification will be performed.

3.3. How was the sample size calculated?

The sample size calculation is based on the primary outcome measure, which is the change from baseline to six months in motor function in OFF-drug phase measured with the Movement Disorders Society Unified Parkinson's Disease Rating Scale Part Motor Examination (MDS-UPDRS III). We consider a difference of five points on the MDS-UPDRS III in the OFF-drug phase the non-inferiority margin (-Δ). Five points is the minimally clinically important difference (MCID) for the MDS-UPDRS III (1). Standard deviations seen in previous DBS studies, with similar patient populations vary between 7 and 16 (2-10). For this reason, we estimated that the standard deviation will be around 11 points in our study. Based on this, a sample size of 120 patients (i.e., 60 patients in each group) would provide 80% power to detect that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority margin of -5 points on the MDS-UPDRS III. The attrition rate is anticipated to be 10%. Therefore, 66 patients will need to be randomized per treatment arm (132 patients in total).

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(10) Okun MS, Gallo BV, Mandybur G, Jagid J, Foote KD, Revilla FJ, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol. 2012;11(2):140-9.

3.4. WHAT IS THE HYPOTHESIS TESTING FRAMEWORK FOR THIS STUDY?

The DBS-ITAP trial investigates whether imaging-based programming is non-inferior to threshold assessment-based programming of DBS in Parkinson's disease with respect to motor improvement. Therefore, the primary outcome will be analysed using a non-inferiority hypothesis testing framework, with the non-inferiority margin specified in the sample size calculation. The primary outcome is the between-group difference in the change in motor function from baseline to six months in the OFF-drug phase, measured using the MDS-UPDRS part III.

A hierarchical testing procedure will be used for the important secondary outcome of the between-group difference in number of DBS programming-related healthcare contacts (outcome N). First, non-inferiority will be tested for the primary outcome. The important secondary outcome of DBS programming-related healthcare contacts will only be tested for superiority if imaging-based programming is shown to be non-inferior to threshold assessment-based programming for the primary outcome. This is because we hypothesise that imaging-based programming will require fewer DBS programming-related visits, which will be assessed based on the number of outpatient clinic visits and telephone consultations required during the follow-up period.

The remaining secondary outcomes will be considered exploratory. This applies to outcomes A-P, except for outcome N (DBS programming-related healthcare contacts). The secondary outcomes are:

A. Motor symptoms in ON-drug phase (MDS-UPDRS III) (1)
B. Duration of OFF-drug phase (MDS-UPDRS IV) (1)
C. Dyskinesia duration (MDS-UPDRS IV) (1)
D. Dyskinesia severity (MDS-UPDRS IV) (1)
E. Non-motor symptoms (MDS-UPDRS I) (1)
F. Motor aspects of experiences of daily living (MDS-UPDRS II) in ON-drug phase (1)
G. Level of physical disability, measured with the Academic Medical Centre Linear Disability Score (ALDS) (2)
H. Disease specific quality of life (Parkinson's Disease Questionnaire 39) (3)
I. Adverse effects
J. Patient satisfaction on the outcome of treatment
K. Patient evaluation of the burden of therapy
L. Proportion of patients for whom it is necessary to switch to the other intervention arm during the follow-up period
M. Total duration of programming sessions
N. Number of DBS programming-related healthcare contacts (i.e., number of hospital visits and telephone consultations)

O. Final DBS settings (i.e., electrical current)
P. Proportion of patients at six months who are stimulated at same contact point (for both hemispheres) suggested by threshold assessment or imaging

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3.5. Will interim analyses be performed in this study?

No interim analyses will be performed and there are no statistical or clinical guidelines for stopping the study early.

3.6. When will the final statistical analysis of the study data be performed?

The statistical analysis of the primary outcome and all secondary outcomes will be performed after the last follow-up of the last patient has been completed and after closure of the database. As the current estimate the final follow-up will be in October 2026. The current estimate is that these statistical analyses will be performed October-December 2026.

3.7. At which time points are the outcomes measured and which "windows" are allowed?

The time points of the visits are presented in Table 13.1 on page 47 of the protocol. All visits, except the baseline visit, have a planned visit window of two weeks before or after the nominal time points. For the final visit (Visit 5), at which the primary outcome is assessed, a planned visit window of four weeks before or after the nominal time point applies. If the final visit cannot be performed within this window, the visit should be performed as close as possible to the nominal time point, and the primary outcome will still be performed.

Section 4. Statistical Principles.

4.1. WHICH LEVEL OR LEVELS OF STATISTICAL SIGNIFICANCE WILL BE USED IN THE STUDY?
For the primary outcome, non-inferiority will be concluded if the lower bound of the one-sided 95% confidence interval for the between-group difference (imaging-based programming minus threshold assessment-based programming) in mean change in MDS-UPDRS III from baseline to six months is greater than the prespecified non-inferiority margin of -5 points. If non-inferiority is demonstrated for the primary outcome, the important secondary outcome of DBS programming-related healthcare contacts will be tested for superiority at a one-sided significance level of 0.05. The remaining secondary outcomes are considered exploratory. For these outcomes, between-group treatment effects will be estimated using an appropriate effect measure for each outcome, together with corresponding two-sided 95% confidence intervals.
4.2. WILL THE ANALYSIS ADJUST FOR MULTIPLICITY OF STATISTICAL TESTING TO ENSURE CONTROL OF TYPE I ERROR RATE?
No additional adjustment for multiplicity will be applied. The hierarchical testing sequence, in which the secondary confirmatory hypothesis is only tested if non-inferiority is demonstrated for the primary outcome, controls the overall type I error rate.
4.3. WHICH CONFIDENCE INTERVALS WILL BE REPORTED?
Two-sided 95% confidence intervals will be reported for the estimated treatment effects for the primary and secondary outcomes, where appropriate. For continuous outcomes, confidence intervals will be reported for the between-group difference in means (or another appropriate effect estimate). Outcomes reported descriptively using frequencies and proportions, including adverse effects, Likert-scale outcomes, switching to alternative programming arm, and stimulation at the predicted contact points, will not require confidence intervals.
4.4. HOW IS COMPLIANCE DEFINED AND ASSESSED?
Compliance is defined as receiving the allocated DBS programming strategy in accordance with the study protocol, including any protocol-defined cross-over where applicable. Compliance will be assessed based on study records of DBS programming sessions and reported as the proportion of participants who remain compliant throughout the study.

4.5. How will compliance be presented?

As the proportion of participants who remain compliant throughout the study.

4.6. What are defined as protocol deviations in this study?

Protocol deviations are defined as any deviations from the study protocol that may affect the integrity of the trial or the interpretation of its results. These include:

- Inclusion of patients who do not meet the eligibility criteria;
- Failure to apply the allocated DBS programming strategy as specified in the protocol;
- Unjustified or undocumented deviations from the assigned programming method during programming sessions;
- Missing or incomplete primary outcome assessments;
- Failure to adhere to the scheduled follow-up visits or assessment time points.

Switching from one programming strategy to the other during follow-up (i.e., cross-over), when clinically indicated and documented, is considered a protocol deviation.

Minor deviations that do not impact the primary outcome or intervention integrity (e.g., small scheduling delays in follow-up assessments) will not be classified as protocol deviations, provided they are documented.

4.7. How will protocol deviations be presented in the reporting of this study?

All protocol deviations will be line-listed according to intervention arm. In addition, the number and percentage of patients in each intervention arm experiencing one or more protocol deviations will be presented.

4.8. Which analysis populations will be defined?

The following analysis populations will be defined:

The intention-to-treat (ITT) population will include all randomized patients, analysed according to their randomized treatment allocation, irrespective of adherence, treatment switching, or protocol deviations. The ITT population will be used to estimate the treatment policy estimand.

The per-protocol (PP) population will include all randomized patients who received the allocated DBS programming strategy, had no major protocol deviations considered to potentially affect the primary outcome, and had a primary endpoint. Switching to the other DBS programming strategy will be considered a major protocol deviation and will therefore exclude a participant from the PP population. The PP population will be used to estimate the hypothetical estimand, estimating the difference between arms that would be observed if all participant would follow the assigned treatment policy (no switching).

Section 5. Study populations.

5.1. Which data were collected from participants, who were screened for eligibility for inclusion in the study, and how will these data be presented in study reports?

Patients with Parkinson's disease who were referred by a neurologist because they were considered potentially eligible for deep brain stimulation (DBS) underwent an initial consultation at the outpatient clinic. If, following this consultation, the patient was also considered a potential candidate for DBS, they were scheduled for a two-day inpatient screening assessment as part of routine clinical care to further evaluate their potential benefit from DBS.

Approximately two weeks prior to the scheduled admission, patients were contacted by telephone to arrange the admission. During this telephone call, they were asked whether they were interested in participating in medical research. Patients who expressed an interest were subsequently contacted by a physician-researcher, who provided further information about the study and sent the study information materials to the patient.

At the beginning of the screening admission, an in-person informed consent discussion was conducted, during which the study was explained in detail and patients had the opportunity to ask questions. Written informed consent was obtained before any study-specific procedures were performed.

No study data were collected from patients who indicated that they were not interested in participating in scientific research.

All patients who provided informed consent and entered the study underwent a baseline assessment before the multidisciplinary evaluation of DBS eligibility. Baseline assessment included demographic and clinical data. Following this assessment, a multidisciplinary team determined whether the patient was a suitable candidate for DBS. Patients who were not considered suitable for DBS were not randomized and did not continue in the trial. Patients considered suitable for DBS were randomized to one of the two study arms.

In study reports, screening and inclusion will be presented in a CONSORT flow diagram showing the number of patients assessed for participation, the number completing baseline assessment, the number judged unsuitable for DBS by the multidisciplinary team, and the number randomized. Reasons for non-randomization will be reported.

Baseline demographic and clinical characteristics will be summarized descriptively for the randomized population.

5.2. What are the inclusion and exclusion criteria for the study?

To be eligible to participate in this study, a subject must meet all the following criteria:
a. Parkinson's disease diagnosis based on the clinical diagnostic criteria of Movement Disorder Society (MDS);
b. Scheduled for DBS screening (baseline screening Visit 1);
c. Age of 18 years or older;
d. Understand the Dutch language.

A potential subject who meets any of the following criteria will be excluded from participation in this study:
a. Legally incompetent adults;
b. No written informed consent;
c. Previous functional stereotactic neurosurgery;
d. Dementia;
e. Current depression or psychosis.

5.3. Which information will be presented in the flow chart for this study?

The mock-up of the CONSORT flow diagram is presented in the appendix to this statistical analysis plan.

5.4. What is the expected level of, timing of and reasons for withdrawal from the intervention and/or from follow-up and how will this be presented in the study reports?

Withdrawal from the intervention and/or loss to follow-up is expected to be limited in this study, as participants are patients undergoing DBS treatment with regular clinical follow-up.

Switching from the allocated intervention may occur if the assigned DBS programming strategy does not provide sufficient clinical benefit or is not well tolerated. Based on clinical experience, switching from the threshold assessment-based programming arm to the imaging-based programming arm may occur in a proportion of patients, whereas switching from the imaging-based programming arm to the threshold-assessment arm is expected to be rare.

Loss to follow-up is expected to be minimal. Potential reasons for withdrawal from follow-up include withdrawal of consent, medical complications, or inability to attend study visits. Withdrawal may occur at any time during follow-up but is expected to be infrequent before completion of the primary outcome assessment. Loss to follow-up is expected to be unrelated to DBS programming allocation and therefore to be approximately evenly distributed between the two groups.

In study reports, the number and percentage of participants in each study arm who discontinue the allocated intervention, switch between intervention arms, or are lost to follow-up will be presented, together with the reasons and timing of these events. Switching between intervention arms will be reported separately from withdrawal from follow-up. The duration of follow-up and completeness of primary outcome data will also be summarized descriptively per study arm.

5.5. Which baseline characteristics of participants will be presented?

- Age in completed years at randomization
- Age at onset of Parkinson's disease in years
- Sex
- Duration of Parkinson's disease in years at randomization
- Hoehn and Yahr stage
- Levodopa equivalent dose per day in mg

A mock-up of the baseline characteristics table is presented in the appendix to this statistical analysis plan.

5.6. How will the baseline characteristics be summarized?

Categorical baseline characteristics will be summarized by presenting the number and percentage in each category. Continuous, normally distributed variables will be summarized by presenting the mean and standard deviation. Continuous, non-normally distributed variables will be summarized by presenting the median and interquartile range. As this is a randomized clinical trial, we will not statistically test for differences between treatment groups on baseline characteristics.

Section 6. Analysis.

6.1. How are the outcomes of this study defined?

The primary outcome is the between-group difference in motor symptom improvement from baseline OFF-drug phase to 6 months after programming, measured using the MDS-UPDRS III in the OFF-drug phase at baseline and the OFF-drug/ON-stimulation phase at follow-up. The outcome will be expressed as the change in MDS-UPDRS Part III score from baseline to follow-up.

The following secondary outcomes will be assessed at 6 months after initial programming unless otherwise specified:
A. Between-group difference in the total MDS-UDPRS part III score between the MED ON state at baseline and the MED ON/DBS ON state at follow-up;
B. Between-group difference in the number of hours spent in the OFF-drug phase per day, measured using question 4.3.2 of the MDS-UPDRS part IV;
C. Between-group difference in the number of hours of dyskinesia per day, measured using question 4.1.2 of the MDS-UPDRS part IV (score 0-4);
D. Between-group difference in the functional impact of dyskinesias, measured using question 4.4 of the MDS-UPDRS part IV (score 0-4);
E. Between-group difference in the total MDS-UPDRS part I score change between baseline and follow-up;
F. Between-group difference in the total MDS-UPDRS part II score change between baseline and follow-up;
G. Between-group difference in the total Academic Medical Centre Linear Disability Score change between baseline and follow-up;
H. Between-group difference in the total Parkinson's Disease Questionnaire-39 score change between baseline and follow-up;
I. Adverse effects, including the number and proportion of patients experiencing adverse effects (AEs) and serious adverse effects (SAEs), and the frequency of individual AE types;
J. Patient satisfaction with treatment outcome, measured using a study specific 5-point Likert scale and reported as the distribution of patients (n, %) across categories;
K. Patient-reported burden of programming period, measured using a study specific 5-point Likert scale and reported as the distribution of patients (n, %) across categories;
L. Switching to the alternative intervention arm during follow-up, reported as the number and proportion of patients (n, %) per group;
M. Total programming duration, defined as the total time spent on programming during follow-up, measured in minutes;
N. Number of DBS programming-related healthcare contacts, including the number of outpatient visits and telephone consultations during follow-up;
O. Final DBS settings, including the final stimulation amplitude in mA;
P. Proportion of patients at follow-up stimulated at the same contact point(s) as predicted by the randomized programming method, defined as a binary outcome (1=both hemispheres stimulated at the predicted contact point(s); 0=one or both hemispheres differ), reported as the number and proportion of patients (n, %).

Baseline measurements will be performed prior to randomization. Follow-up assessments will be conducted according to the study visit schedule, with the primary endpoint assessed at 6 months after initial programming. Adverse effects and intervention-related data, including programming duration and use of care, will be recorded throughout the follow-up period.

6.2. WILL ANY CALCULATIONS OR TRANSFORMATIONS BE USED TO DERIVE ANY OUTCOME FROM THE ORIGINAL DATA?

Calculations are used to derive the following outcomes:

- Disease duration
- Levodopa Equivalent Dose
- Percentage dyskinesias per day
- Percentage OFF per day
- Improvement on MDS-UPDRS III

The formulas are added in Appendix C.

6.3. WHAT ANALYSIS METHOD WILL BE USED AND HOW WILL THE TREATMENT EFFECTS BE PRESENTED?

The primary outcome will be analysed in the ITT population using an ANCOVA model, with the MDS-UPDRS III score at 6 months as the dependent variable, treatment group as the independent variable, and the baseline MDS-UPDRS III score as the covariate. The treatment effect will be presented as the adjusted mean difference between the Imaging and Threshold groups, together with a one-sided 95% confidence interval. Non-inferiority will be concluded if the lower bound of the one-sided 95% confidence interval is greater than the prespecified non-inferiority margin of -5 points. Missing data for the primary outcome will be handled using multiple imputation, as specified in section 6.7. A per-protocol analysis will be performed as a key supportive analysis. Given the non-inferiority design, non-inferiority will be considered demonstrated only if the non-inferiority criterion is met in both the ITT and PP analyses. To address selection bias in the PP population due to intercurrent events (switching and missing the primary outcome assessment), baseline balance in the PP population will be assessed, evaluated for predicting switching, and adjusted for if required.

The important secondary outcome of DBS programming-related healthcare contacts (outcome N) will be tested for superiority if non-inferiority is demonstrated for the primary outcome. It will be analysed using Poisson regression. If overdispersion is present, negative binomial regression will be used instead. The treatment effect will be presented as an incidence rate ratio comparing the Imaging and the Threshold groups, together with a two-sided 95% confidence interval. Superiority will be tested at a one-sided significance level of 0.05.

The remaining secondary outcomes will be considered exploratory. Continuous secondary outcomes, including MDS-UPDRS I and II, MDS-UPDRS III in the ON-drug phase, ALDS, PDQ-39, hours spent in the OFF-drug phase, hours of dyskinesias, total programming duration and final stimulation amplitude, will be analysed using ANCOVA where baseline measurements are available, or linear regression when appropriate. If the distribution of a continuous outcome is substantially skewed, an appropriate transformation or alternative regression model may be used. Treatment effects will be presented as adjusted mean differences with corresponding two-sided 95% confidence intervals.

Ordinal outcomes, including patient satisfaction, patient-reported burden of programming period, and functional impact of dyskinesias, will be analysed using ordinal logistic regression and presented as odds ratios with corresponding two-sided 95% confidence intervals.

Binary outcomes, including occurrence of at least one AE or SAE and individual AE types, will be summarized as n (%) per treatment group. Where appropriate, between-group treatment effects will be estimated using differences in proportions and/or odds ratios with corresponding two-sided 95% confidence intervals. Switching to the alternative intervention and correct prediction of the stimulated contact point will be reported descriptively as n (%) per treatment group.

6.4. WILL ANY ASSUMPTIONS FOR STATISTICAL METHODS BE CHECKED?
Normality will be assessed by visual inspection of histograms and Q-Q plots.. For continuous outcomes analysed using linear regression, model assumptions will be assessed based on the distribution of the residuals. If assumptions are not adequately met, appropriate transformation of the outcome variable, such as a natural logarithm transformation for right-skewed data, or a non-parametric alternative will be considered.
6.5. WILL SENSITIVITY ANALYSES BE PERFORMED?
A per-protocol analysis will be performed as a sensitivity analysis to assess the robustness of the primary outcome results with respect to protocol adherence. If missing data occur for the primary outcome, sensitivity analyses using best-case, worst-case, and completed-case analyses will be performed to assess the robustness of the results to missing data. The results of these sensitivity analyses will be compared with the primary ITT analysis.
6.6. WILL SUBGROUP ANALYSES BE PERFORMED?
No subgroup analyses will be performed.
6.7. HOW WILL MISSING DATA BE REPORTED IN THE STUDY REPORTS AND HANDLED IN THE STATISTICAL ANALYSIS?
Maximum effort will be made to minimize the quantity of missing data, specifically for the primary outcome and the important secondary outcome of DBS programming-related healthcare contacts. For missing data of the primary outcome, multiple imputation will be used in the primary analysis. For the primary outcome, the imputation model will include treatment allocation and the baseline MDS-UPDRS III score. For the PP analysis, multiple imputation will be performed within the PP set, excluding any influence of post-switching outcomes. For the important secondary outcome of DBS programming-related healthcare contacts, multiple imputation will also be used if outcome data are missing. The imputation model will account for treatment allocation. For other secondary outcomes, participants with missing outcome data will not be included in the respective analysis. Reasons for missing outcome data will be evaluated and the potential impact of missingness on the interpretation of the results will be assessed.
6.8. WILL ADDITIONAL ANALYSES ON THE PRIMARY OR SECONDARY OUTCOMES BE PERFORMED?
No additional analyses will be performed on the primary or secondary outcomes.

6.9. How will harms be reported?
AEs and SAEs will be summarized descriptively by treatment group in the ITT population. Safety data will be presented as the number and proportion of participants experiencing at least one AE or SAE, as well as the frequency of individual AE types, per treatment group. No formal statistical hypothesis testing will be performed for safety outcomes.
6.10. Which statistical software will be used to carry out the statistical analyses?
All statistical analysis will be performed in IBM SPSS Statistics for Windows, Version 31.0 (IBM Corp, Armonk, NY).

Section 7. References.

7.1. WHAT IS THE TITLE, DATE AND VERSION NUMBER OF THE CURRENT DATA MANAGEMENT PLAN?
The current data management plan has the title “Data management plan for the DBS-ITAP trial,” version number 2.0, is dated 29-JAN-2024 and is stored in the trial master file.
7.2. WHAT IS THE TITLE, DATE AND VERSION NUMBER OF THE CURRENT DATA VALIDATION AND DERIVATION PLAN?
The current data validation and derivation plan has the title “Data validation and derivation plan for the DBS-ITAP trial,” version number 1, is dated 28-MAR-2024 and is stored in the trial master file.
7.3. WHERE IS THE STUDY MASTER FILE STORED?
The trial master file is stored at the location G:\divd\neu\movement\DBS-ITAP\TMF-ISF\.
7.4. WHERE ARE THE SYNTAX FILES FOR DATA EXTRACTION, MANIPULATION AND PREPARATION AND STATISTICAL ANALYSIS STORED?
The syntax files for data extraction, manipulation and preparation and statistical analysis are stored at the location G:\divd\neu\movement\DBS-ITAP\TMF-ISF\O. Data management. The research nurse, who performs the assessment of the primary outcome and is blinded to the treatment allocation, do not have access to this folder.
7.5. WHICH STANDARD OPERATING PROCEDURES WILL BE ADHERED TO WHEN USING AND ANALYSING DATA FROM THIS STUDY?
When using and analysing data from the DBS-ITAP randomized clinical trial, researchers will adhere to the Amsterdam UMC standard operating procedure RDM001 Research data management.

7.6. WHICH REPORTING GUIDELINES WILL BE ADHERED TO WHEN REPORTING ON THIS STUDY?

When reporting the results of this randomized clinical trial, the researchers will adhere to the SAMPL (Statistical Analyses and Methods in the Published Literature) and CONSORT (CONsolidated Standards Of Reporting Trials) reporting guidelines. In addition, they will adhere to the CONSORT extension for non-inferiority and equivalence trials.

Section 8. Appendix.

Additional Tables, Figures and Documents.

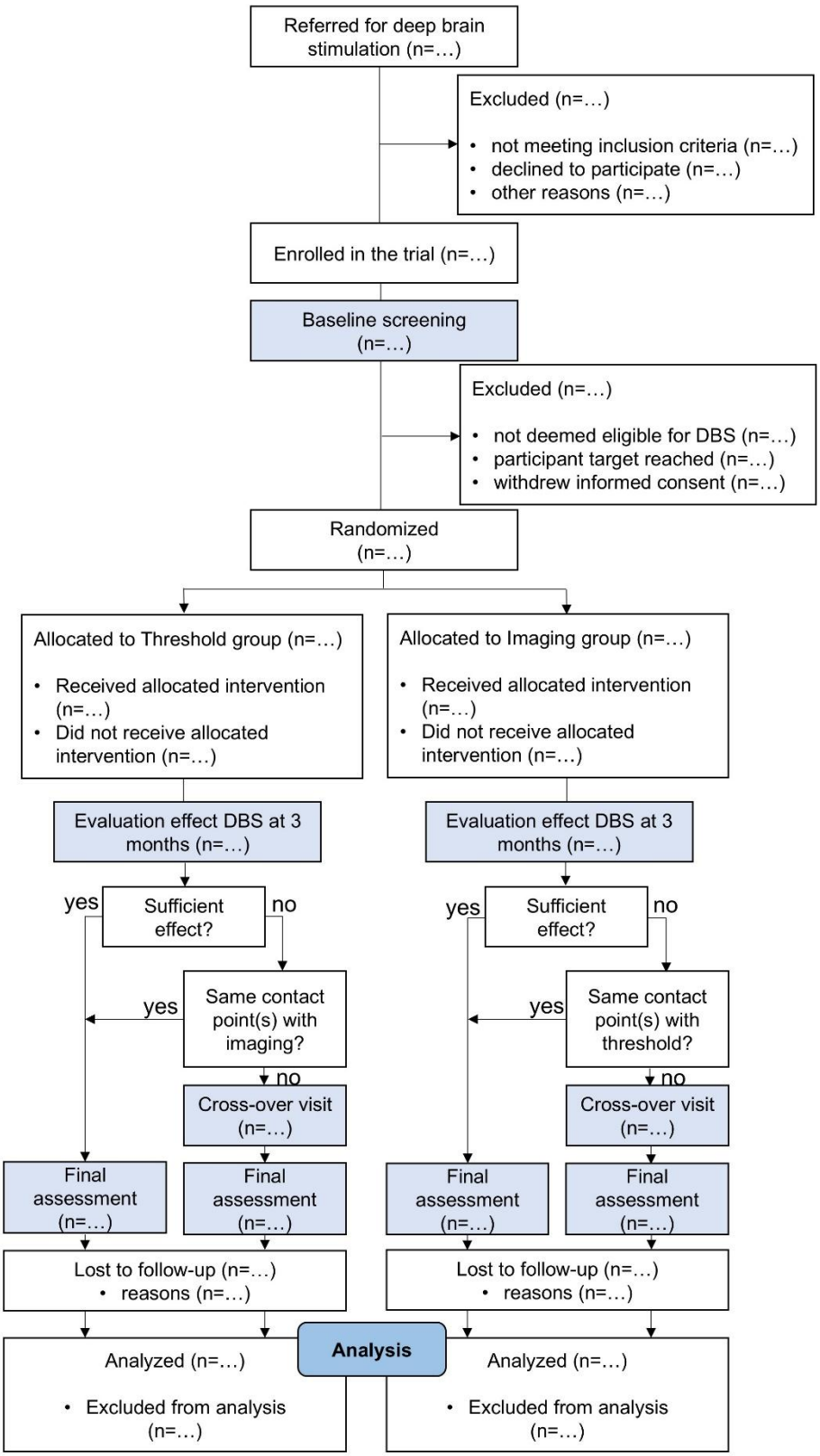


Figure 1. The CONSORT flow chart of patients enrolled in the DBS-ITAP trial

	Imaging-based programming (n=66)	Threshold assessment-based programming (n=66)
Age (years)		
Age at onset of Parkinson's disease (years)		
Men		
Duration of Parkinson's disease (years)		
On-drug phase Hoehn and Yahr stage (median [range])		
Levodopa equivalent dose		

Table 1. The baseline characteristics of patients randomized in the DBS-ITAP trial.

Data are mean (SD), n, or n (%), unless otherwise stated.

Appendix C. Formulas as used in the database.

Disease duration is calculated with the following formula:
{AGE}-{AGE_ONSET}

LED levodopa regular is calculated with the following formula:
'##allowempty##'; '##setemptytozero##'; {PRE_LD_REG_NR_DAY}*1

LED levodopa CR/HBS is calculated with the following formula:
'##allowempty##'; '##setemptytozero##'; {PRE_LD_CR_HBS_NR_DAY}*0.75

LED duodopa is calculated with the following formula:
'##allowempty##'; '##setemptytozero##'; {PRE_DUO_NR_DAY}*1.11

LED subcutane levodopa is calculated with the following formula:
'##allowempty##'; '##setemptytozero##'; {PRE_SUB_LEVO_NR_DAY}*0.75

LED levodopa total is calculated with the following formula:
'##allowempty##'; '##setemptytozero##';
{LED_cr_hbs_levo_pre_DAY}+{LED_reg_levo_pre_DAY}+{LED_duo_pre_DAY}+{LED_sub_levo_pre_DAY}

LED entacapone is calculated with the following formula:
'##allowempty##';
'##setemptytozero##';
var splitted = "{PRE_PARKINS_MED_DAY}".split(';');
if (splitted.indexOf("5") > -1) (
{LED_total_levo_pre_DAY} * 0.33
);

LED pramipexol is calculated with the following formula:
'##allowempty##'; '##setemptytozero##'; {PRE_PRAMIPEXOL_NR_DAY}*100

LED ropinirol is calculated with the following formula:
'##allowempty##'; '##setemptytozero##'; {PRE_ROPINIROL_NR_DAY}*20

LED rotigotine is calculated with the following formula:
'##allowempty##'; '##setemptytozero##'; {PRE_ROTIGOTINE_NR_DAY}*30

LED apomorfine is calculated with the following formula:
'##allowempty##';
'##setemptytozero##';
{PRE_APOMORFINE_NR_DAY}*10

LED amantadine is calculated with the following formula:
'##allowempty##';
'##setemptytozero##';
{PRE_AMANTADINE_NR_DAY}*1

LED selegiline is calculated with the following formula:
'##allowempty##';
'##setemptytozero##';
{PRE_SELEGILINE_NR_DAY}*10

LED rasagiline is calculated with the following formula:
'##allowempty##';
'##setemptytozero##';
{PRE_RASAGILINE_NR_DAY}*100

LED safinamide is calculated with the following formula:

'##allowempty##';
'##setemptytozero##';

if ({PRE_SAFINAMIDE_NR_DAY} > 0) (
  150
);

LED trihexyfenidyl is calculated with the following formula:
'##allowempty##';
'##setemptytozero##';

if ({PRE_TRIHEXY_NR_DAY} > 0) (
  100
);

LEDD is calculated with the following formula:
'##allowempty##';
'##setemptytozero##';
{LED_total_levo_pre_DAY}+{LED_enta_pre_DAY}+{LED_ropi_pre_DAY}+{LED_roti_reg_pre_DAY}
+{LED_prami_pre_DAY}+{LED_sele_pre_DAY}+{LED_rasa_pre_DAY}+{LED_apo_pre_DAY}+
{LED_aman_pre_DAY}+{LED_safi_pre_DAY}+{LED_trihexy_pre_DAY}

Percentage dyskinesias is calculated with the following formula:
({pre_UPDRS_4_1B}/{pre_UPDRS_4_1A})*100

Percentage OFF is calculated with the following formula:
({pre_UPDRS_4_3B}/{pre_UPDRS_4_1A})*100

Improvement MDS-UPDRS III OFF vs ONOFF is calculated with the following formula:
{TOT_UPDRS3_OFF}-{VIS5_TOT_UPDRS3_ONOFF}