Trials

STUDY PROTOCOL

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Imaging-based versus threshold assessment-based deep brain stimulation programming in Parkinson's disease: study protocol for a randomized controlled trial {1a}

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Abstract

Background Deep brain stimulation (DBS) of the subthalamic nucleus (STN) effectively treats motor fluctuations in Parkinson's disease. The clinical outcome depends on optimal programming, which involves selecting active contacts and adjusting stimulation parameters to maximize clinical benefit while minimizing adverse effects. The conventional clinically guided approach, the monopolar review (MPR), is complex and time-consuming due to numerous parameter combinations, interindividual anatomical variability, and differences in DBS lead placement. Recent advances in neuroimaging offer the potential to guide contact selection based on patient-specific anatomy.

Methods A single-centre, prospective, randomized, open-label trial with blinded endpoint assessment (PROBE design) is being conducted in patients with Parkinson's disease undergoing STN-DBS to determine whether imaging-based contact selection is non-inferior to the current standard MPR for contact selection in treating motor symptoms. A total of 132 patients are randomized to either imaging-based programming (Imaging group) or threshold-assessment-based programming (i.e., MPR, Threshold group). In the Imaging group, contacts are selected using patient-specific 3D anatomical models derived from preoperative 7 T MRI and postoperative CT, visualizing the STN and simulating volumes of tissue activated (VTA) aligned with the motor subdivision. The primary outcome is the mean change from baseline to 6 months in the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III score during the off-drug phase. Secondary outcomes include motor symptoms in the on-medication phase, duration of off-medication time, dyskinesia severity and duration, non-motor symptoms, motor aspects of daily living, physical disability, disease-specific quality of life, (severe) adverse effects, treatment satisfaction and burden, crossover to the alternate programming arm, use of care, programming duration, final DBS settings, and concordance between 6-months stimulation contacts and initial selections. Follow-up is 6 months after initial programming.

Discussion The trial evaluates whether imaging-based DBS programming can achieve motor improvements comparable to clinical threshold-assessment-based programming, while potentially offering greater efficiency,

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speed, and stability of stimulation settings. Although the study is designed as a non-inferiority trial, we hypothesize that imaging-based contact selection may ultimately provide a superior approach by enabling faster optimization with fewer parameter adjustments.

Trial registration The DBS-ITAP trial was registered at clinicaltrials.gov (NCT06223399) on January 23, 2024, https://clinicaltrials.gov/study/NCT06223399.

Keywords Parkinson's disease, Deep brain stimulation, Programming, Imaging, Randomized controlled trial

Introduction

Background and rationale {9a}

Parkinson's disease is characterized by cardinal motor symptoms, including bradykinesia, rigidity, and tremor, which result from degeneration of the substantia nigra and consequent dopamine deficiency. During the first 5 years, symptoms are generally well controlled with dopamine replacement therapy, such as levodopa and dopamine agonists [1]. As the disease progresses, most patients develop motor fluctuations, with alternating periods of mobility—often accompanied by dyskinesia—and immobility. Although pharmacological adjustments can initially mitigate these fluctuations, they often become refractory over time. In such cases, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has proven highly effective [2, 3]. DBS involves implanting electrode leads in the brain, connected to a subclavicular pulse generator. High-frequency electrical currents delivered through the electrode contacts modulate abnormal neuronal activity, improving motor fluctuations, reducing disability, and enhancing quality of life [4]. DBS electrodes typically feature four to 16 contacts arranged across four contact levels, each capable of delivering electrical current.

Approximately 4 weeks after electrode implantation [5], DBS is activated and programming of the system begins. The first step is to determine the optimal contact level—or combination of contact levels—using a threshold assessment, also known as a monopolar review (MPR). During the MPR, the current required to achieve symptom improvement and the current inducing adverse effects are evaluated for each contact level. Stimulation is typically increased in 0.5 mA increments, with Parkinson's symptoms and adverse effects assessed at each step. This procedure is performed while patients are off-medication (off-drug phase). The results guide the selection of active contact levels and stimulation amplitude, which are then fine-tuned alongside pharmacological adjustments over the following months. For patients with bilateral DBS and four contact levels per electrode, the MPR can take approximately 3 h. The procedure is lengthy, burdensome, and prone to bias due to patient fatigue and the large number of assessments. Time constraints often prevent thorough testing of all contacts, including steering contacts, leaving some patients with suboptimal settings [6]. Further fine-tuning over subsequent months remains time-consuming and inefficient, imposing a sustained burden on both patients and healthcare providers.

As an alternative to the MPR, imaging-based programming (IBP) can be used to determine the optimal contact level—or combination of contact levels. In IBP, high-resolution anatomical imaging, specifically T2-weighted MRI, is combined with patient-specific connectivity information obtained through probabilistic tractography. These data are integrated into dedicated DBS programming software to simulate the volume of tissue activated (VTA), defined as the region enclosed within an iso-surface of the activation function [7–15] (Fig. 1).

This approach enables a more targeted and informed programming strategy by visualizing the spatial relationship between the VTA and surrounding anatomical structures. Postoperative CT scans are used to localize the electrode leads, which are then co-registered with preoperative MRI to precisely map the electrodes within the patient's individual anatomy. Based on this mapping, stimulation settings can be selected that maximize VTA coverage of the intended target while minimizing spread to adjacent structures. These MRI-guided settings provide a starting point for subsequent DBS programming.

Explanation for the choice of comparator {9b}

The monopolar review approach was selected as the comparator because it represents the standard method for DBS programming, routinely used in our centre and widely recognized as the standard of care internationally.

Objectives {10}

The aim of this trial is to determine whether the effectiveness of STN-DBS for treating Parkinson's motor symptoms using IBP is non-inferior to the current standard MPR for contact selection. Although the study is designed as a non-inferiority trial, our broader clinical objective is to demonstrate that IBP provides meaningful advantages in efficiency, speed, and consistency, ultimately enhancing patient care. If successful, this approach could reduce the reliance on the burdensome MPR and establish a new standard that can be widely adopted across DBS centres.

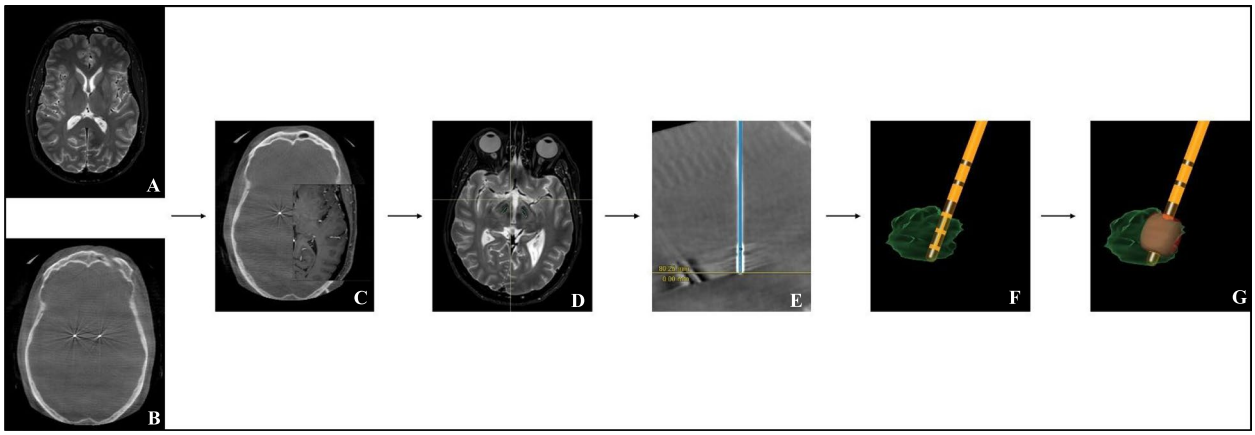


Fig. 1 Workflow for DBS lead localization and stimulation modelling (IBP). **A** Preoperative MRIB. **B** Postoperative CT. **C** Merging of MRI and CT. **D** Anatomical structures visualization. **E** Localization of DBS lead. **F** Patient-specific model showing DBS lead within the STN. **G** Simulation of the VTA within the STN

Methods: patient and public involvement, and trial design

Patient and public involvement {11}

Patients or the public were not involved in the design or conduct of this trial, as the study procedures only minimally differ from standard care in our centre.

Trial design {12}

The study is a non-inferiority, prospective, randomized, open-label, blinded endpoint (PROBE) clinical trial. We evaluate the effectiveness of STN-DBS in the treatment of Parkinson's disease using IBP, compared with the current standard practice approach, MPR. Figure 2 shows the CONSORT flowchart.

Methods: participants, interventions and outcomes

Trial setting {13}

The study will take place in the Amsterdam University Medical Centre, Amsterdam, the Netherlands.

Eligibility criteria for participants {14a}

Participants are recruited from the Amsterdam University Medical Centre, Amsterdam, the Netherlands. The study targets patients with Parkinson's disease who experience severe motor fluctuations, dyskinesias, (painful) dystonia, or bradykinesia that are refractory to medication. To be eligible for participation, patients must meet all of the following inclusion criteria: (a) a diagnosis of Parkinson's disease according to the Movement Disorder Society (MDS) clinical diagnostic criteria; (b) scheduled for DBS screening; (c) aged 18 years or older; and (d) sufficient proficiency in the Dutch language. Exclusion criteria are as follows: (a) legal incompetence; (b) absence of written informed consent; (c) prior functional stereotactic neurosurgery; (d) presence of dementia; or (e) current depression or psychosis.

Eligibility criteria for sites and those delivering interventions {14b}

Not applicable, no additional eligibility criteria apply as investigators are already trained in DBS-programming.

Who will take informed consent? {32a}

Potential participants are referred to our centre for DBS by their treating neurologist. Each patient undergoes an initial outpatient assessment to determine suitability for DBS. If considered a potential candidate, the patient is informed about the study and provided with at least 2 weeks to review the study information and address any remaining questions before signing the informed consent form. The informed consent is obtained by a physician-researcher or research nurse.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

Not applicable, no biological specimens are collected as part of the study.

Intervention and comparator

Intervention and comparator description {15a}

DBS system programming begins approximately 4 weeks after surgery. Initially, relatively low stimulation amplitudes are used, because participants are still taking substantial doses of antiparkinsonian medication, which in combination with DBS may cause adverse effects such as dyskinesias. Over the following months, participants are seen regularly to adjust both DBS settings and medication

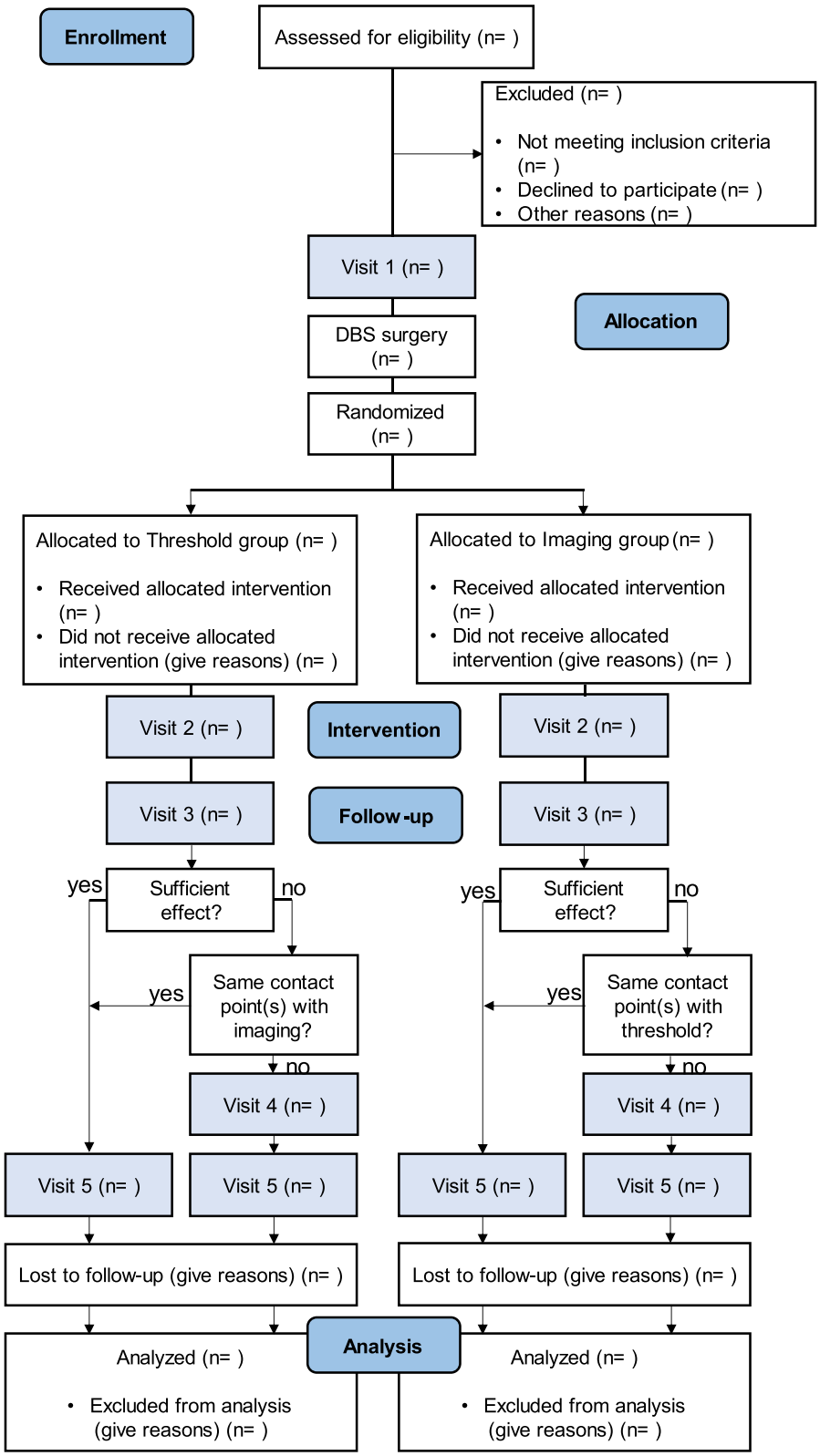


Fig. 2 CONSORT flowchart of the study. Visit 2 is ±4 weeks after DBS surgery. Visit 3 is ±3 months after Visit 2. Visit 5 is ±6 months after Visit 2

as needed. Optimal DBS settings are typically achieved within 6 months after the initiation of programming.

Monopolar review-based selection of contact levels

Participants randomized to the Threshold group are admitted to the hospital for one day, arriving in their off-medication phase. A specialized nurse conducts a full MPR, which involves determining the electrical current required at each DBS contact level to achieve symptom improvement while identifying the onset of adverse effects. The current is increased in 0.5 mA increments, starting from 0 up to a maximum of 5.0 mA. At each step, Parkinson's symptom severity and potential adverse effects are evaluated. The contacts that provide the best trade-off between clinical benefit and minimal adverse effects are selected for stimulation on each lead. Frequency and pulse width are initially set to default values of 125–130 Hz and 60 μs, respectively. The initial stimulation amplitude, typically around 0.5 mA, is determined by the specialized nurse based on the patient's clinical response and the planned gradual reduction of Parkinson medication over subsequent months. Following programming, participants are monitored during the on-medication phase to ensure they do not experience disabling dyskinesias. Adjustments to the contact levels are made if clinically indicated.

Imaging-based selection of contact levels

For participants in the Imaging group, the preoperative MRI is co-registered with the postoperative CT scan using Brainlab software (Brainlab AG, Munich, Germany) and the GUIDE XT™ module (GUIDE™, Boston Scientific, Valencia, US). Based on these co-registered images and the patient-specific anatomy, the VTA is simulated using the software. The VTA is then aligned with the motor subdivision of the STN, enabling identification of the optimal stimulation area for each electrode lead. While MPR typically results in the selection of a single active contact, IBP often leads to the activation of multiple contact levels, each with specific percentages (e.g., ventromedial 70%, dorsomedial 30%) to maximize VTA overlap with the motor region of the STN. Achieving this level of precision is challenging with conventional MPR-based programming due to time constraints and procedural complexity.

The primary target is the dorsolateral STN, which is well-established for its motor outcome effects [16]. Since March 2022, all eligible Parkinson's disease patients undergoing DBS at our centre are automatically enrolled in a prospective 7 Tesla (7 T) MRI study (clinicaltrials.gov, number: NCT05843084). As part of the study protocol, surgical procedures utilize 7 T MRI guidance instead of standard 3 T imaging. Consequently, most participants have access to 7 T imaging, with exceptions made only when 7 T is not feasible (e.g., due to implants). This has resulted in IBP being predominantly based on higher resolution 7 T scans. The combination of high-resolution T2-weighted imaging and diffusion-weighted imaging (DWI) allows probabilistic tractography to visualize the connectivity-based motor subdivision of the dorsolateral STN.

This method is routinely used to guide electrode placement intraoperatively and, in this study, is also applied to guide postoperative programming. By mapping structural connections between the STN and specific cortical motor areas, 7 T-based tractography may enhance anatomical precision in stimulation targeting and improve alignment between lead placement and optimal contact selection during IBP. The fusion process, as well as the selection of contact levels and stimulation parameters, is performed by a research team member experienced in Brainlab and GUIDE XTTM. The proposed contact level(s) are then reviewed by the nurse specialist responsible for programming. Like MPR, participants are admitted for a one-day hospital stay off medication. The nurse specialist tests the proposed contact levels to determine the current that may induce adverse effects. Initial current levels start lower (approximately 1 mA) than the optimal value suggested by imaging, taking into account the gradual reduction of Parkinson medication over the following months. The applied current is adjusted by the specialized nurse based on the clinical response. Frequency and pulse width are initially set to default values of 125–130 Hz and 60 μs, respectively, and participants are monitored in the on-drug phase for disabling dyskinesias.

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

Participants who demonstrate insufficient clinical benefit from their assigned intervention during the follow-up period will undergo a clinical reassessment. If deemed appropriate by the treating investigator, the allocated intervention may be modified, and the participant may cross over to the alternative intervention arm. The reason for crossover will be documented.

Strategies to improve adherence to intervention/comparator {15c}

Because the study visits align with routine clinical assessments for DBS treatment at our centre, participant burden is minimized, and a high level of adherence is expected.

Concomitant care permitted or prohibited during the trial {15d}

The investigated interventions concern DBS programming. Both allocation arms will receive standard clinical care, with no study-specific restrictions.

Ancillary and post-trial care {34}

After the follow-up period, participants will resume standard clinical care, including DBS treatment, under the care of their treating healthcare provider. Insurance coverage is provided to compensate for any harm directly resulting from study participation, in line with institutional and regulatory requirements.

Outcomes {16}

Primary outcome measures

The primary outcome is the change in Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III score [17] from baseline off-medication to 6 months after initial DBS programming in off-medication/on-DBS state, compared between the Imaging and Threshold groups.

Secondary outcome measures

Secondary outcomes include:

a. Motor symptoms during the on-medication state, measured with MDS-UPDRS III;
b. Motor complications, measured with MDS-UPDRS Part IV;
c. Severity of non-motor symptoms, measured with MDS-UPDRS Part I;
d. Motor experiences in daily living, measured with MDS-UPDRS part II;
e. Functional health status, measured with the Academic Medical Centre Linear Disability Score (ALDS) [18];
f. Disease specific quality of life, measured with the Parkinson's Disease Questionnaire 39 (PDQ-39) [19];
g. Occurrence of (serious) adverse effects during the follow-up period;
h. Patient satisfaction with treatment outcome;
i. Patient-reported treatment burden;
j. Proportion of patients requiring a switch between intervention arms during follow-up;
k. Healthcare utilization, including hospital visits and phone consultations;
l. Total time spent on DBS programming;
m. Final DBS settings;
n. Proportion of patients at 6 months receiving stimulation at the same contact levels as initially suggested.

See Table 1 for further specification and the rating scales used.

Harms {17}

No additional harms are anticipated, as the DBS procedure and clinical trajectory correspond to standard care; imaging-guided programming in the intervention group is not expected to introduce additional risks. Adverse events (AEs) and serious adverse events (SAEs) will be systematically collected and documented in the eCRF at each study visit or when they become known. AEs are defined as any undesirable medical occurrence during the study, irrespective of causality. SAEs are defined per standard criteria (death, life-threatening events, hospitalization, significant disability, or other medically important conditions) and will be reported to the sponsor without undue delay, and by the sponsor to the accredited METC via ToetsingOnline in accordance with CCMO timelines. All participant-reported or investigator-observed AEs will be recorded. Hospital admissions unrelated to an AE (e.g., elective procedures or protocol-specified admissions) will not be reported as SAEs. Standardized terminology will be used to ensure consistent classification and reporting.

Table 1 Clinical rating scales

Clinical rating scale	Performed by	Domain	Best Score	Worst Score
MDS-UPDRS part I	Investigator/Participant	Non-motor aspects of experiences of daily living	0	52
MDS-UPDRS part II	Participant	Motor aspects of experiences of daily living	0	52
MDS-UPDRS part III	Investigator	Motor examination	0	132
MDS-UPDRS part IV	Investigator	Motor complications	0	36
ALDS	Investigator	Disability	100	0
PDQ-39	Participant	Quality of life	0	100
Likert Scale	Investigator	Patient satisfaction and patient burden	0	5

	TRIAL PERIOD				
	Enrolment		Post-randomization		Close-out
TIMEPOINT[b]	**$-t_i$ to 0**	**0**	**4 weeks±1 week[a]**	**3 months±2 weeks[b]**	**6 months±1 month[b]**
ENROLLMENT:					
Eligibility screen	X				
Informed consent	X				
Randomization		X			
INTERVENTION:					
Imaging-based programming		X			
Monopolar review		X			
ASSESSMENTS:					
Demographic characteristics		X			
ECG, MRI brain, CT brain, blood analysis		X			
Parkinson medication		X	X	X	X
MDS-UPDRS part I in ON-phase		X			X
MDS-UPDRS part II in ON-phase		X			X
MDS-UPDRS III in OFF- and ON-phase		X			X[c]
MDS-UPDRS part IV in ON-phase		X			X
Hoehn and Yahr stage in ON-phase		X			X
ALDS in OFF- and ON-phase		X			X
Treatment burden				X	
Treatment satisfaction				X	
Adverse effects/complications		X	X	X	X
Duration of programming sessions			X		X
Number of hospital visits					X

Fig. 3 Participant timeline: schedule of enrolment, interventions, and assessments according to SPIRIT [20]. [a]Time period from 0. [b]Time period from 4 weeks follow-up (programming visit). [c]MDS-UPDRS III in four conditions: condition 1— medication OFF/stimulation ON; condition 2 — medication OFF/stimulation OFF; condition 3 — medication ON/stimulation OFF; condition 4 — medication ON/stimulation ON

Participant timeline {18}

For an overview of the study procedures, see Fig. 2 and for the participant timeline see Fig. 3. The study includes five assessment visits: an eligibility visit at the outpatient clinic; a baseline screening during hospitalization (Visit 1); a follow-up visit 2 to 4 weeks post-surgery during a day admission (Visit 2); a post-surgery check via phone 3 months after initial programming (Visit 3); and a 6-months post-programming assessment of study endpoints during a day admission (Visit 5). For patients who experience insufficient benefit from their assigned intervention arm, an additional MDS-UPDRS III assessment is conducted in the standardized off- and on-medication phases (Visit 4) before reprogramming the DBS according to the alternative method.

Sample size {19}

The sample size for this study is based on the change in motor function measured using MDS-UPDRS III from baseline in the standardized off-medication phase to 6 months after the initial DBS programming in the standardized off-medication/on-DBS phase. A five-point difference on MDS-UPDRS III is set as the non-inferiority margin (Δ), because this corresponds to the minimum clinically important difference (MCID) for the MDS-UPDRS III [21]. Based on standard deviations reported in similar patient populations from previous DBS studies, which range from 7 to 16 [2, 22–29], we estimate a standard deviation of approximately 11 points for the change scores in our study. A sample size of 120 participants (60 per group) provides 80% power to detect non-inferiority if the treatments are truly equivalent. Non-inferiority will be concluded if the one-sided 95% confidence interval around the estimated difference in change between groups excludes a difference of five or more points in favour of the Threshold group. Accounting for an expected attrition rate of approximately 10%, 66 patients will need to be randomized per treatment arm, resulting in a total of 132 participants.

Recruitment {20}

Approximately 100 patients with Parkinson's disease undergo DBS treatment at our centre each year. As the study procedures coincide with routine clinical assessments and impose minimal additional burden, we anticipate timely and efficient recruitment to achieve the target sample size.

Assignment of interventions: randomisation

Sequence generation: who will generate the sequence {21a}

Participant randomization is performed by the physician-researcher using a web-based system (Castor EDC, Amsterdam, the Netherlands). This online randomization procedure ensures concealed allocation.

Sequence generation: type of randomisation {21b}

Participants are assigned in a 1:1 ratio to either the Imaging group or the Threshold group, without stratification.

Allocation concealment mechanism {22}

Allocation concealment is ensured through the secure web-based randomization system (Castor EDC, Amsterdam, the Netherlands). The system automatically generates and reveals the allocation only after participant enrolment. Access to the randomization system is restricted to authorized study personnel, maintaining concealment until assignment.

Implementation {23}

The randomization sequence is generated automatically by the Castor EDC system. Participants will be enrolled by the study investigators. A designated study team member will perform the randomization using the system and communicate the allocation outcome to the team member responsible for DBS programming.

Assignment of interventions: blinding

Who will be blinded {24a}

Blinding of participants to treatment allocation is not feasible. However, outcome assessments are conducted by a study team member who is blinded to treatment allocation and has no other clinical or trial-related contact with participants.

How will be blinding be achieved {24b}

Blinding will be achieved by ensuring that the outcome assessor has no access to DBS programming parameters and therefore cannot infer group allocation. Participants will be instructed not to disclose any information regarding their DBS settings or programming procedures to the blinded assessor. The clinical procedures and patient interactions are otherwise similar between groups to maintain blinding.

Procedure for unblinding if needed {24c}

Any instances of unintentional unblinding are recorded.

Data collection and management

Plans for assessment and collection of outcomes {25a}

Data will be collected on paper case report forms (CRFs) and subsequently entered into the electronic data capture system (Castor EDC, Amsterdam, the Netherlands). Castor EDC is a GCP (Good Clinical Practice)-compliant data management system with an integrated audit trail to ensure traceability and data integrity. All data

management procedures will be conducted according to harmonized standard operating procedures (SOPs). Source data verification will be performed by the study monitor during on-site monitoring visits to ensure accuracy and completeness. Outcome assessments and baseline data collection will follow standardized procedures consistent with clinical practice at our centre. Study personnel involved in data collection will be appropriately trained to ensure consistency and reliability of measurements.

Plans to promote participant retention and complete follow-up {25b}

As the study visits coincide with routine DBS care appointments, a high level of participant retention is anticipated. If a participant misses a scheduled visit, study personnel will contact the participant to determine the reason for absence and, if possible, reschedule the visit at the earliest convenience. Data collected up to the point of withdrawal or discontinuation will be retained and included in the analyses, in accordance with the participant's consent and applicable data protection regulations.

Data management {26}

Data management will be conducted in accordance with a predefined Data Management Plan. Study data will be collected on paper case report forms (CRFs) and subsequently entered into the electronic data capture system (Castor EDC, Amsterdam, the Netherlands). Castor EDC is a GCP-compliant system that includes built-in validation checks for completeness, correctness, and consistency, as well as a comprehensive audit trail. Each participant will be assigned a unique, meaningless Subject ID. The subject identification log, which links identifiers to Subject IDs, will be stored separately from study data in a secure location. Access to the electronic data capture system is protected through individual login credentials and role-based permissions, with all user activity logged automatically. The database design and data dictionary were developed prior to implementation, and all validation and derivation rules are documented. Both automated and manual data quality checks are performed, including on-site data monitoring. Any data changes are traceable through the system's audit trail and must include a reason for the modification (e.g., using the "Confirm changes" function in Castor). Study personnel involved in data entry and management are trained in the use of the data collection system, and training is documented. Access to study data and the delegation of study-related responsibilities are managed and documented by the Principal Investigator. Source documentation is available for all study-specific data collections.

Confidentiality {33}

Participant confidentiality will be maintained throughout the study in accordance with Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and applicable data protection regulations. Personal identifiers will be stored separately from study data in a secure location accessible only to authorized study personnel. Each participant will be assigned a unique Subject ID, and all study data will be pseudonymized in the electronic data capture system (Castor EDC, Amsterdam, the Netherlands). Only the Principal Investigator and designated staff will have access to the subject identification log linking personal identifiers to study codes. Any transfer or reporting of data will use pseudonymized information only. Following study completion, data will be archived and retained for 15 years according to institutional and regulatory requirements.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

The primary statistical analysis follows the intention-to-treat principle. The additional effect of patients receiving the other intervention (crossovers), when the allocated arm gives insufficient results, is calculated in a secondary per-protocol analysis. Baseline characteristics are summarized using descriptive statistics. All analyses report statistical uncertainties as 95% confidence intervals, and p-values below 0.05 are considered significant. The primary outcome is the difference between the Imaging and Threshold groups in the change from baseline in the off-medication state to 6 months after initial DBS programming in the off-medication/on-DBS phase on the MDS-UPDRS III score. This difference is primarily assessed using the mean difference in change with a (one-sided) 95% confidence interval, adjusted for baseline MDS UPDRS-III score. Since the non-inferiority margin is set at a 5-point change, non-inferiority is concluded when the (one-sided) 95% confidence interval for the mean group difference (Imaging group minus Threshold group) excludes a difference of five points or more in disadvantage of the Imaging group, indicating that the Imaging group is not unacceptably worse than the Threshold group in clinical effect. For secondary outcomes, appropriate parametric or nonparametric statistical tests are applied to compare the Imaging and Threshold groups. If baseline differences between the Imaging group and the Threshold group are observed, multivariate regression analysis is performed to adjust for potential confounding effects.

Who will be included in each analysis {27b}

All randomized participants will be included in the primary intention-to-treat analysis according to their allocated group. The per-protocol analysis will include only those participants who completed the intervention as assigned without major protocol deviations or crossovers.

How missing data will be handled in the analysis {27c}

Maximum effort will be made to minimize the quantity of missing data, specifically for the primary outcome and the main secondary outcome parameters. For the analysis of the primary outcome, cases for whom this parameter is missing will not be included in the analysis. Regarding the secondary outcomes, missing cases will not be included in the analysis. Reasons for missing the primary or secondary outcome parameters will be evaluated and it will be discussed to what extent the missingness may influence the (interpretation of the) results.

Methods for additional analyses (e.g. subgroup analyses) {27d}

No subgroup or adjusted analyses are planned. The primary and secondary outcomes will be analysed as specified in the main statistical analysis plan.

Interim analyses {28b}

No interim analyses are planned. The trial will proceed until completion as outlined in the study protocol, and no formal stopping guidelines have been defined.

Protocol and statistical analysis plan {5}

Upon publication, the de-identified participant-level data may be made available to researchers for secondary analyses, upon reasonable request and subject to data protection regulations and approval by the Principal Investigator. The full study protocol will be made available as a supplementary document with the primary publication. Statistical code used for the analyses may be shared upon reasonable request, following review to ensure compliance with institutional and data privacy policies.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {3d}

This single-centre study is conducted at Amsterdam UMC. The trial is coordinated and managed locally by the study team, which includes the Principal Investigator, co-investigators, and designated study personnel. The study team is responsible for the day-to-day conduct of the trial, including participant recruitment, data collection, and safety monitoring. Regular meetings are held among study personnel to review study progress, discuss any operational or safety issues, and ensure adherence to the study protocol and GCP guidelines. Given the monocentric design, a separate Trial Steering Committee has not been established.

Composition of the data monitoring committee, its role and reporting structure {28a}

Given the monocentric design and the minimal risk associated with the study interventions, no independent Data Monitoring Committee (DMC) has been established. Ongoing monitoring of study conduct, participant safety, and data integrity will be performed by the study investigators in accordance with GCP and institutional procedures. Any safety concerns or protocol deviations will be reviewed and addressed by the Principal Investigator and study team.

Frequency and plans for auditing trial conduct {29}

Monitoring of this study will be performed in accordance with the Amsterdam UMC monitoring policy for investigator-initiated studies classified as negligible risk, as outlined in the study-specific monitoring plan. The Clinical Monitoring Centre (CMC) of Amsterdam UMC will conduct the monitoring activities.

The Clinical Research Associates (CRAs) from the CMC are independent of the study team and sponsor and are qualified and trained in GCP and the Human Research Act (WMO). The primary objectives of monitoring are to verify that the rights and well-being of participants are protected, that study data are accurate and verifiable, and that the trial is conducted in compliance with the approved protocol and regulatory requirements. For this study, minimal intensive monitoring will be performed. One on-site monitoring visit will take place after approximately 10% of participants have been enrolled, and a second visit will occur after at least two participants have completed the 6-month follow-up. A remote close-out will be performed after the final participant's last visit. Additional visits may be scheduled if high-priority issues or safety concerns arise. Monitoring findings and required corrective actions will be documented in written monitoring reports and communicated to the Principal Investigator. The study team is responsible for timely follow-up and resolution of any issues identified during monitoring. No separate independent audit of trial conduct is planned, as the study is considered negligible risk and subject to routine institutional quality assurance oversight.

Protocol amendments {31}

Any substantial amendments to the study protocol, including changes to eligibility criteria, outcomes, or

analysis plans, will be submitted to the accredited METC for review and approval prior to implementation.

Participants who have already been enrolled will have to sign an updated informed consent form. All protocol deviations and breaches will be documented and tracked using standardized breach reporting forms in accordance with GCP and institutional policies, to ensure transparency and data integrity.

Dissemination policy {8}

The results of this study will be disseminated through publication in peer-reviewed scientific journals and presentation at relevant national and international conferences. Trial results will also be reported in the publicly accessible trial registry in accordance with regulatory requirements. Participants who wish to be informed of the study outcomes will receive a lay summary of the main results after study completion. There are no publication restrictions. Authorship will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE). The investigators and sponsor are committed to transparent and unbiased reporting of all study findings, regardless of the direction or magnitude of the results.

Discussion

DBS programming using the MPR is a complex and time-consuming process that requires extensive expertise and training. It is also prone to potential bias due to the high number of assessments and resulting patient fatigue. In contemporary clinical practice, time constraints often limit comprehensive testing of DBS systems, which can result in some patients being maintained on suboptimal settings, despite advancements in current-steering technologies [6]. Given these challenges, along with the increasing complexity of DBS programming driven by rapid technological advances, there is a growing need for alternative programming approaches, such as IBP.

Using high-resolution preoperative MRI (7 T T2-weighted imaging) and postoperative CT, a patient-specific 3D anatomical model can be created. This model provides detailed visualization of the STN, into which the electrode is projected, and allows overlay of a simulated VTA. In most cases in this study, T2 imaging is complemented with probabilistic tractography based on DWI to identify the connectivity-derived motor subdivision of the STN. This well-defined anatomical target serves as the foundation for both electrode placement and stimulation programming. Consequently, DBS programming can rely more on neuroanatomical data, reducing the need for extensive trial-and-error approaches to optimize stimulation outcomes.

Switching the programming strategy from MPR to IBP could enhance the effectiveness of DBS treatment by: (a) selecting stimulation contact levels more quickly, thereby reducing programming time and associated effort of physicians [30, 31]; (b) minimizing the duration during which patients experience unnecessary adverse effects from inappropriate contact selection [30]; (c) enabling faster adjustment of stimulation parameters alongside the postoperative reduction of Parkinson medication, while maintaining comparable symptom relief [30], adverse-effect rates, and power consumption [31]; and (d) simplifying the programming process, reducing the need for extensive training [31]. Moreover, the greatest clinical benefit of IBP is anticipated for patients whose symptoms are not adequately controlled through conventional programming. These patients often require multiple reprogramming sessions, with frequent changes in settings, which can make optimization difficult and lead to patient dissatisfaction. IBP could address this by providing a clear, structured starting point based on neuroanatomical rationale.

Seven cross-over trials [6, 31–36] suggest that IBP of STN DBS for Parkinson's disease is technically feasible, safe, user-friendly in clinical practice, and provides good patient satisfaction and symptom control, while also significantly reducing programming time. However, no studies to date have compared IBP with MPR over a longer follow-up period—a key consideration, as stimulation parameters are often optimized over up to 6 months post-initial programming in clinical practice. Therefore, a randomized controlled trial comparing IBP with standard clinical programming using MPR is needed to evaluate effectiveness in motor symptom control, adverse effects, programming duration, and quality of life. This study design is more representative of real-world clinical practice than previous research.

Several aspects of the study design warrant discussion. First, it is not feasible to blind the DBS programmer or the participant to treatment assignment. Therefore, the study uses a PROBE design to maintain blinding wherever possible. The assessor of the primary endpoint is blinded, and participants are instructed not to disclose their assigned treatment to the trial nurse conducting the postoperative assessments, ensuring a blinded evaluation of the primary outcome.

Because this study is conducted at a single specialized centre, the findings may not be fully generalizable to other centres, which may differ in expertise or procedural practices. Implementing IBP in broader clinical settings could present practical challenges, such as the need for specialized equipment or training. Nevertheless, this study has the potential to serve as a proof of principle, demonstrating that IBP can effectively identify

the optimal contact level, potentially reducing the time required for initial programming. Although conducted at a centre with access to 7 T MRI, the approach primarily relies on T2-weighted STN visualization, which is achievable with the widely available 3 T MRI. While lower-resolution imaging may make precise STN subdivisions harder to resolve, the anatomical insights from 7 T MRI can still guide contact level selection. The results of this study could help establish methods to make IBP more broadly accessible, even in centres with limited resources.

Furthermore, decision-making in IBP relies on the VTA and its overlap with the STN. However, the precise stimulation targets and regions to avoid are not fully defined. Several factors, such as nerve fibre diameters and the density of surrounding structures, may influence the shape of the VTA, but their exact impact remains unclear. This uncertainty arises because it is not fully known how these variables are incorporated when creating the VTA using the GUIDE XT software. Consequently, selecting stimulation parameters in IBP often depends on the programmer's judgment and interpretation of how the VTA interacts with a patient's unique anatomy [35]. For this trial, a consensus was reached among several research team members experienced with the software to determine imaging-based stimulation parameters, ensuring that the selection process does not solely rely on an individual programmer's interpretation. Our approach aims to construct a VTA that maximally overlaps with the motor subdivision of the STN. Although the exact shape and functional borders of the VTA remain uncertain, we assume that the core of the VTA, closest to the electrode, produces the strongest therapeutic effect. Partial VTA spread outside the STN is therefore acceptable, particularly if it allows full coverage of the motor subdivision.

Importantly, IBP does not currently account for nearby anatomical structures when predicting potential adverse effects. Stimulation is targeted solely at the motor STN, while adverse effects, such as speech or balance disturbances, are monitored during amplitude titration. Nevertheless, by visualizing the STN and its proximity to adjacent tracts, clinicians can better anticipate and discuss potential effects with patients. For example, a narrow STN located near speech fibres can alert both clinician and patient to the possibility of temporary adverse effects, enabling more informed and reassuring communication.

Another limitation of this study is that our available CT scans do not allow determination of lead orientation, making it impossible to program individual directional contact points (i.e., directional steering) for participants with a Medtronic system. Consequently, stimulation is applied at the level of contact rings, which may increase the risk of side effects. However, because our centre does not yet routinely use directional programming, participants in the Threshold group would likely not have received directional programming under standard care. Importantly, directional stimulation remains available during the follow-up period for both groups, ensuring that optimal stimulation settings can still be achieved if clinically indicated.

In conclusion, we have developed a protocol for a prospective, randomized, open-label, blinded-endpoint trial comparing IBP with the current clinical standard, MPR. This study aims to determine whether ongoing clinical threshold assessment is necessary or if it can be replaced by a more efficient, anatomy-guided approach. The results of this trial could be adopted by other centres to integrate IBP into clinical practice. If IBP demonstrates equivalent motor outcomes while providing advantages in speed, efficiency, and patient experience, it has the potential to become the new standard for DBS programming. This would reduce reliance on exhaustive clinical testing and patient feedback, offering a more effective and patient-friendly approach to DBS care.

Trial status

This manuscript is based on protocol version 9, dated 10 May 2024. The first participant was enrolled on 3 January 2024, and the last participant was enrolled on 23 December 2025. The anticipated trial completion date, defined as the date of the last visit of the last participant, is September 2026. At the time of manuscript submission, participant follow-up is ongoing.

Abbreviations

ALDS	Academic Medical Centre Linear Disability Score
CT	Computed tomography
DBS	Deep brain stimulation
EDC	Electronic data capture
IBP	Imaging-based programming
ITAP	Imaging-based vs. Threshold Assessment-based Programming
MCID	Minimal clinically important difference
MDS	Movement Disorder Society
MPR	Monopolar review
MRI	Magnetic resonance imaging
PDQ	Parkinson's Disease Questionnaire
UMC	University Medical Centre
UPDRS	Unified Parkinson's Disease Rating Scale
VTA	Volume of tissue activated
STN	Subthalamic nucleus

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Authors' contributions {3a}

AvdW, RS, and RdB contributed to the conception and design of the trial. YW, MB, RS, AvdW, and RdB contributed to data acquisition. AvdW drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version.

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Data availability {6}
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate {30}
The study is conducted according to the principles of the Declaration of Helsinki (version of 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and acts. Ethical approval was provided by the medical ethics committee (METC) of Amsterdam UMC, the Netherlands. Study monitoring is performed in accordance with ICH GCP guidelines. Written informed consent is obtained from study participants.

Consent for publication
Not applicable.

Competing interests {7b}
The authors declare no competing interests.

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