

Official Title: **Randomised, Double-Blind, Crossover Clinical Trial: Deep Brain Stimulation of the Posterior Subthalamic Area versus the Ventral Intermediate Nucleus of the Thalamus in Refractory Essential Tremor**

Document Type: STUDY PROTOCOL

Version Date: 19 February 2019

Study Title

Randomised, Double-Blind, Crossover Clinical Trial Comparing Bilateral Deep Brain Stimulation of the Posterior Subthalamic Area versus the Ventral Intermediate Nucleus of the Thalamus in Essential Tremor

Brief Summary

Essential tremor is one of the most common movement disorders and may become disabling in patients who do not respond adequately to pharmacological treatment. Deep Brain Stimulation (DBS) targeting the Ventral Intermediate Nucleus (VIM) of the thalamus has traditionally been the standard surgical approach. However, stimulation of the Posterior Subthalamic Area (PSA) has emerged as a promising alternative, potentially offering improved tremor control.

This study aims to compare the clinical efficacy, energy expenditure, safety and quality of life of DBS targeting the PSA versus the VIM using a randomised, double-blind, crossover design in patients with medically refractory essential tremor.

Detailed Description

Deep Brain Stimulation is an established therapeutic option for patients with severe essential tremor who are refractory to medication. Although VIM stimulation has long been considered the gold standard, increasing evidence suggests that PSA stimulation may provide superior tremor suppression and functional outcomes.

This study is designed as a prospective, randomised, double-blind, crossover clinical trial. Participants undergoing bilateral DBS implantation will receive electrodes positioned to allow stimulation of both targets (PSA and VIM). Following surgery, patients will undergo two blinded stimulation periods in which each target is activated in a randomised sequence.

Neurological and neuropsychological assessments will be performed at baseline and during each stimulation phase. The crossover design allows each participant to serve as their own control, thereby increasing statistical power and reducing inter-individual variability.

Study Design

- **Study Type:** Interventional (Clinical Trial)
- **Allocation:** Randomised
- **Intervention Model:** Crossover Assignment

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- **Masking:** Double-Blind (Participant and Outcome Assessor)
 - **Primary Purpose:** Treatment
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Estimated Enrollment

The sample size was calculated through a hypothesis of non-inferiority, considering that the effect of the experimental technique (PSA-DBS) is no less than the standard technique (VIM-DBS) in tremor control (first endpoint: total score on the Fahn-Tolosa-Marin Tremor Rating Scale, FTM-TRS). The calculation was based on previous results and our experience, considering the mean postoperative FTM-TRS scores of 15 ± 15 in the VIM group and 10 ± 8 in the PSA group, with power of 80 %, a significance level 5 % and assuming that the non-inferiority limit is 5, with the previous post-surgical mean scores and a standard deviation of 11.5 units for both groups. Taking into account a 20% increase in anticipation of possible losses and due to the nature of the crossover study, the recruitment target was 11 patients (22 measurements in VIM and 22 in PSA). In case of missing data due to loss to follow-up or withdrawal of consent, the patient will not contribute to the analysis. This was calculated with Ene 3.0 software.

Arms and Interventions

Experimental Arm 1: PSA Stimulation

- Deep Brain Stimulation targeting the Posterior Subthalamic Area
- Optimised stimulation parameters during blinded phase

Experimental Arm 2: VIM Stimulation

- Deep Brain Stimulation targeting the Ventral Intermediate Nucleus of the thalamus
- Optimised stimulation parameters during blinded phase

Intervention Description

All participants will undergo surgical implantation of bilateral DBS electrodes along a single-trajectory covering the VIM and PSA. Post-operatively, they were randomly (a random block randomization) assigned to group 1 (1^o PSA – 2^o VIM) or group 2 (1^o VIM – 2^o PSA), undergoing stimulation on each target for 3 months. At the end of each period, blind assessments were performed, always by the same evaluator (blind to target and stimulation parameters). Patient and physician are blinded to the stimulation site during the crossover phase.

Outcome Measures

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Primary Outcome

- **Change in tremor severity** measured by a validated tremor rating scale (Fahn-Tolosa-Marin Tremor Rating Scale)
 - Time Frame: at the end of each stimulation phase
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Secondary Outcomes

- Stimulation efficiency measured by stimulation amplitudes and total electrical energy delivered (TEED)
 - Quality of life assessed using generic and specific scales
 - Stimulation-related side effects
 - Neuropsychological performance assessed using a multi-domain assessment
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Eligibility Criteria

Inclusion Criteria

- Confirmed diagnosis of bilateral ET or ET-plus according to the Movement Disorders Society criteria.
 - Refractoriness to medication: at least two attempts at medical treatment with at least two groups of different medication (fundamentally propranolol and primidone), which were ineffective (insufficient tremor control or adverse effects).
 - Subjects of both sexes, older than 18 years old.
 - Sufficient competence to collaborate and comply with the study protocols.
 - Ability to provide informed consent
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Exclusion Criteria

- Clinically relevant cognitive decline which may interfere with the study.
 - Clinically relevant active psychiatric disorder.
 - Contraindication for general surgery or bilateral DBS.
 - Unsuitable electrode location according to neuroimaging.
 - Participation in other interventional study.
 - Cerebral atrophy (width of the third ventricle >10 mm) or other anatomical anomalies that would interfere with optimal stereotactic localization.
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Study Procedures

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1. **Screening and recruitment**
2. **Baseline neurological and neuropsychological assessment**
3. **Surgical implantation of bilateral DBS electrodes**
4. **Randomisation of the stimulation sequence**
5. **Initial programming phase (unblinded optimisation)**
6. **Blinded assessments at the end of each crossover phase**
7. **End of crossover phase**
8. **Open-label phase (during 6 months after crossover phase)**
9. **Final evaluation and data analysis**

Statistical Analysis

A within-subject comparison will be performed using appropriate statistical tests for crossover designs (e.g. paired analyses). Both primary and secondary outcomes will be analysed, adjusting for potential carryover effects.

Safety Monitoring

Adverse events related to surgery and stimulation will be recorded and classified according to severity and relationship to the intervention.

Study Duration

Approximately **5 years**, including recruitment, intervention, and follow-up.

Study Location

University Hospital Virgen de las Nieves, Granada, Spain

Investigators

- Principal Investigator:

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 6. Bartolomé Marín-Romero. Neuropsychologist (University Hospital Virgen de las Nieves, Granada, Spain)
 7. José Pablo Martínez Barbero. Neuroradiologist (University Hospital Virgen de las Nieves, Granada, Spain).

Dissemination Plan

Results will be disseminated through:

- Peer-reviewed scientific journals
- National and international conferences

Ethics and Informed Consent

Ethical Approval

This study will be conducted in accordance with the ethical principles set out in the **Declaration of Helsinki**, as well as applicable national and European regulations, including **Regulation (EU) 536/2014 on clinical trials** and relevant data protection legislation.

The study protocol, informed consent form, and all relevant study documentation have been submitted for approval to a duly authorised **Research Ethics Committee** prior to study initiation.

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The trial will not commence until written approval has been obtained from the Ethics Committee and, where applicable, from the competent regulatory authority.

Any protocol amendments will be submitted for ethical review and approval before implementation, except where necessary to eliminate immediate hazards to participants.

Regulatory Compliance

The study will be conducted in compliance with:

- **Good Clinical Practice (GCP)** guidelines (ICH-GCP E6(R2))
- Applicable local regulatory requirements
- Institutional policies of the participating centre

All study personnel will be appropriately trained in GCP and study-specific procedures.

Informed Consent Process

Written informed consent will be obtained from all participants prior to the performance of any study-specific procedures.

Participants will receive both oral and written information regarding:

- The purpose and nature of the study
- Study procedures and duration
- Potential risks and benefits
- Alternative treatment options
- Data handling and confidentiality
- Their rights as research participants

Adequate time will be provided for participants to consider participation and to ask questions. Consent will be obtained by a qualified member of the research team.

Participants will be informed that their participation is entirely voluntary and that they may withdraw from the study at any time without providing a reason and without any impact on their standard medical care.

Risks and Benefits

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The potential risks associated with participation include those inherent to Deep Brain Stimulation surgery and stimulation-related adverse effects, such as:

- Surgical complications (e.g. haemorrhage, infection)
- Neurological or neuropsychiatric side effects
- Device-related complications

Potential benefits include improved tremor control and functional capacity, although these cannot be guaranteed.

A careful risk–benefit assessment has been conducted, and the study is considered ethically justified.

Confidentiality and Data Protection

All participant data will be handled in accordance with the **General Data Protection Regulation (GDPR) (EU) 2016/679** and applicable national data protection laws.

Participants will be assigned a unique study identification number, and all data will be pseudonymised. Identifiable information will be kept separate from research data and stored securely.

Access to identifiable data will be restricted to authorised study personnel. Data may be inspected by regulatory authorities or ethics committees for monitoring purposes, in compliance with confidentiality requirements.

Data Handling and Record Keeping

All study data will be recorded in a secure and validated data collection system. Records will be retained for the period required by applicable regulations.

Participant Withdrawal

Participants may withdraw from the study at any time without prejudice.

Data collected prior to withdrawal may be retained and used for analysis unless the participant explicitly requests otherwise, in accordance with applicable regulations.

Publication Policy

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Study results will be published in peer-reviewed journals and presented at scientific conferences. Participant confidentiality will be preserved in all publications.