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Choice of anaesthesia in microelectrode recording-guided deep-brain stimulation for Parkinson's disease (CHAMPION): study protocol for a single-centre, open-label, non-inferiority randomised controlled trial

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ABSTRACT

Introduction Deep brain stimulation (DBS) implantation under general anaesthesia (GA) has been applied to patients with Parkinson's disease (PD) with severe comorbidities or disabling off-medication symptoms. However, general anaesthetics may affect intraoperative microelectrode recording (MER) to varying degrees. At present, there are few studies on the effects of sedatives or general anaesthetics on multiunit activity characteristics performed by MER in patients with PD during DBS. Therefore, the effect of the choice of anaesthesia on MER remains unclear.

Methods/design This is a prospective randomised controlled, non-inferiority study that will be carried out at Beijing Tiantan Hospital, Capital Medical University. Patients undergoing elective bilateral subthalamic nucleus (STN)-DBS will be enrolled after careful screening for eligibility. One hundred and eighty-eight patients will be randomised to receive either conscious sedation (CS) or GA at a 1:1 ratio. The primary outcome is the proportion of high normalised root mean square (NRMS) recorded by the MER signal.

Ethics and dissemination The study was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2022-147-02). Negative study results will indicate that GA using desflurane has a non-inferior effect on MER during STN-DBS compared with CS. The results of this clinical trial will be presented at national or international conferences and submitted to a peer-reviewed journal.

Trial registration number NCT05550714.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a randomised controlled, non-inferiority study to observe the effect of anaesthesia modality on microelectrode recording (MER) mapping in patients with Parkinson's disease (PD) during subthalamic nucleus (STN)-deep brain stimulation (DBS).
⇒ This study includes a strict randomised system, clear inclusion and exclusion criteria, and a rigorous uniform protocol to compare intraoperative and postoperative variables between two groups.
⇒ The main parameter, normalised root mean square (NRMS), is the primary outcome for evaluating the electrode position and satisfies the need for real-time computation feasibility.
⇒ The study is limited in that it will occur in a single centre; therefore, future multicentre trials will be needed to confirm the effects of different types of anaesthesia on patients with PD undergoing STN-DBS surgery.

INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease.[1] Loss of nigrostriatal dopaminergic neurons causes a group of neurological disorders with PD-like movement problems, such as rigidity, slowness and tremor.[2] In industrialised countries, the estimated prevalence of PD is 0.3% in the general population, 1.0% in people older than 60 years and 3.0% in people older than 80 years; incidence rates of PD are estimated to range between 8 and 18 per 100 000 person-years.[3] Currently, the main treatments for PD include drugs and deep brain stimulation (DBS). DBS surgery is used for treating motor symptoms when drug treatment is poorly controlled or the side effects are unacceptable. The subthalamic nucleus (STN) is one of the most commonly used targets in the treatment of PD-DBS.[4] The accuracy of the final implantation position of deep brain electrodes is key to the success of PD-DBS.[5 6] Before the operation, neurosurgeons primarily define the STN by high-resolution imaging techniques. During electrode placement, microelectrode

recording (MER) is widely applied to determine the precise location and boundary of the anatomic target nucleus by identifying the characteristic discharge activity of neurons. Clinical tests are generally performed to assess the clinical effects and side effects, and the therapeutic window can also be defined.[7]

MER localises the specific brain target according to the changes in background activity and spontaneous firing of the action potential. The change in firing pattern and the sudden change in background activity often reveal the process by which the microelectrode enters another anatomical region.[8] When the electrode enters the STN, the background activity increases suddenly, and the characteristic spike activity is observed on the basis of a noisy background, which manifests as regular tonic discharge, irregular cluster discharge and tremor-related neuronal activity.[9] This is due to the high cell density of multicell discharge in the STN.[10] The need for real-time computation feasibility is a crucial guideline when choosing the parameters to work with. These were done despite many previous trials assessing STN spike-related information such as oscillations, firing rates (FR), and burstiness due to the computational difficulty and susceptibility to errors.[11–13] The literature generally recommends using the root mean square (RMS) value of the electrode recorded sampling signal (measured in volts) as the main parameter to evaluate the electrode position.[14] RMS values may vary with electrode properties and other operating-related disturbances; therefore, it is important to normalise RMS by calculating the RMS of each time period in the trajectory divided by the average RMS of the first five stable sessions in the same trajectory. A custom method of coarse quantisation is adopted: all observations with normalised RMS (NRMS)<1.25, that is, below a 25% increase from the NRMS baseline (which is equal to 1 due to the normalisation), are clustered together (Low-NRMS cluster). Within the STN, the high NRMS was mostly above 1.5.[14 15] We will use a more stringent standard of an average NRMS greater than 2.0 after entering the STN as the primary outcome to indicate good signal amplitude.

The type of anaesthesia is an important factor not only for the accuracy of MER but also for the safety of the operation. At present, the optimal anaesthesia choices for the management of patients with PD during DBS include local anaesthesia (LA), conscious sedation (CS) and general anaesthesia (GA).

LA and/or CS are preferred, and asleep-awake-asleep (AAA) using dexmedetomidine (DEX) is the most commonly used anaesthetic method among clinical centres due to its obvious benefits. Continuous infusion of DEX has been successfully used for DBS under AAA anaesthesia.[16–18] DEX is a highly selective alpha-2-adrenoreceptor agonist, and it produces dose-dependent sedation without respiratory depression.[19] Its anxiolytic and sedative effects seem to occur through activation of the locus coeruleus, which modulates arousal, sleep and anxiety. This non-cortical site of action may lead to a state of 'cooperative sedation'.[19] The safety of sedation has been proven. Some studies have shown a decrease in STN activity under DEX infusion and suggested that high-dose DEX infusion should be avoided during STN-DBS.[12 20] At present, it is generally believed that low-dose DEX (0.2–0.5 µg/kg/hour) has no significant effect on the quality of MER in the STN.[8] However, LA and/or CS may not be feasible for some patients (unable to keep supine position during the operation, dyspnoea, severe pain, physical deformity, severe anxiety, fear and severe circulatory diseases, etc).[21] In addition, awake patients may not be able to cooperate with surgeons due to disabling off-medication symptoms or medical comorbidities. There is also an increased risk of inadvertent accidental intracerebral haemorrhage during surgery due to coughing or tremors.[22] Therefore, it is still necessary to perform DBS surgery under GA so that the above-mentioned deficits can be overcome.

With the application of intraoperative imaging-guided technology, a number of studies on DBS surgery under GA have been conducted in recent years, but the clinical results are controversial. Some researchers suggested that postoperative clinical symptom improvement was better in awake surgery,[23] although some researchers supported that there was no significant difference in symptom improvement between asleep and awake surgery.[24 25] A previous meta-analysis demonstrated that the clinical outcomes and postoperative complications, including intracranial haemorrhage and infection, were similar between GA and LA DBS surgery, and the subgroup analysis showed that MER might not affect target positioning and postoperative clinical outcomes.[26] A recent randomised clinical trial (RCT) indicated that MER-guided DBS of the STN in PD under GA and LA did not have a difference in outcome with regard to cognitive, mood and behavioural adverse effects.[27] Thus, for patients who cannot tolerate awake DBS surgery, GA may still be an appropriate choice.[27 28] However, the effects of GA on MER mapping, as the vital indication of the accuracy of the target location for DBS surgery, were not fully assessed.

Although previous studies have considered decreases in or the absence of microelectrode signals under certain forms of GA,[29 30] some studies have attempted to preserve the signals by using different anaesthetics of GA.[31 32] To minimise the effect on MER of general anaesthetics, inhalation anaesthesia is superior to intravenous anaesthesia (propofol);[31 33] volatile anaesthetics have been proven to inhibit presynaptic sodium channels and are critical for neuronal action potentials,[34] which could explain the decreased neuronal FR. Some reported that STN neuronal signals could be identified under light desflurane GA, and its long-term clinical outcomes were comparable to those of LA.[7] Chen *et al*[35] showed that successful localisation of the STN was possible under desflurane anaesthesia even at minimum alveolar concentrations (MAC) up to 0.8. They also found no differences in the STN coordinates and the depth of the STN between GA and LA.[36] It has been reported that using 0.5–0.8 MAC

Table 1 Schedule of enrolment, intervention and assessments

	Study period							
	Enrolment	Allocation	Postallocation					
Time point	At arrival	After evaluation	During treatment	2 hours after treatment	24 hours after treatment	2 days after treatment	3 days after treatment	6 months after treatment
Enrolment:								
Eligibility screen	○							
Informed consent	○							
Allocation		○						
Interventions:								
GA			○					
CS			○					
Assessments:								
Baseline variables	○							
Intraoperative data			○					
Accuracy of target location					○			
Cognitive function	○				○	○	○	○
Surgical experience satisfaction					○			
Clinical efficacy								○
Quality of life	○							○
DBS satisfaction								○
Adverse events			○	○	○	○	○	○

CS, conscious sedation; DBS, deep brain stimulation; GA, general anaesthesia.

desflurane to maintain GA can obtain a reliable MER signal.[35]

At present, most existing studies have been retrospective cohort studies or small sample exploratory studies. There are little high-quality clinical data to confirm the feasibility of GA for MER during STN-DBS. Therefore, we designed this RCT to compare MER mapping in patients with PD with GA or CS during STN-DBS to explore alternative anaesthesia methods for DBS patients.

METHODS AND ANALYSIS

Trial design

This trial is a single-centre, open-label, non-inferiority randomised controlled study in which the endpoint outcome evaluator is blinded. All trial procedures are summarised in table 1. Online supplemental file 1 shows the completed checklists.

Patients with PD will be screened and recruited at the Beijing Tiantan Hospital, Capital Medical University. This trial was expected to last for approximately 2 years, from 15 October 2022 to 31 October 2024. This trial was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2022-147-02). The participant flow chart is briefly illustrated in figure 1.

Participants

Patients diagnosed with PD based on the UK bank criteria undergoing elective bilateral STN-DBS will be considered for recruitment in this study. The inclusion criteria will include age range from 50 to 80 years old, American Society of Anesthesiologists physical status II–III, receiving bilateral STN-DBS, and completion of the informed consent. The lower age limit of inclusion criteria is set at 50 because 50 is considered to be the boundary of early-onset and late-onset PD.[37]

The exclusion criteria will include the following: suffering from obstructive sleep apnoea, body mass index (BMI)>30 kg/m^2, suspected difficult airway condition, suspected to be uncooperative during surgery (ie, severe tension and anxiety), a history of allergy to anaesthetics or severe dysfunction of organs (ie, heart failure, renal or liver dysfunction). For BMI, we considered respiratory function and blood oxygen saturation during the operation, as we noticed that sleep apnoea occurred especially in those with BMI>30 kg/m^2. For safety considerations, the present trial will exclude patients who suffer from sleep apnoea.

Before recruitment, the neurosurgeon and anaesthesiologist must discuss together to reach an agreement that the candidate is suitable for GA or CS. The reasons for unsuccessful recruitment must be recorded.

Randomisation and grouping

Randomisation will occur at the time of patient admission to the operating room for STN-DBS. Prior to randomisation, written informed consent (online

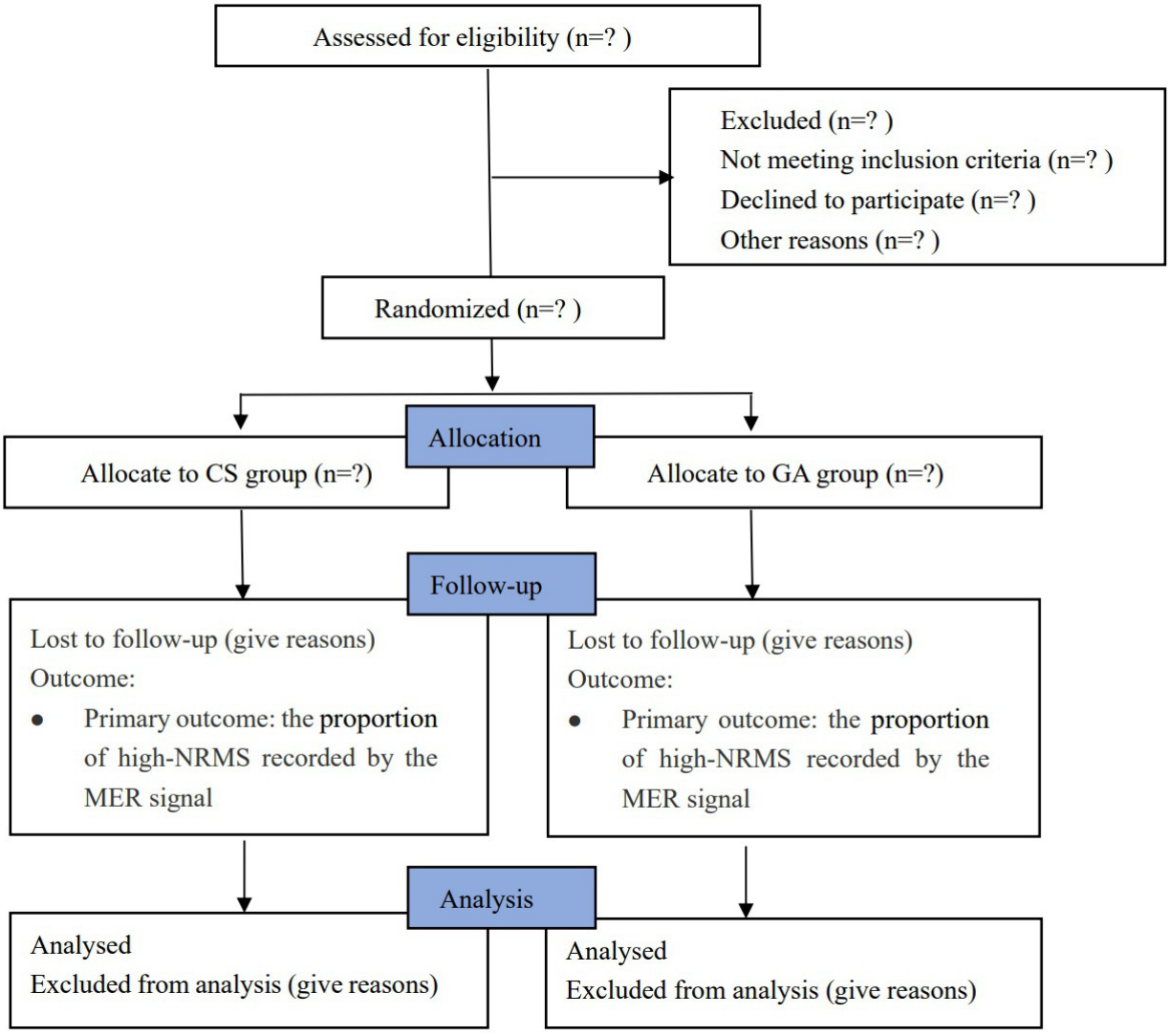

Figure 1 Consolidated Standards of Reporting Trials flow diagram for the CHAMPION clinical trial. CS, conscious sedation; GA, general anaesthesia; MER, microelectrode recording; NRMS, normalised root mean square.

supplemental file 2) must be signed with full understanding by the patient or the patient's legal representatives. Enrolled participants will be randomised for treatment with GA or CS in a 1:1 ratio. To balance the number of patients assigned to each group, blocked randomisation will be conducted via a computer-generated table (blocks of 4), and patients will be stratified by age (≥65 years old and <65 years old). The step of stratified randomisation is important as an attempt to ensure that no bias affects the representative nature of the patient sample under study. We choose the midpoint of the age range, that is, 65 years old, to be the stratification line because age is considered one of the most important factors that influence the development of PD. A designated staff member who does not participate in anaesthesia management or follow-up will perform recruitment and randomisation procedures, including generating the allocated randomisation sequence. The staff member will carry out the allocated sequence through opaque, sealed and stapled envelopes. Each envelope will have a fixed number to ensure that they are opened in the correct order. The treatment assignment will remain blinded until the end of the observation of the last subject.

Standard operating procedures will be followed for groups to confirm that no principal differences are generated and to ensure uniform adherence to the protocol. All participants in this study will receive scalp nerve blocks with 0.5% ropivacaine to block the bilateral supraorbital, ototemporal, supratrochlear and lesser occipital nerves before the operation. The outcome assessors who are blinded to the information about anaesthesia of the enrolled patients will evaluate the outcome variables to ensure unbiased reporting. Because the anaesthesiologists, neuroelectrophysiological experts and neurosurgeons participate in the whole treatment, they will be unblinded during the study. All eligible candidates and their medical agents will also be unblinded during the study.

Intervention

GA and CS in this study are defined on the basis of the practice guidelines for sedation and analgesia by non-anaesthesiologists.[38] Patients in both the GA and CS groups will be treated and monitored by anaesthesiologists.

CS group: A loading dose of DEX 0.5 µg/kg will be infused intravenously at a constant speed within 15 min after the patient enters the operating room, followed by continuous DEX infusion of 0.2–0.5 µg/kg/hour until the end of the first stage of the operation. Pulse oxygen saturation (SpO_2) will be kept above 94% with 40%–60% inhaled oxygen at 3 L/min flow, and the end tidal CO_2 partial pressure ($PetCO_2$) will be monitored via an anaesthetic gas sample line at the nasal vestibule and kept normocapnia. The bispectral index (BIS) value will be maintained at 60–80.

GA group: The patients will not use any preoperative sedative drugs and will receive rapid sequence induction with endotracheal intubation. Anaesthesia will be induced by the infusion of sufentanil citrate 0.1–0.2 µg/kg and propofol 1.5–2.0 mg/kg. Muscle relaxation will be achieved with cisatracurium (0.2 mg/kg). Before endotracheal intubation, lidocaine cream will be applied at the cuff of the endotracheal tubes. The tidal volume will be maintained at 6–8 mL/kg. Mechanical ventilation will be initiated to achieve normocapnia ($PetCO_2$ 35–45 mm Hg) with a 40%–60% fraction of inspired oxygen. Anaesthesia will then be maintained with remifentanil (0.05–0.1 µg/kg/min), cisatracurium (0.1 mg/kg/hour) infusion and desflurane inhalation 0.5–1.0 MAC. During MER, the desflurane concentration will be adjusted to maintain 0.5–0.6 MAC. If the desflurane concentration needs to be adjusted to less than 0.5 MAC during MER for various reasons, remedial measures will be implemented.

Standard management protocols during STN-DBS

In all patients, the surgical technique will involve two phases, including implantation of the probes and implantation of the pulse generator, according to the standard operation procedure. A stereotactic frame will be placed at the beginning, and then participants will receive CT imaging of the head. The surgical planning system will be used to coregister the CT image with the MRI completed the day before surgery. The connecting plane of the anterior commission-posterior commission will be determined, and the STN will be taken as the surgical target. Then, the three-dimensional coordinates of the stereotactic target will be calculated by the surgical planning system. The operation will be completed by the same group of surgeons. Levodopa drugs will be stopped 12 hours before the DBS operation to avoid interference with intraoperative MER.

All randomised patients will receive standard monitoring, including non-invasive blood pressure (BP), heart rate (HR), ECG, SpO_2, inspired oxygen fraction and $PetCO_2$. All patients will be monitored by BIS to assess the depth of sedation with a BIS probe placed on the forehead. Ropivacaine (0.5%) will be used to block the bilateral supraorbital, ototemporal, supratrochlear and lesser occipital nerves before the operation.

Physiological parameters will be recorded by using a designed data collection table. During the operation, the fluctuation of BP should be controlled and maintained at less than 20% of the baseline value. In the case of increased BP (systolic BP>140 mm Hg or increased BP>20% of the baseline value), urapidil should be infused intravenously at 10–25 mg/time; if hypotension occurs (systolic BP<90 mm Hg or BP drops >20% of the baseline value), deoxyepinephrine 20–60 µg will be intravenously infused; if the HR decreases to less than 60/min, atropine 0.2–0.5 mg/time intravenously will be needed.

The surgical procedures have been described in detail in previous studies.[14 39–41] On each side, after incising the scalp and making a burr hole under anaesthesia, a shielded tungsten microelectrode will be inserted into the brain towards the target area by a microdrive. Electrophysiological signals will be recorded to guide the implantation of the DBS leads using a Neuro Omega system (Alpha Omega, Nazareth, Israel). The MER track will start from 10 mm above the presumed target at steps of 0.5–1 mm. After 2–3 s of signal stability, the discharge (mode, frequency, amplitude, background signal, etc) The position of the dorsal border of the STN is defined as the point at which the increase in baseline activity and FR with rhythmic burst activity are detected suddenly. Finally, the electrode will be implanted into the STN, and a satisfactory neuronal discharge signal will be obtained. In our centre, only one electrode will be used in STN-DBS surgery to minimise the risk of haemorrhage related to MER.

All patients will be followed up by blinded outcome assessors while they are hospitalised. The follow-up plan will include the inpatient period and 6 months postoperation. The inpatient follow-up period will include the evaluation of respiratory function, vital signs, operation-related complications (second operation, infection, intracranial haemorrhage, etc) and anaesthesia-related adverse events at 2 hours, 24 hours, 2 days and 3 days after the operation. The patients' satisfaction with the operation experience (based on a seven-point Likert scale) and the accuracy of the DBS electrode (defined by the neurosurgeon's review of the postoperative CT scan) will be evaluated within 24 hours after the operation. Cognitive function will be measured by the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) 24 hours, 2 days and 3 days after the operation. The 6-month postoperative follow-up will be performed at the outpatient centre, and clinical efficacy will be assessed by the improvement of the United Parkinson's Disease Rating Scale (UPDRS)-III (conditions: med on/off, stim on/off) and levodopa equivalent daily dose (LEDD). The Parkinson's Disease Quality of Life Questionnaire (PDQ-39) will be used to assess changes in the quality of life of the patients. Cognitive function and the incidence of adverse events in patients with PD will be reassessed, and DBS satisfaction 6 months after the

operation will be evaluated according to a seven-point Likert scale.

MER analysis

Raw MER data will be obtained and converted with converter software (Alpha Omega, Nazareth, Israel), from which the NRMS values can be calculated. MER data will be analysed and visualised offline in MATLAB 2020b (Mathworks, Natick, Massachusetts, USA) with the FieldTrip toolbox[42] and customised scripts. All recordings will be manually visualised offline, and recordings with evident artefacts will be discarded before analysis. Signals shorter than 5 s will also be excluded from further analysis. The electrophysiological data will be downsampled to 1000 Hz and filtered with a low-pass filter at 100 Hz to obtain the LFP data, after which a notch filter will be applied to remove the 50 Hz line noise. The spectrogram of the LFP will be generated using a short-time Fourier transform of a 1 s sliding Hanning window with 50% overlap, and the power spectral density (PSD) will be calculated using Welch's method with the above-mentioned windows and overlap parameters between 1 and 45 Hz with a frequency resolution of 0.98 Hz. The PSD will then be normalised by dividing the sum power and averaged across recordings in each hemisphere. The power of theta (4–8 Hz), alpha (8–13 Hz) and beta (13–30 Hz) bands will be calculated by averaging the power across the corresponding frequency band. The FR will be calculated using customised scripts developed from the Osort toolbox.[43]

Outcomes

The primary endpoint is the proportion of high NRMS recorded by the MER signal (with the average NRMS recorded by MER after entering the STN greater than 2.0), which will be used to compare the difference in neuronal electrical activities between the CS and GA groups.

The secondary endpoints include the following efficacy and safety parameters:

1. NRMS and their stratified proportions in the CS and GA groups during MER recording.
2. FR.
3. Lengths of STN.
4. Total electrode path times.
5. Beta band (13–30 Hz) oscillations calculated by spectrum analysis during MER recording.
6. Proportion of intraoperative remedial measures implemented.
   If the characteristic discharge activity of neurons cannot be recovered after maintaining the target anaesthetic concentration during MER, the following procedures should be implemented: (1) reduce the concentration of anaesthetics for a short time and wait for the recovery of electrical signals; (2) readjust the target position based on the experiences of neurosurgeons and (3) if the STN cannot be successfully identified by MER, implant electrodes with preoperative imaging localisation.
7. Duration of operation and MER.
8. The accuracy of the DBS electrode (defined by the neurosurgeon's review of the postoperative CT scan) will be evaluated within 24 hours after the operation.
9. Clinical efficacy 6 months after STN-DBS measured with the improvement of the UPDRS-III (conditions: med on/off, stim on/off).
10. Clinical efficacy 6 months after STN-DBS measured with LEDD reduction.
11. Cognitive function as assessed by the MMSE and MoCA at baseline and 24 hours, 2 days, 3 days and 6 months after the operation.
12. Quality of life 6 months after STN-DBS, as assessed by the PDQ-39.
13. The incidence of operation-related complications (second operation, infection, intracranial haemorrhage, etc) up to 6 months after randomisation.
14. The incidence of anaesthesia-related adverse events, such as nausea, vomiting and intraoperative awareness, during hospitalisation.
15. Surgical experience satisfaction 24 hours after the operation and DBS satisfaction 6 months after the operation will be assessed using the seven-point Likert scale.
16. All adverse events involved with this study will be recorded in detail.

Sample size calculation

According to the preresearch results of our centre, the proportion of high NRMS in the CS group was 0.94, and the non-inferiority margin was −0.1 (meaning a <10% absolute difference). The sample size of 178 patients will provide 80% power to show the difference α=0.025 (one tailed) between the GA group and the CS group with a ratio of 1:1. Assuming a drop-out rate of 5%, the total sample size of this study is planned to be 188.

Statistical analysis

Generally, continuous variables will be documented as the mean (SD) for normally distributed data and the median (IQRs) for skewed distributions. Categorical variables will be documented as the number (proportion), and the relative risk will be calculated with 95% CIs. The difference between two groups will be documented as absolute differences calculated by independent t-tests for continuous variables, the Mann-Whitney U test for skewed variables and the χ^2 or Fisher's exact test for categorical variables, with 95% CIs. For the primary endpoint of the proportion of high-NRMS recorded by MER signal, we will use the χ^2 or Fisher's exact test to compare between-group differences. Non-inferiority will be established if the lower bound of the two-sided 95% CIs for the difference in proportions of patients who achieved the primary outcome is greater than the predefined non-inferiority margin. The secondary outcomes will be statistically analysed via t-tests, Mann-Whitney U tests, and χ^2 or Fisher's exact tests, as appropriate.

The imputations with the mean or median will be applied for missing values. Sensitivity analysis will be used to explore the statistical nature of the missing data. All statistical tests will be two sided with a significance level of 0.05, and the effect sizes will also be reported. Because of the potential for type I errors due to the lack of adjustment for multiple comparisons, the findings for secondary outcomes and sensitivity should be interpreted as exploratory.

The statistical software STATA V.14.0 will be applied for all statistical analyses. Statistical significance will be defined according to a type I error of 0.05.

Data monitoring committee

The study will be monitored by an independent data monitoring committee (DMC), which is composed of three specialists in anaesthesiology, neurosurgery and statistics. The DMC will audit the study via telephone calls or regular interviews. If severe adverse events occur, the DMC will be responsible for determining whether the study should be terminated. Generally, meetings will be held at the kick-off meeting, routine meeting when 50% of patients are enrolled, final meeting and emergency meeting (if necessary).

Reporting of adverse events

All adverse events related to this study will be recorded using a standardised checklist containing common adverse events. The adverse events will be closely detected until resolution or a stable situation has been reached. When an adverse event occurs, it should be reported to the research department immediately, and the principal investigator will determine the severity and causality of this event. All adverse events associated with this study will be reported to the ethics committee within 24 hours of awareness, and the principal investigator will be responsible for the adverse events.

Patient and public involvement

Patients and the public were not directly consulted in the research problem or outcome measures. Patients did not participate in the study design, recruitment or conduct of this trial. Study findings will be available to participants on request.

Protocol amendment

The chief investigator will be responsible for amending the protocol and making the final decision. If there are any modifications, such as eligibility criteria, outcomes or analyses, the principal investigator will communicate with and gain approval from the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University prior to implementation and communicating the changes with all relevant parties.

ETHICS AND DISSEMINATION

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University on 28 September 2022 (reference number: KY2022-147-02). It was registered on ClinicalTrials.gov on 21 September 2022 (NCT05550714). The first participant was recruited on 15 October 2022, and the estimated completion date is 31 October 2024. The results of this clinical trial will be presented at national or international conferences and submitted to a peer-reviewed journal.

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Contributors RH and JZ conceived the primary idea of the study. SX, WX, LS, AW, RH and JZ initiated the study design and helped with protocol development and implementation. SX drafted this protocol in close cooperation with RH. SX and LS contributed equally to this work and are co-first authors. RH and JZ are corresponding authors. SX, LC, XL, YT, WY and WX helped in data collection and revision of the protocol. All authors contributed to refinement of the study protocol. All authors have read and approved the final protocol.

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Competing interests None declared.

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