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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

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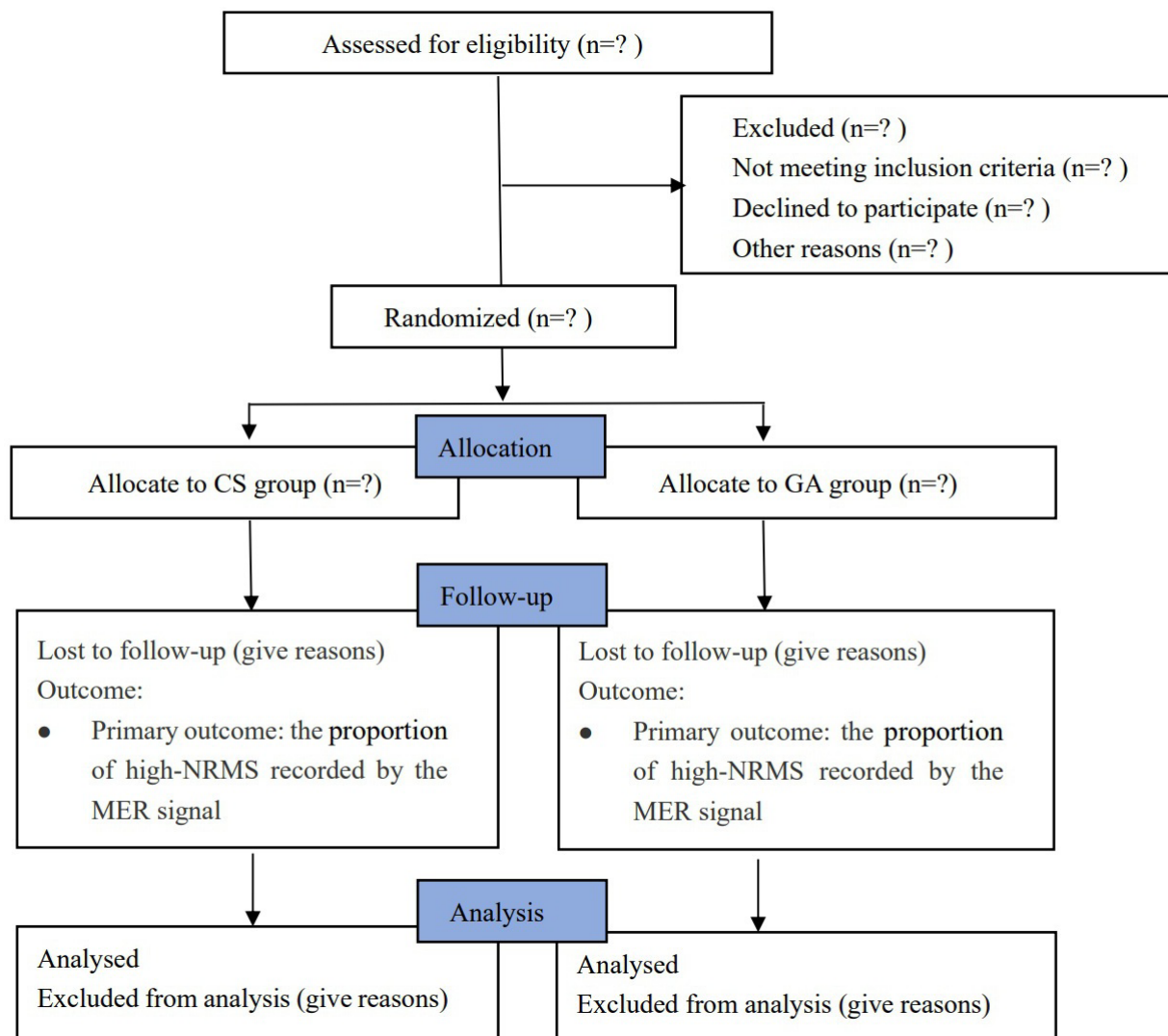
Figure 1 Consolidated Standards of Reporting Trials flow diagram for the CHAMPION clinical trial. CS, conscious sedation; GA, general anaesthesia; MER, microelectrode recording; NRMS, normalised root mean square.

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 ($\geq$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 $0.5\,\mu g/kg$ 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–$0.5\,\mu g/kg/hour$ 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–$0.2\,\mu g/kg$ 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–$0.1\,\mu g/kg/min$), 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 $\alpha=0.025$ (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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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3,18
	2b	All items from the World Health Organization Trial Registration Data Set	18
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18
	5b	Name and contact information for the trial sponsor	/
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	/
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16-17

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Introduction

| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 6-7 |

| | 6b | Explanation for choice of comparators | 6 |

| Objectives | 7 | Specific objectives or hypotheses | 7 |

| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 8 |

Methods: Participants, interventions, and outcomes

| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 10 |

| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10 |

| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11-12 |

| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 10 |

2

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11

3

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17

4

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	/

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18

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Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17-18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___/___
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___/___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___/___
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	___/___
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17

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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____Yes_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____/_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Supplementary file 2

Informed Consent	Version 2.3	Date：2022.8.31

INFORMED CONSENT

CHoice of Anaesthesia in Microelectrode Recording-guided DeeP-brain StImulation for ParkinsON's Disease (CHAMPION)

Project entrust organization: Beijing Tiantan Hospital, CMU

Contract Research Organization: N/A

Version：2.3

31st, Aug, 2022

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Informed Consent	Version 2.3	Date：2022.8.31

INFORMATION SHEET

You have been diagnosed with **Parkinson's disease,** and you will receive elective bilateral subthalamic nucleus-deep brain stimulation.

We would like to invite you to participate in our study, which is **"Choice of Anaesthesia in Microelectrode Recording-guided Deep-brain Stimulation for Parkinson's Disease"**, to observe the effect of general anaesthesia and conscious sedation on microelectrode recording and clinical outcome. This study was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University. During our study, we will follow the Declaration of Helsinki.

Before you decide whether to participate in this clinical trial, please take time to review this information carefully. This form describes the purpose, procedure, study duration, risks and possible benefits of participating in the study. You may also wish to talk to others, including your friends, family, or discuss with your anesthesiologist, about your participation in this study.

1. PURPOSE OF THIS STUDY

Deep brain stimulation (DBS) implantation under general anaesthesia has been applied to Parkinson's disease patients with disabling off-medication symptoms or medical comorbidities. However, general anaesthetics may affect intraoperative microelectrode recording to varying degrees. At present, there are few studies on the effects of sedative or general anaesthetics on multiunit activity characteristics performed by microelectrode recording in Parkinson's disease patients during DBS. Therefore, the effect of the choice of anaesthesia on microelectrode recording remained unclear in this population. Additionally, there is a lack of high-quality clinical data to confirm the feasibility of general anaesthesia for microelectrode recording during subthalamic nucleus-DBS. We designed this randomized controlled study to compare microelectrode recording mapping and clinical efficacy after surgery in Parkinson's disease patients with general anesthesia or conscious sedation to explore alternative anesthesia methods for DBS patients.

2. NUMBER of PARTICIPANTS

In total, 188 patients will be included in the study.

3. DURATION OF THIS STUDY

This study will last 2 years, and we will collect postoperative information until 6 months postoperatively.

4. PROCESS OF THIS STUDY

If you are willing to participate in the study, please sign this informed consent form, and you will be examined including the following:
- Physical examination and medical history inquiry
- Vital signs: respiratory, body temperature, heart rate and blood pressure.
- Severity of Parkinson's disease symptoms: the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III and Hoehn and Yahr Scale.

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Informed Consent	Version 2.3	Date：2022.8.31

- Blood test
- Electrocardiography

If you met the inclusion and exclusion criteria, the neurosurgeon and anesthesiologist evaluated your safety, and with the agreement of both of them, you could be allocated into two groups randomly. With the computer-generated table, you will be randomly allocated to receive one of anesthesia management in an equal chance. We will implement your anesthesia according to your group. During the whole study, we will collect your response to different anesthesia methods and your health status through close intraoperative monitoring and a series of examinations at 2 h, 24 h, 2 days and 3 days after you receive treatment. We will notify you to conduct face-to-face follow-up at the functional neurosurgery clinic 6 months after the end of treatment to assess the clinical efficacy, cognitive function, quality of life, adverse events and satisfaction. This study will compare MER mapping information and clinical efficacy to determine which anesthesia treatment is better for Parkinson's disease patients and finally to optimize the treatment of patients.

5. THE DIFFERENCE OF TWO ANESTEHSIA MANAGEMENT

The type of anaesthesia is an important factor not only for the accuracy of microelectrode recording but also for the safety of the operation. At present, the optimal anaesthesia choice and management for Parkinson's disease patients during DBS include local anaesthesia, conscious sedation and general anaesthesia. Conscious sedation is preferred, and asleep-awake-asleep using dexmedetomidine (DEX) is the commonly used anaesthesia method among clinical centres for its obvious benefits: allowing the surgeon to analyse the spike characteristics of microelectrode recording and evaluate the clinical benefits and side effects through intraoperative clinical tests. However, it may not be applicable to some special patients (unable to keep supine position during the operation, dyspnoea, severe pain, physical deformity, severe anxiety, fear and severe circulatory diseases, etc.). Additionally, it is too serious to cooperate with surgeons when awake for patients disabling off-medication symptoms or medical comorbidities. There is also an increased risk of accidental intracerebral haemorrhage during surgery due to coughing or tremor. Therefore, it is still necessary to perform microelectrode recording tests under general anesthesia.

Many studies on DBS implantation under general anaesthesia have been conducted in recent years, but the clinical results of these studies vary. Some researchers considered that postoperative symptom improvement was better in the local anaesthesia groups, although some researchers suggested that symptom improvement is similar between general anaesthesia and local anaesthesia surgery. Abandoning awake clinical testing does not lead to less motor improvement. At present, there is a lack of high-quality clinical data to confirm the feasibility of general anaesthesia for microelectrode recording. The purpose of this study was to compare microelectrode recording mapping in Parkinson's disease patients with general anaesthesia or conscious sedation during the subthalamic nucleus (DBS) to explore alternative anaesthesia methods for DBS patients.

6. OTHER TREATMENT CHOICE

In clinical practice, anesthesia management for Parkinson's disease patients includes general anesthesia and conscious sedation. If you do not participate in this study, your intraoperative anesthetic scheme is mainly arranged and formulated by the anesthesiologist according to clinical experience.

7.　WHO CAN BE SELECTED for the study?

    1)　Age ranges from 50 to 80 years old,

    2)　American Society of Anesthesiologists (ASA) physical status II to III,

    3)　After receiving bilateral STN-DBS,

    4)　Signing the informed consent.

8.　WHO SHOULD NOT PARTICIPATE in the STUDY

If you have the following condition, you should not participate in the study:

    1)　Suffering from obstructive sleep apnea,

    2)　Body mass index (BMI) > 30 kg/m^2,

    3)　Suspected difficult airway condition,

    4)　Suspected to be uncooperative during surgery (i.e., severe tension and anxiety),

    5)　Severe organ dysfunction (i.e., heart failure, renal or liver dysfunction),

    6)　Known allergy to the anaesthetics.

9.　POSSIBLE BENEFITS of PARTICIPATING in theSTUDY

Your prognosis may or may not improve as a result of participating in this study, and the information from this study will help determine which anesthesia management can be safer and more effective applied to other patients with similar conditions.

10.　POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFORT, INCONVENIENCES of PARTICIPATING in the STUDY

The monitoring methods, anesthesia methods, anesthetic drugs and anesthesia maintenance used in this study are all routine clinical practice, and there will be no additional risks related to the study. It is possible that related discomfort or adverse events will happen during your anesthesia and operation, including respiratory depression, circulation depression, arrest, cardiac arythm, myocardial infarction, pulmonary embolism, drug adverse reactions and cerebrovascular complications (hemorrhage and infarction). If you experience adverse reactions or discomfort due to surgical procedures and anesthesia, the researchers will make corrections promptly.

During the study, you need to undergo doctor inquiry and questionnaire, which may cause inconvenience to you.

11.　CONFIDENTIALITY OF PERSONAL INFORMATION

Your medical records (study records/CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests and other tests on your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

12.　HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers. Your anesthesiologist will be ready to answer any of your questions before, during and after the study.

13.　RELATED EXPENSES

You need to pay for routine anesthetic drugs, equipment, operation, monitoring and examination. Our assessment of Parkinson's disease severity, cognitive function, quality of life, clinical efficacy, etc., through the scale is free of charge, and your participation in this study will not increase your additional costs. If any medical expense occurs due to an adverse event, you will be exempted from the charge.

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14. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in STUDY and WITHDRAW from STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or affect your medical service or other benefits.

Before making a decision, you can discuss with your family or friend, or you can talk with your doctor for any question, until you fully understand this study.

15. HOW THE STUDY MAY EFFECT YOUR LIFE?

You may feel the visit and examination uncomfortable, and special arrangement is needed. You can consult your doctor in any steps of the study.

In addition, signing this informed consent means that you agree not to participate in any other clinical research related to drugs or medical devices during the whole study period.

16. CONSULTING

If you have any related questions, please contact Dr. Xie Sining (phone: 010-59976656 or cell phone: 13581874076).

If you have any concerns about your personal benefit, or you want to complain or express your concerns about the study, please contact the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (phone: 010-59978555 or e-mail: ttyyirb@163.com).

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Informed Consent	Version 2.3	Date：2022.8.31

SIGNATURE PAGE of AGREEMENT

Study tile: CHoice of Anaesthesia in Microelectrode Recording-guided DeeP-brain StImulation for Parkinson's Disease

Principal investigator: Ruquan Han, Beijing Tiantan Hospital, CMU

DECLARATION of CONSENT

I have read the introduction about the study above and have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risks and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration and know that:

· I can ask my doctor for more information at any time.

· I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study, especially if I withdraw due to medication, it will be of great benefit to the whole study if I tell my doctor about my condition and complete the corresponding physical examination and physical and chemical inspection.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I agree that the ethics committee of the drug regulatory authority or the representative of the sponsor may have access to my research information.

I will be provided with a signed and dated copy of the informed consent.

Ultimately, I agreed to participate in the study and promised to follow my doctors' advice as much as possible.

Signiture of patient/legal relative:

Relation:

 Date: **(yyy/mm/dd)**

I confirm that I have explained the details of the trial to the patients, including its rights and possible benefits and risks, and have given them a signed copy of the informed consent.

Aignature of doctor:

 Date: **(yyy/mm/dd)**