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PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD): study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction Deep brain stimulation (DBS) has been validated as a safe and effective treatment for refractory cervical dystonia (CD). Globus pallidus internus (GPi) and subthalamic nucleus (STN) are the two main stimulating targets. However, there has been no prospective study to clarify which target is the better DBS candidate for CD. The objective of this trial is to compare directly the efficacy and safety of GPi-DBS and STN-DBS, thereby instructing the selection of DBS target in clinical practice.

Methods and analysis This multicentre, prospective, randomised, controlled study plans to enrol 98 refractory CD patients. Eligible CD patients will be randomly allocated to GPi-DBS group or STN-DBS group, with the DBS electrodes implanted into the posteroventral portion of GPi or the dorsolateral portion of STN, respectively. The primary outcome will be the improvement of symptomatic severity, measured by the changes in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity subscale and the Tsui scale at 3 months, 6 months and 12 months after surgery. The secondary outcomes include the improvement of the TWSTRS-disability subscale, TWSTRS-pain subscale, quality of life, mental and cognitive condition, as well as the differences in stimulation parameters and adverse effects. In addition, this study intends to identify certain predictors of DBS efficacy for CD.

Ethics and dissemination The trial has been approved by the Medical Ethics Committee of Chinese PLA General Hospital (S2022-613-01). The results of this study will be published in international peer-reviewed journals and shared in professional medical conferences.

Trial registration number NCT05715138.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia study is the first randomised controlled study comparing the efficacy and safety of globus pallidus internus-deep brain stimulation (DBS) and subthalamic nucleus-DBS for cervical dystonia.
⇒ The primary outcomes are evaluated blindly through randomly shuffled, de-identified, standardised videos to minimise potential biases.
⇒ This trial uses the technique of imaging fusion to control the confounder of electrode position, which is deemed to be the major influence factor of DBS efficacy.
⇒ One possible limitation is that investigators are not blinded because of the nature of the surgical intervention.

INTRODUCTION

Background and rationale

Cervical dystonia (CD), also known as spasmodic torticollis, is a type of focal dystonia, mainly manifesting as involuntary head turning or tilting, or holding a prolonged and twisted posture.[1 2] CD limits the neck activity by involving one or a group of neck muscles and is often accompanied by pain and psychological disorders, seriously compromising patients' life quality.[2]

Medical treatment of CD is unsatisfactory. Oral medications are often ineffective or overshadowed by concomitant side effects.[2] Although most CD patients can be alleviated by injection of botulinum toxin, the remission is temporary so patients require multiple injections.[3] Moreover, 25% of patients do not respond to botulinum toxin, and 20%–40% of patients discontinued botulinum toxin treatment due to lack of benefit.[4 5] Denervation and myotomy of the involved muscles is an effective surgery for CD once, but it becomes powerless in face of complicated cases.[6]

Deep brain stimulation (DBS) has been substantiated to be a safe and effective therapy for primary CD, even for those medically refractory cases.[7] The globus pallidus internus (GPi) was considered the preferred DBS target for various types of dystonia (including CD) with remarkable short-term and long-term efficacy.[7–16] In addition, stimulation of the subthalamic nucleus (STN) has drawn increasing

attention in recent years with the superiorities of lower stimulation parameters requirement and shorter onset time. A series of studies have demonstrated that STN-DBS is a promising alternative to GPi-DBS, with a long-term symptomatic improvement rate ranging from 50% to 90%,[17–21] similar to and even higher than that of GPi-DBS. For studies focusing on CD only, both GPi-DBS[10 22–27] and STN-DBS[17 28 29] show significant therapeutic effect. However, the question of which nucleus is the better DBS candidate for CD has not been clarified.

Previous comparisons of both targets were mainly about dystonia as a whole (including focal, segmental and generalised dystonia). There was a prospective crossover study directly comparing the efficacy and safety of GPi-DBS and STN-DBS by implanting two sets of DBS electrodes for each dystonic patient and stimulating alternately one of them.[30 31] The results seemed to favour STN-DBS at the 6-month follow-up,[30] but no significant between-group difference was found at the over 10-year follow-up.[31] Furthermore, another crossover study evaluated the effect of 24-hour stimulation of either STN or GPi for eight dystonic patients and also found no significant between-group difference.[32] Retrospectively, STN-DBS was proven to outperform GPi-DBS in terms of movement improvement at the 1-month follow-up, but this superiority disappeared later, and at the 12-month follow-up, GPi-DBS was more efficient than STN-DBS in treatment of axial symptoms.[33] Moreover, another meta-regression analysis indicated that STN-DBS, relative to GPi-DBS, is associated with a better outcome in the univariate regression model but not in the multivariate model.[34] However, these studies did not distinguish specific phenotypes (not focus on CD). Additionally, the prospective studies were degraded by their small sample size and the retrospective analyses yielded inconsistent results.

For CD specifically, there have been no prospective studies to compare GPi-DBS with STN-DBS. From a retrospective perspective, a meta-analysis comparatively analysed the results of 13 relative studies, including 58 CD patients undergoing GPi-DBS and 28 CD patients undergoing STN-DBS.[35] They found that when the factor of follow-up time was not taken into account, the improvement rates of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) subscores (severity, disability and pain) were all significantly higher in the GPi-DBS group than that in the STN-DBS group, though the TWSTRS total score was not significantly different. Nevertheless, when the follow-up time was limited to 3 years, neither TWSTRS total score nor subscores showed a significantly between-group difference.[35] Similarly, another meta-analysis also failed to detect any significant difference—the improvement rates of the TWSTRS total score were 60.4% (GPi-DBS) and 56.6% (STN-DBS), respectively (p=0.936).[36] However, the two meta-analyses included low-quality studies and showed significant heterogeneity and publication bias. Surgeons still have confusion in the face of target selection before surgery. As such, a well-designed randomised controlled trial (RCT) is entailed to ascertain which one (STN or GPi) is the optimal DBS target for CD.

Objective

The PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD) study aims to compare GPi-DBS with STN-DBS for drug-refractory CD in the following aspects: (a) improvement of dystonic symptoms (severity, disability and pain), (b) improvement of life quality, mental status and cognitive status, (c) stimulation parameters, (d) adverse effects. In the end, the study intends to identify the potential factors that are associated with DBS efficacy in both groups.

METHODS AND ANALYSIS

Study design and setting

The PASTS-CD study is an investigator-initiated, multicentre, prospective, randomised, parallel-controlled equivalence clinical trial, following the rules of Standard Protocol Items: Recommendations for Interventional Trials guidelines.[37] The method of minimisation for randomisation will be used to produce two paralleling arms with an allocation ratio of 1:1, both of which undergo the same procedures except for the difference in DBS target (GPi or STN). The flow chart of the trial is presented in figure 1. This study will be implemented from 1 September 2023 to 30 November 2026 in four tertiary hospitals in China. This study only incorporates hospitals that have been qualified in DBS surgery for more than 5 years with more than 20 DBS operations per year, and where DBS surgery-related complication rate is less than 5%. In addition, all investigators will go through a standardised training before trial initiation.

Participants

Recruitment

The investigators will post the recruitment announcement on each centre's official website and WeChat account. CD patients who are willing to participate in the trial will visit the dystonic outpatient of each centre.

Inclusion criteria

1. Diagnosed as idiopathic or hereditary isolated CD.
2. Severe functional impairment.
3. Oral medication and injection of botulinum toxin become ineffective after at least two attempts (>6 months since last injection).
4. No secondary causes of CD.
5. Age 18–80 years old.
6. Normal neurological examination except for dystonia.
7. Normal brain MRI.

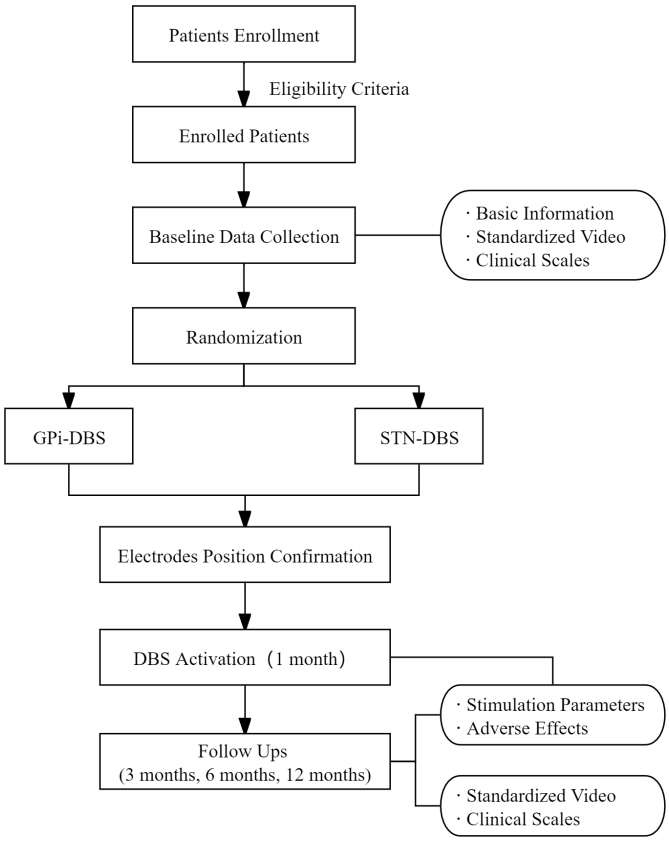

Figure 1 Flow chart of the PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia study. DBS, deep brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus.

8. The subject or their family members can fully understand the trial and sign the informed consent.
9. Good compliance and willingness to receive regular follow-ups.

Exclusion criteria

1. Diagnosed as secondary CD.
2. CD with obvious trunk/limb involvement, or Meige syndrome.
3. History of severe mental disorders, dementia, or epilepsy.
4. Previous dystonia surgery (pallidotomy, thalamotomy, DBS, etc).
5. Accompanied by other neurological diseases (Parkinson's disease, essential tremor, multiple sclerosis, stroke, etc).
6. The patient has or needs other implantable devices (cardiac pacemakers, defibrillators, cochlear implants, spinal cord stimulators, etc).
7. Pregnant women or women who are waiting to become pregnant during the trial.
8. Poor health condition.

Dropout or suspension of the trial

1. Postoperative infection that requires removal of DBS electrodes.
2. Severe displacement of DBS electrodes position from the predefined targets (>3 mm for STN-DBS group and >5 mm for GPi-DBS group).
3. Occurrence of severe adverse events or other serious diseases that interfere with the efficacy assessment.
4. Loss to follow-up.
5. Requests from patients to withdraw from the trial.

Interventions

Baseline evaluation

For each eligible patient, the basic information, medical history, disease characteristics and medications (especially the time and frequency of botulinum toxin injection) will be recorded in the electronic medical record system in detail. Besides, physical examination, routine blood tests and MRI scanning are assigned before surgery. Every patient will be videotaped as per a standardised scheme (see online supplemental material) without drug withdrawal. These videos will be collected and transferred to two neurological raters who will complete the TWSTRS-severity subscale and Tsui scale blindly and separately at the end of the trial. Moreover, the TWSTRS-disability subscale, TWSTRS-pain subscale, 36-item Short Form General Health Survey (SF-36), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) will also be completed before surgery. The timeline of data collection is shown in table 1. After signature of the informed consent form, candidate patients will be randomised into the GPi-DBS group or the STN-DBS group.

DBS surgery

Certain minor differences in surgical procedures are allowed among involved centres as long as the electrodes are placed safely and accurately, but some critical steps must keep in line with each other. Specifically, on the day of surgery, a stereotactic head frame is fixed on the patient's head, followed by a CT scan. The frame CT images and the preoperative MRI (1.0×1.0×1.0 mm^3, no gap) will be fused in a surgical planning system, where the coordinates of the targets and trajectories are determined. DBS electrodes are implanted with the assistance of a stereotactic frame or neurosurgical robot under general anaesthesia with bi-spectral index monitoring (BIS). After completion of burr holes, microelectrode recording (MER) is monitored intraoperatively to further assist the targeting of nuclei. The dosage of propofol should be reduced on recording, keeping the value of BIS fluctuating around 70, so as not to affect neuronal discharges.[38] An eligible firing pattern should be recorded as described by Gross *et al*.[39] If not, the target should be adjusted or use two-channel or multiple-channel recording. Passive limb movements can be helpful to identify the sensorimotor subregion of the nuclei. Given that patients are under general anaesthesia and their heads are immobilised by the frame, intraoperative macrostimulation can be omitted. Subsequently, according to the randomised

Table 1 Participant timeline of data collection

	Enrolment	Allocation/surgery	Postsurgery	Follow-up			
Timepoint (weeks±1)	1	0	1	4	12	24	48 (close-out)
Enrolment							
Eligibility screen	X						
Informed consent	X						
Medical history	X						
MRI scanning	X		X				
Allocation		X					
Interventions							
GPi-DBS surgery		X					
STN-DBS surgery		X					
DBS				X	X	X	X
Assessments							
Standardised video*	X				X	X	X
TWSTRS-disability	X				X	X	X
TWSTRS-pain	X				X	X	X
SF-36	X					X	X
HAMA	X					X	X
HAMD	X					X	X
MMSE	X					X	X
MoCA	X					X	X
Medication	X				X	X	X
Stimulation parameters				X	X	X	X
Adverse effects		X	X	X	X	X	X

*For assessment of TWSTRS-severity and Tsui scale.
DBS, deep brain stimulation; GPi, globus pallidus internus; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SF-36, 36-item Short Form General Health Survey; STN, subthalamic nucleus; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

allocation, the corresponding quadripolar electrodes will be implanted into posteroventral GPi (GPi-DBS group) or dorsolateral STN (STN-DBS group), bilaterally. The implanted electrodes can be selected from anyone of the following three manufacturers: Medtronic (Minneapolis, USA), PINS Medical (Beijing, China) and SceneRay (Suzhou, China). Of note, in light of the volume difference between the two nuclei, electrodes with contact intervals of 1.5 mm are chosen for GPi-DBS, but 0.5 mm for STN-DBS. Afterwards, inserted leads will be fixed at the burr hole site and an implantable pulse generator will be connected and implanted at the right subclavicular area subcutaneously.

Electrode position confirmation

If possible, an intraoperative MRI scanning is strongly recommended to verify the implantation accuracy. Otherwise, a postoperative MRI or CT scanning is compulsory before discharge from hospitals. In order to exclude the effect of electrode position on the DBS efficacy, the intraoperative or postoperative images are fused with the preoperative images. If the deviating Euclidean distance between the lead tip and the predefined target exceeds 3 mm (STN-DBS group) or 5 mm (GPi-DBS group), the subject will be dropped out.

Follow-up

One month later, the DSB will be activated by a specialised DBS programmer in the outpatient department. To evaluate stimulation effects and adverse effects of both electrodes, all contacts will be screened in a monopolar mode with the voltage increasing gradually from 1 V to 4 V and pulse width and frequency kept at 60 µs and 130 Hz. For those whose symptoms improve rapidly, the optimal parameters will be documented and used for chronic stimulation. For those who lack an acute improvement, the activated contact is identified based on the results of MER or the 3D reconstruction of the electrodes via the Lead DBS software (the contact closest to the posteroventral GPi or the dorsolateral STN), and the voltage is set at 25% below the threshold for causing a stimulation-related adverse effect. At the 3-month follow-up, a standardised video will be recorded and TWSTRS-disability and pain subscales are completed by a centrally trained rater. At

the 6-month and 12-month follow-ups, in addition to the standardised video and TWSTRS subscales, all the other scales (ie, SF-36, HAMA, HAMD, MMSE and MoCA) will also be evaluated (table 1). Of note, to focus on the effect of DBS and exclude the confounding effect of medication, botulinum toxin injection is forbidden during the follow-up period, and in a week leading up to each evaluation, the patient should take the same oral drugs as before surgery. Furthermore, throughout the implementation of the trial, all adverse effects must be handled in safety and documented in detail, regardless of surgery-derived, device-related or stimulation-induced events. Regular programming will also be performed at each follow-up to find the best parameters. The initial stimulating setting can be modulated at any time when the patients feel unsatisfactory about the symptom control or encounter a stimulation-induced adverse effect.

Outcome measurements

The primary outcomes are the changes (improvement rates) of the TWSTRS-severity subscale and the Tsui scale at 3 months, 6 months and 12 months after surgery. The reason why these two scales are chosen as the primary outcomes is that both of them are obtained from standardised videos, while the TWSTRS disability and pain subscales can be acquired via questionnaires. The Tsui scale is a rational complement to the TWSTRS-severity subscale by adding the assessment of head tremor.

The secondary outcomes are the changes (improvement rates) of the TWSTRS-disability subscale, TWSTRS-pain subscale, the difference of stimulation parameters and adverse effects at 3 months, 6 months and 12 months after surgery, as well as the SF-36 questionnaire, HAMA scale, HAMD scale, MMSE scale and MoCA scale at 6 months and 12 months after surgery. The improvement rate of each scale can be calculated by the following formula: (score at each follow-up time point−baseline score)/baseline score×100%. Stimulation parameters are mirrored by the total electrical energy delivered (TEED=-voltage^2×pulse width×frequency×1 second/impedance).[40] The higher the TEED, the shorter the battery life of the stimulator. To quantify the adverse effects, the Timed Up and Go test is used to evaluate the severity of bradykinesia (the most common adverse effect for GPi-DBS) and the Abnormal Involuntary Movement scale is used to estimate the severity of dyskinesia (the most common adverse effect for STN-DBS).

Sample size

The sample size is calculated based on one of the primary outcomes—the improvement rate of TWSTRS-severity subscore. According to the results of the latest meta-analysis comparing GPi-DBS with STN-DBS for CD treatment, the improvement rates (%) of TWSTRS-severity subscore at the same follow-up time (3 years) were 53.7±20.4 (GPi-DBS) and 39.3±26.4 (STN-DBS), respectively.[35] Based on the model of two independent sample t-test, 41 patients for each group are required to reach a significant level of 5% (two-tailed) with 80% power. Assuming that 5% of CD patients would be withdrawn from the trial and another 10% of CD patients would be lost to follow-up, a total of 98 CD patients are required (49 patients for each group).

Randomisation and blinding

Patients will be randomly assigned (1:1) to GPi-DBS group or STN-DBS group by using a bespoke web-based randomisation sequence generated by the minimisation method with a random component with gender (male or female), CD subtypes (phasic type or tonic type) and disease duration (<3 years or ≥3 years) as factors of allocation adjustment. Randomisation was stratified by participating centres. A specific neurosurgeon of each centre who will participate in the DBS surgery submits the basic information of the patient to the online system, and then a unique random code and grouping information will be returned automatically. Only this neurosurgeon has access to the central randomisation system.

Investigators (neurosurgeons) are not blinded because of the nature of the surgical intervention, but patients, scale raters and data analysts are blinded. At the time of scale scoring and video recording, each patient wears an operating cap so that scale raters are blinded to the condition of surgery (preoperatively or postoperatively). All standardised videos recorded for evaluation of the TWSTRS-severity subscale and the Tsui scale will be shuffled randomly and scored twice centrally by two experienced neurologists who do not know the grouping information and time points of follow-up. The mean score values of the two neurologists will be documented and uploaded. Furthermore, before data is transferred to data analysts for statistical analysis, the data manager will mask the grouping information and set two groups as A and B instead. Only when the subjects are withdrawn would they be unblinded.

Data collection and management

The schematic chart for data collection is shown in table 1. Prior to the enrolment of the first patient, all investigators (including neurosurgeons, coordinators, scale raters, DBS programmers, data managers, etc) have to receive standardised training in data collection and management. At baseline and each follow-up time point, all information (medical history, scales, videos, programming parameters and adverse effects) will be transferred to a coordinator who will then fill in the case report forms (CRFs). All items in CRFs have to be completed and any correction should be noted and explained. Eventually, two coordinators upload the standardised videos and input the information of CRFs into the electronic data capture (EDC) system—Whole Course Management Service Platform (https://admin.demo.sdc.sinohealth.com/login).

Notably, the EDC system is linked with a patient client that can be installed on patients' or their family's mobile phones, through which, investigators can push

disease-related knowledge or questionnaires (eg, SF-36) to patients and conversely, patients can submit questionnaires and express their complaints to investigators at any time. Before each follow-up time point, patients will receive an alert from this client, thereby improving follow-up compliance.

During data collection, two data monitors will audit the contents of the CRFs to ensure data authenticity and accuracy. In addition, a data manager will review the EDC data online in real-time and check the data consistency. Any data error or query existing, the data manager will send it back to the corresponding centre where the investigators will check the original documents, answer the query and update the data. At the end of the trial, the data manager will lock the EDC database and send the data to two data analysts for analysis.

All data files should be managed with great care and confidentiality. Only authorised investigators can login the EDC system with a password and any modification trace on the DEC platform will be preserved. Additionally, all original scale files and CRFs will be locked in a special cabinet and all video files will be stored in an encrypted folder.

Data monitor

Any adverse events during the study period should be documented in detail, including the information of event date, category, severity, treatment and prognosis. If severe adverse events occur, the principal investigator must be notified within 24 hours.

Two study monitors who are independent of the implementation of this trial and have no competing interests will regularly visit the participating centres to inspect the protocol adherence, recruitment status, data collection, reporting of adverse events and subject dropout rate. The monitoring results will be presented to the principal investigator and the local ethics committee. The interim analyses are unnecessary because plenty of previous studies have confirmed the safety of DBS surgery of both targets.[7 10 14 16 17 29] Here, this trial only concentrates on their potential differences.

Statistical analysis

Outcome statistics will be performed using cases with complete data, that is, per protocol analyses. In addition, for the primary outcomes, an intention-to-treat analysis (including all patients assigned in the trial) will also be performed with missing values imputed by multiple interpolations.

Continuous variables will be presented as means±SD for normally distributed data or as medians (IQRs) for skewed data. Categorical variables will be presented as frequencies or percentages. For difference analyses of baseline information, this study uses the Wilcoxon rank-sum test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Moreover, two-way analysis of variance will be used to analyse the main effects (group or time) and the interaction effects. Within-group post hoc comparisons between different time points will be analysed by paired t-test or Wilcoxon signed-rank sum tests. Between-group comparisons at a certain time point will be analysed using the Wilcoxon rank-sum test. Factors associated with DBS efficacy, such as gender, age at surgery and disease duration, will be included as covariates.[31 34 41] Of note, when analysing the adverse effects, those patients who have been withdrawn due to severe adverse effects should be included. Finally, to explore predictors of DBS outcomes, this study uses simple linear regression first to screen variables relevant to the improvement rates of TWSTRS, and multiple linear regression second to identify independent variables.

A difference of $p<0.05$ (two-tailed) is specified as statistically significant. SPSS V.26 statistical software will be used for statistical analyses.

Patients and public involvement

Patients and the public are not involved in the design and implementation of this trial.

Ethics and dissemination

The PASTS-CD trial protocol has been approved by the Medical Ethics Committee of Chinese PLA General Hospital (S2022-613-01), which is also responsible for re-examining protocol modifications in the future, if any.

The investigators have to explain the objectives of this trial and every surgical detail to the patients or their families, and the informed consent form must be signed before allocation. For those patients with surgical sequelae, this study provides ancillary and post-trial care according to standard medical practice.

The investigators have access to the final results, which will be published in international peer-reviewed journals and shared in professional medical conferences. The raw data can be available from the corresponding author on reasonable request. Patients' information will be deidentified and videos will be mosaicked before exhibition.

DISCUSSION

To the best of our knowledge, the PASTS-CD study is the first prospective RCT study directly comparing the efficacy and safety of GPi-DBS and STN-DBS for refractory CD patients. The results of this trial will be a powerful guide for neurosurgeons in the selection of DBS targets for CD patients.

One notable advantage of this trial is that the primary outcomes are quantified by standardised videos centrally and blindly by two neurologists. The customised scheme of standardised video recording has been tested to suffice for the scoring of the TWSTRS-severity subscale and Tsui scale. This design will eliminate the measurement bias from different scale raters of different centres and the interviewer bias from the subjectivity of scale raters. Another advantage is that this trial controls the confounding effect of electrode implantation accuracy, which is considered to be the most relevant factor to

DBS efficacy.[42 43] Due to the small size of the subcortical nuclei and the complex surrounding structures, a minor deviation from the target will bring about a significant disparity in DBS efficacy and adverse effects. Through measuring the distance between the sensorimotor subregion of target nuclei and the contacts of electrodes, the investigators exclude those subjects in which the volume of tissue activated of DBS electrodes is speculated to show no or a low overlapping with the sensorimotor subregion of target nuclei. According to previous experiences[44 45] and the volume difference between the two targets, the cut-off distance is defined to be 3 mm for the STN-DBS group and 5 mm for the GPi-DBS group. This procedure also minimises the influence of technical discrepancy of different neurosurgeons.

One possible limitation is that the neurosurgeons are not blinded, but this is determined by the nature of the surgical intervention. In fact, the main role of neurosurgeons is implanting the DBS electrodes into the predefined subregion of the two subcortical nuclei, and they do not participate in the subsequent scales scoring and DBS programming. As such, by controlling the accuracy of electrode position, the accompanying bias from the unblinded neurosurgeons will be significantly reduced. In addition, owing to the low incidence of CD, the investigators have to initiate a multicentre study to meet the requirement of sample size. Although multicentre studies may increase heterogeneity to some extent, it is believed that strict protocol implementation, coupled with systematic training and constant study monitoring, will help to minimise the biases and maximise the reliability of results.

Contributors Study conception: ZM and XY. Initial study design: BL and JX. Revision of study design and protocol: ZM. Statistical analysis: HY. Study coordination: XY. Drafting the manuscript: BL and JX. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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