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Deep brain stimulation in Tourette syndrome

Submission date
15/02/2022

Recruitment status
No longer recruiting

Registration date
02/03/2022

Overall study status
Completed

Last Edited
26/06/2025

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study aims to assess whether deep brain stimulation (DBS) reduces tic severity in patients with disabling Tourette Syndrome (TS). TS is characterised by involuntary movements (motor tics) and vocalisations (vocal tics) that start in childhood. The tics are usually mild and diminish over time but in a small number of people they persist, are severe, debilitating, and unresponsive to conventional treatments. Tics can be extremely forceful, cause serious self-harm and distress and constrain normal life activities. DBS is a technique that involves the surgical implantation of two thin wires, called electrodes, in the right and left globus pallidus, an area of the brain that is responsible for the control of body movement. These electrodes are connected to a stimulator placed on the chest under the skin that sends electrical signals to the brain. This type of surgery has been used since the late 1980s to treat patients with neurological disorders. It is routinely used for disorders such as Parkinson's disease and has also been used in a smaller number of patients with Tourette Syndrome. The aim of this study is to find out if DBS of the globus pallidus structure of the brain can reduce severe motor or phonic (vocal) tics in patients who suffer from Tourette Syndrome.

Who can participate?
Patients aged 18 years and over who suffer from severe Tourette Syndrome and have found that conventional treatments, such as medication, do not control their motor or phonic (vocal) tics

What does the study involve?
Participants will be assessed as being suitable for the study by their Neurologist. They will then be referred by their Neurologist to attend the National Hospital for Neurology and Neurosurgery (NHNN) in London for a pre-screening visit with the multidisciplinary team of neurosurgeons, neurologists, neuropsychiatrists and specialist DBS nurses. The study team at NHNN will need details about the participant's Tourette Syndrome symptoms, general medical history, medication history and check if there is any reason they would not be able to undergo surgery. If they are suitable to take part in the study, the research team at the NHNN will invite the participant to attend a baseline visit. At this point, the participant will be invited to reconfirm consent to participate in the study. Patients will be admitted to the hospital under the care of a team with expertise in DBS and TS. They will be implanted with a DBS system in a part of the brain known as the "internal pallidum" which has produced the desired effect of tic reduction in previous small studies. Initially, 6 months will be spent adjusting the amplitude of other parameters of stimulation with the aim of optimising the stimulation to make the

treatment as beneficial as possible. In previous studies, this phase was not long enough to obtain the best possible outcome. After 6 months, patients will be randomly placed into two groups. One group will be kept with DBS switched on and the other will have DBS switched off for up to 2 weeks. After this period, patients will be reassessed and a few days later will be swapped to the other condition. The patients and doctors doing the assessments will not know if the DBS is switched on or off. This will test, in an unbiased way, whether any tic reduction is specifically due to DBS. From previous experience, the tics are expected to come back within one to two days of DBS being discontinued. Patients who cannot tolerate DBS being switched off for the full 2 weeks will be assessed and the DBS will be turned on again sooner. Patients will have the choice of coming into the hospital for this part of the study.

What are the possible benefits and risks of participating?
The DBS device could significantly reduce the severity of participants' tics and other symptoms. If a significant improvement in symptoms is achieved, this will allow participants to function better than they are currently and may improve their quality of life, allowing more independence. The tics may only improve a little, but nevertheless this small improvement may be beneficial. However, there is no guarantee that DBS will improve tics and other symptoms. The results from this study will provide information to doctors regarding DBS treatment of patients with Tourette Syndrome in the future.
This is a clinical study so the researchers cannot be sure that the treatment will be successful. There is a risk of having to undergo surgery and assessment without improvement of motor or phonic (vocal) tics and other symptoms. There are also risks associated with surgery: the surgical procedure carries a very small risk of bleeding in the brain resulting in a stroke (less than 1 in 500 in our centre, which could lead to paralysis or even theoretically death (never occurred at NHNN) as well as a small risk of infection (about 2%) or seizures (about 1%). Infections can be treated with antibiotics but may need the system to be removed to heal, it can usually be replaced a few months later. Seizures might affect temporarily the ability to hold a driving licence. Other possible disadvantages include periods of hospitalisation that are required for surgery and are optional for the randomised phase. There are a large number of study visits, particularly during the randomised phase if participants decide not to be hospitalised. The study also requires travel to the NHNN in London for study visits and time to complete the questionnaires and scales. Future MRI examinations can only be done once specific conditions are met. Having DBS may mean that participants are not eligible to take part in clinical studies in the future.

Where is the study run from?
The National Hospital for Neurology and Neurosurgery (NHNN), University College London Hospitals NHS Foundation Trust (UCLH) (UK)

When is the study starting and how long is it expected to run for?
June 2019 to June 2025

Who is funding the study?
National Institute for Health Research – Efficacy and Mechanism Evaluation (NIHR-EME) programme (UK)

Who is the main contact?
1. Ms Atiyyah Moosa, Op-TICS Trial Manager (CCTU.OPTICS@ucl.ac.uk)
2. Prof. Patricia Limousin, Op-TICS Chief Investigator (CCTU.OPTICS@ucl.ac.uk)

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
300541

ClinicalTrials.gov (NCT)
NCT06388291

Protocol serial number
CPMS 51655, IRAS 300541, NIHR129340

Study information

Scientific Title
Double-blind comparison of optimised deep brain stimulation for severe Tourette syndrome (Op-TICS)

Acronym
Op-TICS

Study objectives
The primary hypothesis for the clinical trial is that chronic stimulation of the globus pallidus internus (GPi) reduces tic severity measured with the Yale Global Tic Severity Scale (YGTSS) in patients with severe Tourette syndrome (TS).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/02/2022, London-Hampstead Research Ethics Committee (Ground Floor, Temple Quay House, Health Research Authority, BS1 6PN, UK; +44 (0)207 104 8345; hampstead.rec@hra.nhs.uk), REC ref: 22/LO/0052

Study design
Randomized; Interventional; Design type: Treatment, Device, Surgery

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Tourette syndrome

Interventions
Op-TICS is an early phase, randomised, double-blind, crossover clinical investigation.

Following consent, at baseline 0, participants will be asked to complete several questionnaires and rating scales independently or with the doctors:
Yale Global Tic Severity Score (YGTSS): to assess the severity of the tics experienced in the week leading up to the visit and will be completed with one of the neuropsychiatrists on the team.
A video recording of the tics will be performed with the patient sitting on a chair, that will allow doctors to assess the Modified Rush Video Rating Scale (MRVRS) by counting the number of tics.
Mini International Neuropsychiatric Interview (MINI): one of the neuropsychiatrists will administer this semi-structured interview to assess for the presence of psychiatric disorders.

The remaining questionnaires and scales to assess attention deficit hyperactivity disorders (ADHD) and obsessive-compulsive disorder (OCD) symptoms, anxiety, mood and an assessment of quality of life will be completed by the patients.

One month later the patient will be admitted to the National Hospital for Neurology and Neurosurgery for the surgery. The surgery will last half a day with a patient under general

anaesthesia. An MRI will be done to guide the implant and confirm the good position of the device. Two thin wires, called electrodes, will be implanted in the right and left globus pallidus according to the surgical procedure used in a previous trial, performed in Tourette syndrome patients, which is similar to the technique used for Parkinson's disease and dystonia. After that the stimulator will be implanted on the chest under the skin and a wire pushed under the skin to connect the electrode to the stimulator. The participants will remain an in-patient for up to 14 days post-surgery to give them time to recover and to start the stimulation.

The clinical investigation has two phases: the first an open-label optimisation adjustment phase and the second the blinded randomised crossover phase.

The open-label adjustment phase will begin soon after the implantation of the device, whilst the participant is an in-patient, and will last for 6 months. Participants will be required to return to the National Hospital for Neurology and Neurosurgery once a month for the deep brain stimulation settings to be adjusted until they reach the optimum for the participant. The optimisation process involves testing the effect of stimulating the different contacts on the electrodes (for Op-TICS the electrodes used will have eight contact points) in the globus pallidus with a gradual increase of the strength of stimulation. The clinical effect of these changes will be observed by the neurologists. To assist with the adjustments, participants will complete a visual analogue scale to report on the severity of their symptoms.

The open-label adjustment phase is followed by a double-blind randomised crossover phase. Participants will be randomised to either:
1. DBS stimulation ON for up to 2 weeks and then OFF for up to 2 weeks OR
2. DBS stimulation OFF for up to 2 weeks and then ON for up to 2 weeks

After the first 2-week assessment period, whichever group the participant belongs to, there will be a 2-day period when the participant's stimulation will be ON. This will allow adjustments to be made before the second 2-week assessment period. Stimulation will be set as per the optimal settings determined during the previous adjustment phase.

Participants will be required to attend the clinic for four visits for the double-blind phase - one at the start of this phase (baseline 1), one at the end of the first 2 weeks (effect 1), one at the start of the second 2 weeks (baseline 2) and one after the last 2 weeks (effect 2). In between these clinic visits the participants will also need to visit the clinic every couple of days to undergo a stimulator charging visit. This is where an unblinded DBS nurse will either charge or 'dummy' charge the stimulator battery.

During the baseline 1 visit participants will be asked to complete the same questionnaires and rating scales that were completed at inclusion, except the MINI. At the subsequent visits participants will complete only two of the scales that focus on the assessment of the tics – the YGTSS – Total Tic Score (a shorter version of the YGTSS) and the MRVRS.

Participants may choose to remain at the National Hospital for Neurology and Neurosurgery as in-patients during this phase.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Not provided at time of registration

Primary outcome(s)
Tic severity measured by the Yale Global Tic Severity Scale (YGTSS) – Total Tic Score at the end of the OFF-stimulation state versus the end of the ON-stimulation state at the end of the blinded randomised phase of the clinical investigation, i.e., Effect 1 (visit 5) vs Effect 2 (visit 7)

Key secondary outcome(s))
1. TIC number and severity measured using the Modified Rush Video Rating Scale (MRVRS) at the end of the OFF-stimulation state (visit 5) versus the end of the ON-stimulation state (Visit 7) in the blinded randomised phase
2. TIC number and severity measured using the MRVRS at baseline 0 and baseline 1
3. TIC number severity and complexity measured using the YGTSS at baseline 0 and baseline 1
4. Quality of life measured using the Gilles de la Tourette Syndrome – Quality Of Life (GTS-QoL) questionnaire at baseline 0 and baseline 1
5. Severity of obsessions and compulsions measured using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) at baseline 0 and baseline 1
6. Severity of depression measured using the Beck Depression Index (BDI) at baseline 0 and baseline 1
7. Severity of anxiety measured using the Beck Anxiety Index (BAI) at baseline 0 and baseline 1
8. Severity of ADHD symptoms and domains of impairment measured using the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) at baseline 0 and baseline 1
9. Safety of DBS indicated by adverse events and serious adverse events at all timepoints throughout the trial

Mechanistic outcomes:
A mechanistic part of the study will look at possible explanations of differing responses in both the open and randomised phase. To identify the factors which predict the degree of response to DBS in TS the researchers will be looking at the role of:
1. Clinical factors: age, disease duration, tic severity at baseline (MRVRS), comorbidity (i.e. Y-BOCS, BDI, BAI and BAARS-IV) at baseline 0 (visit 1) and baseline 1 (visit 4)
2. Electrical parameters of stimulation (total electrical energy delivered and volume of tissue activated by stimulation) measured using optimised parameters used for the double-blind phase (visits 4, 5, 6 and 7)
3. Imaging (contact position and relation with anatomic structures and MRI brain connectivity maps as previously done in patients with Parkinson’s disease undergoing DBS) at baseline 0 (visit 1) and surgery (visit 2)

Completion date
30/06/2025

Eligibility

Key inclusion criteria
1. Adult patients aged 18 years and over
2. Chronic, severe, treatment-refractory Tourette syndrome, as defined by a Yale Global Tic Severity Scale score (TGTSS (global)) >50/100
3. Failure to respond to a minimum of two antipsychotic drugs prescribed separately at

maximally tolerated doses for a minimum of 6 weeks OR, intolerance of these medications causing early cessation due to adverse events
4. Provided agreement to participate and written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
18

Key exclusion criteria
1. Schizophrenia or other primary psychotic disorder (schizophrenia (ICD11 6A20); delusional disorders (ICD11 6A24); schizoaffective disorder (ICD11 6A21)
2. History of substance-induced psychotic disorder (ICD11 6C40.6 Alcohol-induced psychotic disorder; ICD11 6C43.6 Opioid-induced psychotic disorder; ICD11 6C41.6 Cannabis-induced psychotic disorder; ICD11 6C42.6 Synthetic cannabinoid-induced psychotic disorder; ICD11 6C44.6 Sedative, hypnotic or anxiolytic-induced psychotic disorder; ICD11 6C45.6 Cocaine-induced psychotic disorder; ICD11 6C46.6 Stimulant-induced psychotic disorder including amphetamines, methamphetamine or methcathinone; ICD11 6C47.6 Synthetic cathinone-induced psychotic disorder; 6C49.5 Hallucinogen-induced psychotic disorder; ICD11 6C4B.6 Volatile inhalant-induced psychotic disorder; ICD11 6C4C.6 MDMA or related drug-induced psychotic disorder, including MDA; ICD11 6C4D.5 Dissociative drug-induced psychotic disorder including Ketamine or PCP; ICD11 6C4E.6 Psychotic disorder induced by other specified psychoactive substance)
3. Recurrent depressive disorder with a history of attempted suicide (ICD11 6A71)
4. Bipolar disorder (ICD11 6A60)
5. Severe personality disorder judged to be contributing to impaired social function by the physician reviewing eligibility (ICD11 6D10.2)
6. Disorders of Intellectual Development (defined as moderate intellectual disabilities (ICD11 6A00.1); severe intellectual disabilities (ICD11 6A00.2); profound intellectual disabilities (ICD11 6A00.3))
7. Autism Spectrum Disorders with exception of ICD11 6A02.0 Autism spectrum disorder without disorder of intellectual development and with mild or no impairment of functional language
8. Significant cognitive impairment as judged at the discretion of the physician reviewing eligibility
9. Pregnancy or absence of an acceptable method of contraception
10. Contraindications to neurosurgery (such as brain abnormalities, haemostasis disorder or contraindication to MRI) or anaesthesia
11. Severe intercurrent pathology and any other disease that could interfere with the protocol or compromise life expectancy, in the Investigator’s judgement

12. Continued participation in any other interventional clinical trials
13. Any other implanted electronic devices such as implantable cardioverter defibrillators (ICD), permanent pacemakers (PPM) and drug pumps

Date of first enrolment
01/02/2022

Date of final enrolment
30/07/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
National Hospital for Neurology & Neurosurgery
Queen Square
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Study participating centre
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR129340

Results and Publications

Individual participant data (IPD) sharing plan
1. The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository
2. The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Stored in non-publicly available repository, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No