Op-TICS

UCL COMPREHENSIVE CLINICAL TRIALS UNIT

Double blind comparison of optimised Deep Brain Stimulation for severe Tourette syndrome (Op-TICS)

Version	2.0
Date	22 Dec 2021
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2018/321
Trial registration	*ISRCTN Registration TBC*
REC #	IRAS 300541

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1 Administrative information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 5. It describes the Op-TICS clinical investigation, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering patients into the clinical investigation, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, clinical investigation population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the clinical investigation; replication of key aspects of clinical investigation methods and conduct; and appraisal of the clinical investigation's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the clinical investigation. Sites entering patients for the first time should confirm they have the correct version through a member of the trial team at CCTU.

CCTU supports the commitment that its clinical investigations adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials (1). The SPIRIT Statement Explanation and Elaboration document (2) can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The clinical investigation will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) UK Policy Framework for Health and Social Care. Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

1.1.1 Reporting Deviations from the Clinical Investigation Plan

Participating sites will inform CCTU as soon as they are aware of deviations from the Clinical Investigation Plan (CIP), so that the CCTU can fulfil its requirement to report all deviations to the MHRA as soon as they have occurred. Details about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective actions should be provided by email to the MHRA (devices.regulatory@mhra.gov.uk) as soon as possible.

Any deviations from the CIP which affect the rights, safety and well-being of participants will be reported to the relevant Ethics Committee by the CCTU as soon as possible.

1.1.2 Reporting Serious Breaches

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary, within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the clinical investigation, or
- The scientific value of the clinical investigation.

Note: An increase in protocol deviations in relation to the coronavirus pandemic will not constitute a serious breach, therefore there is no requirement to report this to the MHRA unless participants are being put at risk.

1.2 Sponsor

UCL is the clinical investigation sponsor and has delegated responsibility for the overall management of the Op-TICS clinical investigation to CCTU. Queries relating to UCL sponsorship of this clinical investigation should be addressed to the CCTU Director or via the Trial Team.

1.3 Structured clinical investigation summary

Primary Registry and Clinical investigation Identifying Number	TBC
Date of Registration in Primary Registry	TBC
Secondary Identifying Numbers	UCL R&D ID #: 123088 CCTU Ref #: CTU/2018/321 IRAS Ref #: 300541
Source of Monetary or Material Support	National Institute for Health Research Efficacy and Mechanism Evaluation programme (NIHR129340)
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	UCL Comprehensive Clinical Trials Unit, 90 High Holborn, 2nd Floor, London, WC1V 6LJ cctu.optics@ucl.ac.uk cctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Professor Patricia Limousin Professor of Neurology Department of Clinical and Movement Neurosciences Queen Square Box 146 London WC1N 3BG p.limousin@ucl.ac.uk
Public Title	Optimisation of deep brain stimulation in reducing TICS in patients with severe Tourette Syndrome (Op-TICS)
Scientific Title	Double blind comparison of optimised Deep Brain Stimulation for severe Tourette Syndrome
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Tourette Syndrome
Intervention(s)	All participants will have electrodes implanted in the globus pallidus interna and connected to a subcutaneous pulse-generator. This will be followed by a 6 months open-phase period of stimulation for electrical parameter adjustment. Following these 6 months, participants will be randomised into two groups by the order of treatment condition (ON/OFF-stimulation vs OFF/ON-stimulation): one group will be kept with the stimulation on **("ON-stimulation")** and the other switched off **("OFF-stimulation")** for up to two weeks. Tic severity will be assessed and all participants will enter a 2-day interval, in the ON state, before switching to the other treatment condition for another two weeks.
Key Inclusion and Exclusion Criteria	**Inclusion criteria** Adult patients aged 18 and over: 1) with chronic, severe, treatment refractory Tourette Syndrome, as defined by a Yale Global Tic Severity Scale score >50/100. 2) with 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. 3) who have provided agreement to participate and written informed consent. **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; 6C43.6; 6C41.6; 6C42.6; 6C44.6; 6C45.6; 6C46.6; 6C47.6; 6C49.5; 6C4B.6; 6C4C.6; 6C4D.5; 6C4E.6). 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.
Study Type	Early phase, randomised, double-blind, crossover clinical investigation
Planned Date of First Enrolment	Feb 2022
Target Sample Size	20
Primary Outcome(s)	Tic severity score, measured by the Yale Global Tic Severity Scale – Total Tic Score, at the end of the OFF-stimulation state versus the end of the ON-stimulation state in the blinded randomised phase of the clinical investigation.

Key Secondary Outcomes	• Modified Rush Video Rating Scale at the end of the OFF-stimulation state versus the end of the ON-stimulation state in the blinded randomised phase. • Change in the Modified Rush Video Rating Scale between baseline 0 (before surgery) and the end of the open-phase (baseline 1). • Change in the Yale Global Tic Severity Scale between baseline 0 and the end of the open-phase (baseline 1). • Change in the Gilles de la Tourette syndrome quality of life questionnaire measures at baseline 0 and the end of the open-phase (baseline 1). • Change in the Yale-Brown Obsessive Compulsive Scale between baseline 0 and the end of the open-phase (baseline 1). • Change in the Beck Depression Inventory scale between baseline 0 and the end of the open-phase (baseline 1). • Change in the Beck Anxiety Inventory scale between baseline 0 and the end of the open-phase (baseline 1). • Change in the Barkley Adult ADHD Rating Scale – IV between baseline 0 and the end of the open-phase (baseline 1). • Safety of DBS as indicated by the number of participants with any adverse events and number with any serious adverse events.

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Prof Patricia Limousin	UCL Institute of Neurology	Chief Investigator
Prof Tom Foltynie	UCL Institute of Neurology	Professor of Neurology (Co-Applicant)
Prof Eileen Joyce	UCL Institute of Neurology	Professor of Neuropsychiatry (Co-Applicant)
Prof Ludvic Zrinzo	UCL Institute of Neurology	Professor of Functional Neurosurgery (Co-Applicant)
Dr Kate Maclagan	UCL CCTU	Clinical Project Manager (Co-Applicant)
Mrs Kashfia Chowdhury	UCL CCTU	Senior Statistician (Co-Applicant)
Miss Norin Ahmed	UCL CCTU	Trial Statistician
Ms Marisa Chau	UCL CCTU	Clinical Project Manager
Mrs Lisa French	UCL CCTU	Trial Manager

1.4.2 Role of clinical investigation sponsor and funders

Name	Affiliation	Role
UCL	UCL	Clinical investigation Sponsor
Prof Nick Freemantle	UCL CCTU	Sponsor duties have been delegated to UCL CCTU by UCL. The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the clinical investigation. A Clinical Project Manager at the UCL CCTU will oversee the Trial Manager who will be responsible for the day-to-day management of the clinical investigation and providing support to the site staff. The CCTU staff will be involved in approaching sites, case report form development, database construction, protocol and patient information in collaboration with the Trial Management Team.
Delegated NIHR Programme Manager	NIHR EME Programme	Clinical investigation Funder

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Prof Patricia Limousin	UCL Institute of Neurology	Chief Investigator
Mrs Kashfia Chowdhury	UCL CCTU	Senior Statistician (Co-Applicant)
Miss Norin Ahmed	UCL CCTU	Trial Statistician
Ms Gemma Jones	UCL CCTU	Head of Clinical Trial Operations (Co-Applicant)
Miss Grace Auld	UCL CCTU	Clinical Project Manager
Ms Atiyyah Moosa	UCL CCTU	Trial Manager
Miss Lakhvinder Banga	UCL CCTU	Data Manager

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Prof Patricia Limousin	UCL Institute of Neurology	Chief Investigator – chair
Prof Thomas Foltynie	UCL Institute of Neurology	Professor of Neurology (Co-Applicant) – member
Prof Eileen Joyce	UCL Institute of Neurology	Professor of Neuropsychiatry (Co-Applicant) – member
Prof Ludvic Zrinzo	UCL Institute of Neurology	Professor of Functional Neurosurgery (Co-Applicant) – member
Dr Harith Akram	National Hospital for Neurology and Neurosurgery	Consultant Neurosurgeon (Co-Applicant) – member
Dr Himanshu Tyagi	University College London Hospitals NHS Foundation Trust	Consultant Neuropsychiatrist (Co-Applicant) – member
Prof Monty Silverdale	Salford Royal NHS Foundation Trust	Consultant Neurologist (Co-Applicant) – member
Dr Jeremy Stern	St George's Hospital	Consultant Neurologist (Collaborator) – member
Dr Timothy Harrower	Royal Devon & Exeter Foundation Trust	Consultant Neurologist (Collaborator) – member
Ms Gemma Jones	UCL CCTU	Head of Clinical Trial Operations (Co-Applicant)
Miss Grace Auld	UCL CCTU	Clinical Project Manager– member
Mrs Kashfia Chowdhury	UCL CCTU	Senior Statistician (Co-Applicant) – member
Miss Norin Ahmed	UCL CCTU	Trial Statistician- member
Ms Atiyyah Moosa	UCL CCTU	Trial Manager- member and facilitator
Miss Lakhvinder Banga	UCL CCTU	Data Manager – member and facilitator

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Dr Alan Whone	University of Bristol	Independent chair
Professor Patricia Limousin	UCL Institute of Neurology	Non-independent – Chief Investigator
Prof Keith Matthews	University of Dundee	Independent member
Ms Anna Bhandari	Patient Representative	Independent member
Prof Nicholas Jewell	London School of Hygiene &	Independent statistician

	Tropical Medicine	

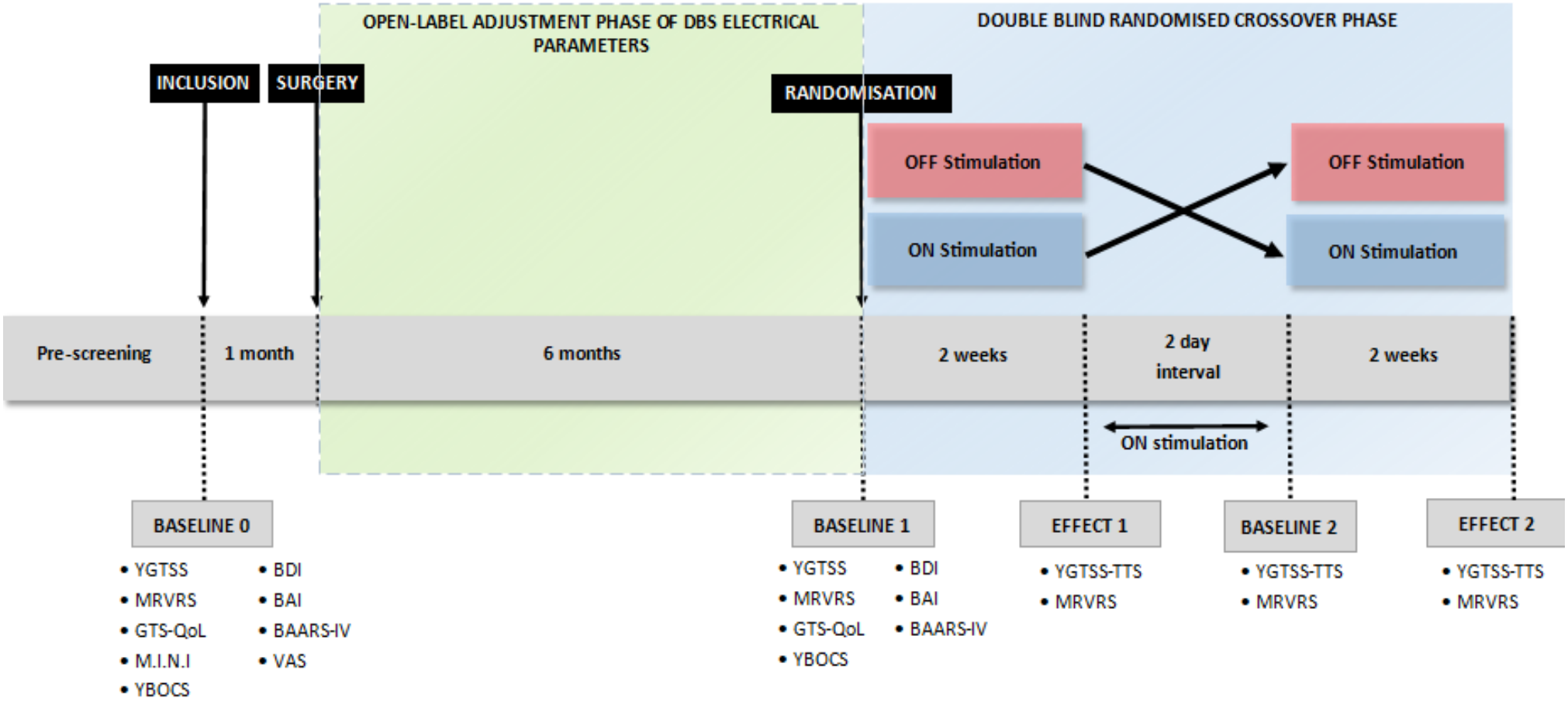
1.4.6 Independent Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Dr Paul Shotbolt	Kings College London	Independent chair
Prof Marie-Laure Welter	Rouen University Hospital	Independent member
Dr Francesca Fiorentino	Imperial College London	Independent statistician

1.4.7 Patient and Public Involvement (PPI) Group

Name	Role and responsibilities
Ms Anna Bhandari	Member
Ms Christine Sharp	Member
Mr Stuart Boyce	Member
Anonymous member	Member

2 Clinical investigation Diagram



3 Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
BAARS-IV	Barkley Adult ADHD Rating Scale – IV
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CCTU	Comprehensive Clinical Trials Unit
DBS	Deep Brain Stimulation
DSUR	Development Safety Update Report
EME	Efficacy and Mechanism Evaluation
EU	European Union
GCP	Good Clinical Practice
GTS-QOL	Gilles de la Tourette syndrome Quality of Life
HRA	Health Research Authority
ICD11	11th revision of the International Statistical Classification of Diseases and Related Health Problems
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ITT	Intention to Treat
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini-International Neuropsychiatric Interview
MRVRS	Modified Rush Video Rating Scale
NHNN	National Hospital for Neurology and Neurosurgery
NIHR	National Institute for Health Research
OCD	Obsessive-compulsive disorder
PI	Principal Investigator
PIS	Patient Information Sheet
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
REC	Research Ethics Committee
R&D	Research and Development
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSA	Site Specific Approval
SMF	Statistical Master File
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TS	Tourette Syndrome
TSC	Trial Steering Committee
UCL	University College London
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
YBOCS	Yale-Brown Obsessive Compulsive Scale
YGTSS (Global)	Yale Global Tic Severity Scale
YGTSS-TTS (Total Tic)	Yale Global Tic Severity Scale - Total Tic Score

4 Glossary

Barkley Adult ADHD Rating Scale – IV (BAARS-IV):
BAARS-IV is a tool used to assess current ADHD symptoms and domains of impairment as well as recollections of childhood symptoms (3)

Beck Anxiety Inventory (BAI):
The BAI is a self-report rating inventory that measures the severity of anxiety symptoms (4,5)

Beck Depression Inventory (BDI):
The BDI is a self-report rating inventory that measures the severity of symptoms of depression (6)

Gilles de la Tourette syndrome Quality of Life (GTS-QoL):
The GTS-QOL is a disease-specific patient-reported scale for the measurement of health-related quality life in patients with Gilles de la Tourette syndrome (7)

Mini International Neuropsychiatric Interview (M.I.N.I.):
The M.I.N.I is a brief structured diagnostic interview for psychiatric disorders (8).

Modified Rush Video Rating Scale (MRVRS):
The MRVRS is a rating scale of five domains of tic disability. Two body views of the participant are recorded (full frontal and head and shoulders only), once with the participant and examiner in the room and once with the participant alone. The recordings of the participant alone are scored (9).

Programmers:
The programmers will be two delegated neurologists responsible for the adjustment of the electrical parameters of DBS during the open phase when the settings are being optimised. They will also be responsible for setting the parameters in the blinded phase – ON-stimulation or OFF-stimulation. The programmers will be unblinded throughout the clinical investigation and will not be involved in the rating.

Tourette Syndrome Visual Analogue Scale (VAS):
This is a numerical symptom severity rating scale, designed for use in the outpatient clinic at the National Hospital for Neurology and Neurosurgery. The scale is 0-10 where 0 indicates the patient has no symptoms and 10 would imply that the symptoms are at their worst severity. This will be used by the programmers, during the optimisation adjustment phase, as an informal tool to aid the adjustment of the electrical parameters of DBS.

Women of Child-Bearing Potential (WOCBP):
WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilisation (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or who are not post-menopausal (post-menopause is defined as amenorrhea for 12 consecutive months, without another medical cause).

WOCBP must be using an acceptable method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimised.

Acceptable methods of contraception:

- Hormonal contraceptives (e.g. oral, patch, injection medications).
- Double barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide).

- Intrauterine device.
- Male partner has had a vasectomy.
- Total abstinence from intercourse with male partners. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), occasional abstinence and withdrawal are not acceptable methods of contraception.

WOCBP must have a negative urine pregnancy test result at the point the participant is hospitalised in advance of the DBS surgery.

Yale-Brown Obsessive Compulsive Scale (Y-BOCS):
The Y-BOCS is a clinician-rated interview to assess the severity of obsessions and compulsions in people with obsessive-compulsive disorder (OCD) (10).

Yale Global Tic Severity Scale (YGTSS Global):
The YGTSS (global) is a clinician-rated scale used to assess tic severity over the prior week. It includes a checklist of motor and vocal tics followed by an assessment of the number, frequency, intensity, complexity and interference, each scored 0-5 and giving a total motor tic score of 0-25, a total phonic tic score of 0-25 and therefore a total tic score (TTS) of 0-50 The impairment of motor tics and phonic tics on daily life is scored separately from 0-50 (11).

Yale Global Tic Severity Scale –Total Tic Score (YGTSS-TTS, Total Tic):
The YGTSS-TTS (total tic) is a sub-domain of the YGTSS (Global) reporting only the total tic score of 0-50.

5 Introduction

5.1 Background and Rationale

Tourette syndrome (TS) is a neuropsychiatric disorder with onset in childhood, associated with the presence of multiple motor tics and at least one phonic tic, persisting for more than one year. It is common, affecting 0.6% to 1% of school children and for the majority of individuals, it diminishes approaching adulthood. Nevertheless, 25% of patients have moderate or severe tics that do not remit (12). When tics are distressing, behavioural therapy and/or medications may provide adequate symptom control (13–15). There is, however, a small number of patients with very severe tics who have been unresponsive to conventional treatments and suffer a major negative impact on physical and social functioning and quality of life. They often have self-injurious behaviours and/or violent tics that can cause significant injury, such as to the spinal cord (16). Comorbid obsessive-compulsive disorder (OCD) and/or attention deficit disorder (ADD) are common, and patients are at a four-fold increased risk of completed suicide (17). TS can prevent effective communication and can disrupt all attempts to engage in social interaction and employment (13).

The most recent estimates of UK prevalence come from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort when 6768 parents of 13-year-olds were interviewed (18). Using narrow or intermediate definitions, this was 0.3 or 0.7% for Tourette's and 0.5 or 1.1% for chronic tic disorders. This is comparable to a meta-analysis of 21 smaller international population-based studies which calculated prevalence as 0.52% (19).

Behavioural therapy, in particular Comprehensive Behavioural Intervention for Tics (CBIT) is a proven effective treatment; nevertheless, less than half of the patients show a positive response to this therapy (14). The mainstay of medical treatment is neuroleptic medications such as haloperidol, risperidone and aripiprazole; however, not all patients are improved and many suffer from adverse events such as weight gain, sedation and involuntary movements (15). Clonidine, benzodiazepines and topiramate are also frequently tried but have a limited efficacy in adults (15). Botulinum toxin injections can be useful for tics restricted to a focal body part but is of limited use in patients with severe widespread tics. Patients included in the study will have failed adequate attempts at treatment with standard pharmacological therapy at therapeutic doses and will have either not responded or been found not suitable for CBIT.

Patients with severe TS are in urgent need of more effective therapies. They are at risk of personal injury through severe tics or self-injurious behaviour. Compared to the general population, they are also at increased risk of completed suicide, premature death of any cause and cardiovascular and metabolic disorder (17,20,21). The combination of severe tics, depression, anxiety, OCD and ADD affects their quality of life and, for many of them, it limits social interaction and prevents access to most jobs. A large proportion of these patients are young adults who have time-limited opportunities to integrate into society and the workplace before they become irreversibly isolated and/or develop physical or mental health disabilities.

Deep Brain Stimulation (DBS) is a neurosurgical procedure involving the precise placement of two leads into deep structures within the brain using standard techniques that have been shown to have acceptable safety and tolerability profiles. These leads are connected to an implantable pacemaker, usually on the chest wall. The system can be programmed to deliver high frequency electrical

stimulation that initially requires optimisation (repeated adjustment for optimum benefit while avoiding unwanted effects). DBS is an accepted treatment for Parkinson's disease, dystonia and tremor. Worldwide, a small number of patients with TS have received DBS, mostly in the thalamus or the internal Globus Pallidum (GPi).

Interventions that can reduce the severity of tics, improving function and quality of life in this small population of patients are urgently needed. These patients face enormous day-to-day challenges as a result of physical tics and also the impact of tics on their mental health. Furthermore, these patients place a high demand on NHS resources as a result of injuries sustained following violent tics. Many are unable to work and therefore place a high demand on financial payments from social care budgets. The conspicuous and often very loud nature of tics can have negative effects on neighbours, local communities and family members leading to social isolation; they frequently need repeated re-housing and carers for support with daily activities.

Being able to reduce the frequency and severity of the tics and possibly other psychiatric co-morbidities could allow patients an improved quality of life and more independence.

5.2 Objectives

The **primary** objective is to assess whether GPi DBS is effective in reducing severe motor or vocal tics, measured with the YGTSS-TTS (total tic) (11), in a double-blind crossover setting, with the participants being on for two weeks (with the electrical parameters determined during 6 months optimisation phase) compared to being off for two weeks.

The **mechanistic** objective is to identify the factors which predict the degree of response to DBS in TS. These factors will include: 1) clinical factors: age, disease duration, tic severity (assessed by MRVRS) and comorbidity (YBOCS, BDI, BAI and BAARS-IV); 2) electrical factors: total electrical energy delivered & volume of tissue activated by stimulation; and 3) imaging: optimal sub-region(s) of the GPi/ GPe and fibre tracts exposed to the stimulation field in association with optimal clinical response.

5.3 Clinical investigation Design

All participants included in the study will be implanted with bilateral GPi DBS according to the surgical procedure used during a previous trial in Tourette Syndrome patients (22) and similar to the technique used for Parkinson's disease and dystonia (23). Surgery is performed under general anaesthesia with MRI-guided and MRI-verified targeting of the GPi.

We have planned a two-stage design, with an **open-label phase** including a 6-month period during which the electrical parameters of stimulation will be optimised for all participants. The optimisation involves testing the effect of stimulating the different contacts (the electrodes used in this study have 8 contacts) in the target area with gradual increase of the amplitude of stimulation and observing the clinical effect. An algorithm adapted from one used in the same target for dystonia will be used (24). Assessments, as detailed in the outcome measure section will be conducted at baseline 0, one month before surgery, and the end of the open phase of stimulation, 6 months after surgery (see the Clinical investigation Diagram).

The open phase will be followed by a **double-blind randomised crossover** phase during which all participants will experience two weeks OFF-stimulation and two weeks ON-stimulation using optimal

settings as determined during the optimisation phase. Two weeks is considered to be sufficient for the majority of any beneficial effects of DBS to wear off. Welter et al (25) reported that patients who were switched off for 72 hours experienced a 57.7% worsening of tics. Participants who did not improve in the open-label phase will also be included using the last setting tried. Participants will be randomised 1:1 to start either with stimulation ON or with stimulation OFF. The participants and the person conducting the assessments will be blinded to the stimulation conditions. There will be a 2-day interval where all participants will be ON-stimulation so that participants are programmed to their baseline setting, before crossing over to the other treatment condition. The 2-day interval is necessary to re-establish participants on their baseline level of tic control and allows them to start the second stimulation setting in a condition similar to baseline 1. It will also allow for any gradual increases in DBS settings to be performed if sudden switches are not tolerated. Participants who find a condition difficult to tolerate before the end of the 2 weeks will be reassessed and switched to the other condition sooner. Participants will be assessed at the start and at the end of each of the two treatment conditions. The main comparison will be between the scores at the end of the ON-stimulation versus the scores at the end of the OFF-stimulation condition during this randomised phase of the clinical investigation (see the Clinical investigation Diagram).

5.4 Risk/benefits: why is the research needed now?

A small but significant group of patients with severe TS have exhausted all the conventional treatments and are currently left without any further options. These patients face enormous day to day challenges as a result not only of physical tics but also the impact of tics on their mental health. Furthermore, these patients place a high demand on NHS resources as a result of injuries sustained following violent tics. Many are unable to work and therefore receive financial payments from social care budgets.

There is no access to DBS for TS in the UK. Further research to assess efficacy of DBS is therefore urgently needed. Potential complications associated with DBS surgery include haemorrhage and infection but the risk of these causing permanent harm is very low in this group of patients who are young (the majority of individuals with TS) and otherwise healthy (risk of bleeding in the brain resulting in stroke – less than 1 in 500 at the NHNN, which could lead to paralysis or even theoretically death – never occurred at the NHNN; 2% chance of infection; 1% chance of seizures). All participants will have routine MRSA and MSSA swabs performed pre-operatively to minimise the risk of infection through self-contamination and perioperative antibiotics (intravenous and topical) administered, as per infection prevention at the National Hospital for Neurology and Neurosurgery. This approach has significantly reduced the infection rates of DBS procedures.

6 Methods

6.1 Site Selection

The clinical investigation sponsor has overall responsibility for site and investigator selection and has delegated this role to CCTU.

6.1.1 Study Setting

The DBS procedure and all subsequent assessments will be performed at the National Hospital for Neurology and Neurosurgery (NHNN), London, UK.

6.1.2 Site/Investigator Eligibility Criteria

It is anticipated that patients will be identified across four UK sites. Two are dedicated Tourette Syndrome clinics providing assessment and management of adults (NHNN, UCLH Foundation Trust and St George's University Hospital NHS Foundation Trust). Two are Movement Disorder units with experience of managing patients with Tourette Syndrome (Salford Royal NHS Foundation Trust and Royal Devon and Exeter Foundation Trust).

Patient Identification Centres (PIC sites) will be used to facilitate recruitment: St George's, Salford and Exeter.

In addition, other centres, across the UK, who regularly refer patients with TS to the NHNN will be informed of this clinical investigation.

The NHNN has confirmed:

- Professor Limousin is willing and appropriate to take Principal Investigator responsibility
- There are suitably trained staff available to recruit patients, enter data and administer the rating scales and questionnaires
- There are suitably trained staff are familiar with the DBS procedure and stimulation modification

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

Professor Limousin will sign an Investigator Agreement to comply with the clinical investigation protocol (confirming specific roles and responsibilities relating to the clinical investigation, and that the NHNN is willing and able to comply with the requirements of the clinical investigation). This includes confirmation of appropriate qualifications, by provision of a CV, familiarity with the appropriate use of any investigational medical devices, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant clinical investigation related duties.

6.1.2.2 Resourcing at site

Professor Limousin is able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period. The NHNN has an adequate number of qualified staff and facilities available for the foreseen duration of the clinical investigation to enable them to conduct the clinical investigation properly and safely.

A delegation of responsibilities log will be completed and staff contact details will be provided.

The NHNN will have sufficient data management resources to allow prompt data return to CCTU.

6.2 Site approval and activation

On receipt of confirmation of capacity and capability, a signed Clinical Trial Site Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to Professor Limousin. The trial manager or delegate will notify the Professor Limousin in writing of the plans for site activation. Recruitment will not be permitted until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The NHNN must conduct the clinical investigation in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority(ies) (as appropriate), and which was given favourable opinion by the Research Ethics Committee (REC) and the Health Research Authority (HRA). Professor Limousin or delegate must document and explain any deviation from the approved protocol and communicate this to the trial team at CCTU.

6.3 Participants

6.3.1 Eligibility Criteria

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of inclusion into the clinical investigation. Questions about eligibility criteria should be addressed PRIOR to attempting to include the patient.

The eligibility criteria for this clinical investigation have been carefully considered and are the standards used to ensure that only medically appropriate patients are entered. Patients not meeting the criteria should not be entered into the clinical investigation for their safety and to ensure that the clinical investigation results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Patients will be considered eligible for enrolment in this clinical investigation if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

Adult patients aged 18 and over:

1) with chronic, severe, treatment refractory Tourette Syndrome, as defined by a Yale Global Tic Severity Scale score (YGTSS (global)) >50/100
2) with 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
3) who have provided agreement to participate and written informed consent

6.3.1.3 Participant 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.

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

The DBS surgery will be performed at the NHNN by neurosurgeons who have experience and expertise in DBS and imaging.

Neurologists, at the NHNN, will adjust the electrical parameters of DBS during the adjustment phase when the settings are to be optimised. They will also set the parameters during the randomised, blinded phase – ON-stimulation or OFF- stimulation. The neurologists will be unblinded throughout the clinical investigation.

A separate team of neuropsychiatrists at NHNN will collect the objective psychiatric scales during enrolment and, in the randomised blinded phase, will conduct the main outcome measure, the YGTSS-TTS (total tic).

6.3.1.5 Co-enrolment Guidance

Participants may not be enrolled in any other interventional clinical trials.

Co-enrolment on observational studies is allowed.

6.4 Study Visits

6.4.1 Pre-screening

Potential patients will mainly be identified and pre-screened from four UK centres (see section 6.1.2).

In addition, other centres who regularly refer patients with TS will be informed of this clinical investigation as well as the network of movement disorder centres and DBS centres. Tourettes Action will also be able to spread information regarding this clinical investigation to their members.

No study specific assessments will be performed. Sites will review the medical history of potential patients to assess eligibility. These patients will then be referred to the NHNN for further screening and inclusion (baseline 0).

6.4.2 Inclusion (baseline 0)

Written informed consent to enter and be randomised into the clinical investigation must be obtained from patients after explanation of the aims, methods, benefits and potential hazards of the clinical investigation and **BEFORE** any clinical investigation-specific procedures are performed, including a urine/serum pregnancy test if applicable. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care. Informed consent will be taken by delegated staff at the NHNN, as this is the centre where the DBS surgery and subsequent follow up visits will occur.

Participants will be asked if they have received a recent COVID-19 vaccination, or have one booked in the near future. The study team will need to take this into account when planning the date of the DBS neurosurgery.

6.4.3 DBS Neurosurgery

All participants will undergo bilateral GPi DBS surgery with the Vercise™ DBS leads that include 8 contacts at the tip and Vercise Gevia™ device, provided by Boston Scientific.

Participants will be admitted to the NHNN where it is anticipated they will stay for up to 14 nights. Prior to the DBS surgery routine blood tests, pre-surgery checks and surgical consent will occur as per standard of care. For applicable participants a urine/serum pregnancy test will be repeated.

The DBS device consists of three implantable components:

1) **Lead** – a thin insulated wire, 1.3mm in diameter, with eight contacts at the tip that is implanted in the brain

2) **Extension –** a thin insulated wire that is threaded under the skin from the head, down the neck and into the upper chest. The lead is connected to the extension.

3) **Neurostimulator –** a small, sealed device, similar to a cardiac pacemaker, that contains a rechargeable battery and electronics. The neurostimulator is implanted beneath the skin on the chest wall. It produces the electrical pulses needed for stimulation. These electrical pulses are delivered through the extension and lead to the GPi in the brain.

Dimensions:
Height: 5.13 cm
Width: 4.60 cm
Depth: 1.08 cm

The DBS neurosurgical procedure will follow that used for routine NHS treatments at the NHNN as per the CE marked indication of the device (26). The lead is implanted in the GPi, by a neurosurgeon, under general anaesthetic. A stereotactic frame is attached to the head and a high-resolution magnetic resonance imaging (MRI) scan will be used to visualise the target. Target coordinates will be calculated for each participant. Two leads are inserted through small holes drilled through the skull and implanted in the targeted site, the GPi. Once the lead has been placed at the target site, the extension wires and neurostimulator are implanted. Another MRI will be performed before the frame is removed to verify accurate electrode location (27).

An incision of about 3 inches and a pocket are made under the collarbone, just under the skin in which to implant the neurostimulator. An extension is passed under the skin of the scalp and neck, to the chest to connect the lead to the neurostimulator.

6.4.4 Optimisation Adjustment phase (open-label)

Neurologists, at the NHNN, will adjust the DBS settings, over a 6-month period to ensure optimisation of the electrical parameters. Participants will be asked to return to the hospital monthly, as required, during this phase of the clinical investigation. The number of visits will be adapted according to the response of the participants. This 6-month period allows the best contact to be selected and the amplitude of stimulation to be increased gradually to ensure the benefit of the setting has time to appear. The stimulation is adjusted non-invasively and transmitted to the neurostimulator via radio telemetry.

During the optimisation phase an algorithm will be followed that was derived from one developed to treat dystonia with GPi DBS (24). This algorithm will allow the neurologists to stimulate the contacts in the target area sequentially to define the optimal one. The amplitude of stimulation, pulse width and frequency will also be adjusted.

Participants who did not improve in the adjustment phase will still be included in the blinded phase. The ON-stimulation setting used will be the last setting tried.

During this phase of the study, participants will be asked to complete a Tourette Syndrome VAS to report on the severity of symptoms experienced since the last clinic visit. The participants will complete this at home prior to their adjustment visits. The information captured will help inform the programmers as to the adjustments required to optimise the electrical parameters.

6.4.5 Double-blind, randomised crossover phase

After completion of the Optimisation Adjustment phase, the participants will be randomised 1:1 into two groups: by the order of treatment condition:

- **"ON/OFF-stimulation"** where this group will have the stimulator switched on for two weeks followed by off, or
- **"OFF/ON-stimulation"** where this group will be switched off for two weeks followed by on.

They will be in each treatment condition for the duration of up to two weeks.

Following two weeks of the first condition, participants will have a 2-day interval (where all participants will be ON-stimulation) before they cross over to the other treatment condition, for up to another two weeks. Baseline parameters will be reinstated as clinically appropriate.

The delegated neurologists (programmers), who are unblinded to the order of treatment condition, will be responsible for setting the electrical parameters in this phase.

The neuropsychiatrists, who are blinded to the ON/OFF stimulation condition, will administer the rating scales during this phase. If possible, participants should be reviewed by the same neuropsychiatrist throughout the course of the clinical investigation.

Participants who find the randomised condition they are allocated difficult to tolerate before the end of the two weeks will be re-assessed and, if needed, will be switched to the other treatment condition sooner. This will be decided according to the clinical judgement of the blinded assessors taking into account the physical and mental health of the participants.

6.4.6 Neurostimulator charging

6.4.6.1 Optimisation Adjustment phase

Participants will perform the recharging of the neurostimulator, during the Optimisation Adjustment phase. Comprehensive training will be provided by the site as well as an instruction sheet for the participant to take home.

6.4.6.2 Double-blind, randomised crossover phase

The recharging of the neurostimulator during the double-blind crossover phase will be performed by an unblinded DBS nurse, twice a week, for both ON and OFF periods. Participants will be asked to return their chargers to the hospital at the baseline 1 visit. A phone call will be made to participants before this visit to remind them of this requirement.

In the ON condition charging will proceed for a fixed duration of 1 hour. For the OFF condition, after the initial connection, the charger will be off but will stay in place for the hour. The nurse will be present for the whole duration.

Participants will have the option to be hospitalised at the NHNN for this phase of the clinical investigation. If this is not possible and the participant is unable to travel to London for the charging visits then it may be possible for the unblinded DBS nurse to perform home visits.

The chargers will be returned to the participants at the end of this phase of the clinical investigation, at effect 2 visit.

To ensure the process of charging in this period maintains the blind, the Blinded Charging Plan is to be referred to.

6.4.7 COVID-19 mitigation

In case of a national lockdown due to the COVID-19 pandemic whilst the study is active, the COVID-19 Mitigation Plan is to be referred to for current and future participants.

6.4.8 Concomitant Care

Any medications the participants are being treated with at the time of enrolment will be kept stable, as much as possible, during the course of the clinical investigation unless there is a clinical reason to change them.

Any concomitant medication administered during the clinical investigation will be captured on the Concomitant Medication Log for each participant.

6.4.9 Completion of the clinical investigation

Attending the Effect 2 visit signals the participants completion of the clinical investigation. The DBS devices will remain in place and stimulation will continue, as per standard of care, unless it is found to be ineffective or participants wish to have it removed. The type of device we are planning to use should last 25 years. After the clinical investigation, the device will be regularly monitored at routine NHS clinic visits. Patients will be managed jointly by their local Tourette Syndrome consultant and a DBS specialist, as per standard of care.

6.4.10 Protocol Treatment Discontinuation

In consenting to the clinical investigation, patients are consenting to clinical investigation treatment, clinical investigation follow-up and data collection. However, an individual patient may stop the clinical investigation early or be stopped early for any of the following reasons:

- Unacceptable device/surgery complications or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant

As participation in the clinical investigation is entirely voluntary, the participant may choose to discontinue clinical investigation treatment at any time without penalty or loss of benefits to which they would otherwise be entitled.

Although not obliged, a reasonable effort should be made to establish the reason for discontinuation, whilst remaining respectful of the participant's rights.

The investigator will discuss the options regarding the DBS device. The participant can decide to retain the device in the ON-stimulation state, retain the device in the OFF-stimulation state or have the device removed.

Participants who discontinue protocol treatment, for any of the above reasons, should be encouraged to remain in the clinical investigation for the purpose of follow up and data collection.

6.5 Outcomes

6.5.1 Primary Outcomes

The primary outcome measure is the tic severity score measured by the YGTSS-TTS (total tic) after two weeks OFF-stimulation versus two weeks ON-stimulation in the double-blind randomised crossover phase (11).

The YGTSS (global) is a clinician-rated scale used to assess tic severity over the prior week. It includes a checklist of motor and vocal tics followed by an assessment of the number, frequency, intensity, complexity and interference, each scored 0-5 and giving a total motor tic score of 0-25, a total phonic tic score of 0-25 and therefore a total tic score (TTS) of 0-50. The impairment of motor tics and phonic tics on daily life is scored separately from 0-50 (11). The TTS has been chosen as it is commonly used in clinical trials for TS. It has been demonstrated that a 25% reduction of the YGTSS-TTS (total tic) is highly indicative of a positive response to a treatment (28).

6.5.2 Secondary Outcomes

Secondary outcomes will include:

- MRVRS at the end of the OFF-stimulation state versus the end of the ON-stimulation state in the blinded, randomised crossover phase.
- Change in the MRVRS between baseline 0 and the end of the open-phase (Baseline 1)
- Change in the YGTSS (global) between baseline 0 and the end of the open-phase (Baseline 1)
- Change in the GTS-QOL questionnaire measures at baseline 0 and the end of the open-phase (Baseline 1)
- Change in the YBOCS between baseline 0 and the end of the open-phase (Baseline 1)
- Change in the BDI scale between baseline 0 and the end of the open-phase (Baseline 1)
- Change in the BAI scale between baseline 0 and the end of the open-phase (Baseline 1)
- Change in the BAARS-IV between baseline 0 and the end of the open-phase (Baseline 1)
- Safety of DBS as indicated by the number of participants with any adverse events and number with any serious adverse events.

6.5.3 Mechanistic Outcomes

A mechanistic part of the study will look at possible explanations of differing responses in both the open and randomised phase. In our previous study, the percentage change in tics ranged from 3% worsening to 57% improvement during the blinded phase (22).

To identify the factors which predict the degree of response to DBS in TS we will be looking at the role of:

- clinical factors: age, disease duration, tic severity at baseline (MRVRS), co-morbidity (i.e. YBOCS, BDI, BAI and BAARS-IV)

- electrical parameters of stimulation (total electrical energy delivered & volume of tissue activated by stimulation)
- imaging (contact position and relation with anatomic structures and MRI brain connectivity maps as we have previously done in patients with Parkinson's disease undergoing DBS (29,30)).

6.6 Table of Assessments

	Pre-screening	Baseline 0	Surgery	Optimisation Adjustment Phase					Baseline 1				Effect 1		Baseline 2				Effect 2
		0d	28 days	(168 days)					196 days (R1)				210 days (R14)		213 days (R17)				227 days (R31)
Flexibility of schedule			-14/+14 days	+/- 14 days					+/- 14days				+/- 2 days						
Visit number		1	2	3A[a]	3B[a]	3C[a]	3D[a]	3E[a]	4	4A[b]	4B[b]	4C[b]	5		6	6A[b]	6B[b]	6C[b]	7
Informed consent		X												2-DAY INTERVAL (ON-STIMULATION) THEN CROSSOVER					
Review of past medical history	X																		
Review of TS medication history	X																		
Pregnancy test[c]		X	X																
Check for surgical contraindications	X	X	X																
MRI		X[d]	X[e]																
Provision of Participant Safety Card		X																	
Provision of TS VAS		X																	
Review of TS VAS				X	X	X	X	X											
YGTSS (global)		X							X										
YGTSS-TTS (total tic)													X		X				X
MRVRS		X							X				X		X				X
GTS-QoL		X							X										
M.I.N.I		X																	
YBOCS		X							X										
BDI		X							X										
BAI		X							X										
BAARS-IV (current and childhood symptoms)		X																	
BAARS-IV (current symptoms)									X										
Electrode Implantation			X																
Adjustment of DBS electrical parameters			X[f]	X	X	X	X	X											

Review of concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Review of AEs			X	X	X	X	X	X	X	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]	X[g]
Phone call to the participant									X[h]										
Neurostimulator Charging[i]									X	X	X	X	X		X	X	X	X	X
Recording of optimised electrical parameters									X										
Recording of best contacts(s)									X										
Randomisation									X[j]										

[a] the 4 weekly visits during the adjustment phase only take place if required for optimisation of the electrical parameters

[b] during the ON-stimulation and OFF-stimulation states the participant is to attend clinic, two times a week, for the device to be charged by a member of the unblinded team

[c] following the urine/serum pregnancy test at the surgery visit, participants are asked to self-report pregnancies in the Optimisation adjustment phase and the double-blind randomised crossover phase

[d] structural and connectivity MRI scan will be obtained pre op for screening and connectivity analysis

[e] MRI to be performed pre-surgery and during the surgery, to confirm the placement of the electrodes

[f] optimisation adjustment will begin after the surgery, whilst the participant remains in hospital

[g] Adverse events are to be assessed by members of the blinded site team

[h] before the participant attends for baseline 1, a member of the site team will phone to remind them to return the stimulator charger at the visit

[i] charging during the optimisation adjustment phase will be performed by the participant at home, twice weekly.

[j] randomisation to occur after completion of the baseline rating scales and assessments

6.6.1 Early Stopping of Follow-up

If a participant chooses to discontinue their clinical investigation treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole clinical investigation, even though they no longer take the clinical investigation treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected, and the participant withdrawn entirely from the clinical investigation.

CCTU should be informed of the withdrawal in writing using the appropriate CRF. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Participants who stop clinical investigation follow-up early will not be replaced.

6.6.2 Loss to Follow-up

Every effort will be made by the sites to continue to follow up recruited participants and minimise loss to follow up. Only participants that cannot be contacted via their own contact details, via General Practitioner or their local consultant will be deemed “lost to follow up”. Consent for this will be sought prior to the patient entering the clinical investigation.

6.6.3 Clinical investigation Closure

The end of the clinical investigation for individual participants will be the date of their last visit.

Clinical investigation closure is defined as the date when all data has been received, cleaned and all data queries resolved at all sites.

The MHRA and REC will be notified within 90 days of clinical investigation completion. A summary report of the research will be sent to the MHRA and REC within 12 months of the end of the clinical investigation.

The funder will be provided a final report at the end of the clinical investigation.

6.7 Sample Size

The primary outcome, YGTSS-TTS (total tic) is a subpart of the YGTSS (global) and is measured on a scale of 0 to 50. In a previous randomised study the mean difference (SD) in the off versus on state was 5.46 (7.02) points during the blinded phase (22). In the open phase of this clinical investigation when the stimulator were fully optimised, the observed difference was 15.66 (9.70) points (22). In the proposed study design the evaluation of the primary outcome will be in the blinded phase but as the optimisation period is longer, we expect an increased effect size.

A sample size of 12 participants would be required to detect a difference of 10 points in the YGTSS-TTS (total tic) scale with 90% power, assuming a SD of 9.70 of the differences between OFF and ON states. We expect in that group a baseline YGTSS-TTS (total tic) of 40, therefore a reduction of 10 points would correspond to 25% that is highly predictive of a positive response to a treatment (28). A rate of withdrawal is expected, with some participants not wanting to be randomised and therefore having to spend up to 2 weeks with the stimulation switched off. Therefore, assuming a conservative attrition rate of 40%, we will need a **total sample size of 20 participants** to detect this difference. All calculations use a two-sided alpha of 0.05 (22,25,28).

6.8 Recruitment and Retention

6.8.1 Recruitment

The clinical investigation will recruit patients over a period of approximately 20 months.

Patients will be identified at four sites across England, with experience in managing TS. Patients not based at NHNN will be referred to the NHNN where the surgery, adjustment of the electrical parameters during the open phase, randomisation stages, and data collection will take place.

In addition, other centres, across the UK can refer patients with TS to the NHNN.

6.8.2 Retention

The importance of complete follow up and clinical investigation completion will be explained to all potential participants at the inclusion visit. Patients likely to have difficulty adhering to the clinical investigation protocol will not be recruited. The clinical team will make every effort to establish good relationships with clinical investigation participants from the first contact to maximise retention.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

A randomisation list of order of treatment condition (ON/OFF-stimulation vs OFF/ON-stimulation) will be computer generated by an independent statistician at the CCTU, and will be held securely in the Statistical Master File (SMF). The random permuted block method with random block sizes will be used to generate the list. The list will contain the order of treatment condition as the allocated treatment and an associated unique treatment code.

At baseline 1, the clinical investigator will contact the independent statistician at the CCTU, who will then allocate the participant to an order of treatment condition based on the next available treatment code on the randomisation list. The statistician must ensure that the treatment code has not already been allocated to a participant. The statistician will also send an email to the clinical investigator immediately after the phone call, to confirm the allocated treatment code and the associated order of treatment condition. Once randomisation is confirmed, the statistician will update the randomisation list to make a note of the used treatment code. The unblinded investigator will apply the randomised order of treatment condition on the participant based on the information provided by the statistician.

The trial team, trial statistician, participants and clinical raters are to remain blinded to order of treatment condition at all times. The email confirmation of treatment allocation will be held securely by the investigator and the independent statistician.

6.9.1.2 Allocation concealment mechanism

The unique treatment code allocated to the participant at the baseline 1 visit will be revealed to the investigator by an independent statistician at the CCTU who is not part of the trial team. The unblinded investigator will know the order of treatment condition (i.e. OFF/ON-stimulation or ON/OFF-stimulation) the participant has been allocated to from the phone call and from a confirmatory email

sent by the statistician. All other clinical investigators and raters will remain blinded to the order of treatment condition. The unblinded investigator will use the unique treatment code on CRFs and all relevant documents to ensure blind is maintained throughout the clinical investigation period.

6.9.1.3 Allocation Implementation

The responsibility for enrolling patients and prescribing clinical investigation intervention to them lies with the CI. Eligibility decisions will be made in line with the approved protocol. Other physicians employed at the same clinical site may enrol and prescribe clinical investigation intervention to participants only if they have received appropriate training on the clinical investigation and appear on the Op-TICS Clinical investigation Delegation log and signed off by the CI.

6.9.2 Blinding

Processes will be put in place to ensure the blinding of participants during the randomised phase. Occasionally participants can experience a transient (few seconds only) sensation when DBS is switched “ON”. To prevent this sensation potentially unblinding the participant to the randomisation sequence, the programmers will start each crossover period by a brief OFF/ON to ensure the participants have the same experience before each condition.

Recharging of batteries will be performed by an unblinded DBS nurse for one hour twice a week for both ON and OFF periods. The nurses will connect the charger to the pulse generator in a similar way. In the ON-stimulation group the charging will proceed for a fixed duration of one hour. For the OFF-stimulation group after the initial connection the charger will be “OFF” (i.e. power not switched on) but will stay in place for the same duration. The nurse will be present for the whole duration. We have tested that this process can effectively blind the charging process.

Due to the nature of the intervention, the delegated programmers who will be responsible for setting the electrical parameters of the stimulators in this phase will also be unblinded to the treatment condition.

The raters will be blinded to the treatment condition and will not have been involved in the programming or the recharging. They will complete the relevant assessments for the clinical investigation. They will decide if the participants can stay on/complete the 2 weeks period during each treatment condition based on the participant’s level of tolerability. If a participant cannot complete the full 2 weeks they will be reassessed, enter the 2-day interval (where they will be ON-stimulation) before crossing over to the other treatment condition and the data will contribute to the primary outcome analysis.

6.9.3 Emergency Unblinding

There will be no unblinding of the treatment condition unless considered important for the participant’s care as assessed by the attending clinicians.

In the event emergency unblinding becomes necessary, the programmers will need to be contacted. A discussion is to be had to determine why unblinding is necessary and if agreed, unblinding can occur. The programmer must first cross-check the participant’s treatment condition against the code list. Once checked the participant is to be managed as per standard clinical practice. The participant will also be asked to confirm if they are happy to remain in the clinical investigation and, if so, will continue to attend study visits as per protocol.

The unblinding will need to be documented in the Unblinding Log and CCTU are to be informed in writing that unblinding has taken place. The participant's medical records will need to be updated with this information.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be given a unique clinical investigation Patient Identification Number (PIN). Data will be collected at the time-points indicated in the Table of Assessments.

Data collected will need to be directly entered by the research team at the local hospital site onto the Sponsor's central database.

Paper worksheets will be provided to the site to be used as a back-up to EDC unavailability and for use as source data worksheets, if required.

Training on data collection and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s).

6.10.2 Data Management

Participants will be given a unique clinical investigation PIN. Data will be entered under this PIN onto the central database. The database and coding frames have been developed by the Clinical Trial Manager in conjunction with CCTU. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

Data collection, data entry and queries raised by a member of the Op-TICS trial team will be conducted in line with the CCTU and trial specific Data Management Standard Operating Procedure.

Identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room.

Clinical trial team members will receive clinical investigation training. All data will be handled in accordance with the Data Protection Act 2018 (and subsequent updates and amendments).

6.10.3 Data Archiving

Once all primary and secondary analysis has been completed the trial data will be archived. Once the trial data has been archived the database will be decommissioned and will no longer be available. Any subsequent/ further analysis will be performed using the archived data.

6.10.4 Data Storage

Clinical investigation data will be stored in a database created specifically for the Op-TICS investigation. The database is hosted by OpenClinica and stored on servers at secure data centres in the London area (provided by Amazon Web Services (AWS)). The servers reside within the virtual private networks at the AWS data centres, and these are protected by firewalls and AWS Shield which protect the servers from infrastructure attacks.

The database will be password protected and only accessible to members of the Op-TICS trial team at CCTU, and external regulators if requested. Database users will only be granted permissions to use the database functionality appropriate to their role in the clinical investigation.

6.10.5 Non-Adherence and Non-Retention

If the participant chooses to discontinue receiving DBS (and/or removal of the device), this will need to be documented in our CRF. Reasons for treatment discontinuation, if possible, will be recorded by the trial team. Every effort will be made to continue to follow-up the participant according to the protocol until the end of the clinical investigation. Participants will be educated about the possible dangers of non-compliance.

6.10.6 Statistical Methods

A CONSORT diagram will be used to describe the course of participants through the clinical investigation. Baseline characteristics will be summarised by the order of treatment condition the participant is randomised to. Continuous variables will be summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) and categorical variables will be presented using frequency distributions by the order of treatment condition.

6.10.6.1 Statistical Analysis Plan

A detailed statistical analysis plan, including a full specification of the analysis principles and details, will be drafted as early as possible and finalised prior to the first substantive analysis, following approval by the TSC and review by the IDMC.

6.10.6.2 Statistical Methods – Outcomes

Statistical analysis will be conducted to assess the treatment effect. We will use mixed effects modelling to compare YGTSS-TTS (total tic) OFF-stimulation versus ON-stimulation at the end of the blinded phase. The baseline and end of state measures will be included as outcome variables. The fixed-effect of the model will include an indicator variable for baseline and treatment effect (ON/OFF). A random patient intercept term will be included to account for clustering within participants.

The secondary outcome measure, the Modified Rush Video Rating Scale (MRVRS) scores in the randomised phase will be compared using a similar mixed-effects model. Paired t-test will be used to compare between the scores at Baseline 0 (1 month before surgery) and Baseline 1 (at the end of the open phase) for YGTSS (global), MRVRS, GTS-QOL, YBOCS, BDI, BAI and BAARS-IV.

Mechanistic analysis will be performed in the open phase and after optimisation in the blinded phase. This is to identify the factors which predict the degree of response to DBS in TS (using the YGTSS (global) and YGTSS-TTS (total tic). We will perform multiple regression analyses looking at the role of: clinical factors (age, disease duration, tic severity (MRVRS), co-morbidity (YBOCS, BDI, BAI and BAARS-IV)), electrical parameters of stimulation (total electrical energy delivered and volume of tissue activated by stimulation) and imaging (contact position and relation with anatomic structures and MRI brain connectivity maps as we have previously done in patients with Parkinson's disease undergoing DBS (29,30).

We plan to carry out supportive analysis on the primary outcome using threshold based sensitivity analysis and complete case analysis. A further sensitivity analysis will be performed on the primary

outcome which will only include participants who have had no complicating factors due to surgical complications and/or any new intercurrent medical problems.

6.10.6.3 Additional Analyses - Subgroup

There is no planned subgroup analysis.

6.10.6.4 Additional Analyses – Adjusted

The regression models for the analysis of the mechanistic outcomes will be adjusted for baseline YGTSS (global) / YGTSS-TTS (total tic) scores or treatment effect; where appropriate.

6.10.7 Analysis Population and Missing Data

6.10.7.1 Analysis Population

Analysis will be conducted on all patients in the optimised population (Open Adjustment phase). Primary outcome analysis will follow the intention-to-treat (ITT) principle where all randomised participants are analysed in their allocated group, whether or not they receive their randomised treatment plan.

6.10.7.2 Missing data

If a participant decides to withdraw consent from clinical investigation treatment and follow-up before the randomised phase, the reason for withdrawal will be noted and presented in the CONSORT flow diagram. If a high number of patients (>20%) drop-out prior to the randomisation phase, we will compare the baseline characteristics of those randomised and those who were not. We will also compare tic severity at end of optimisation phase between those subsequently randomised and those who did not enter the randomised phase and discuss any potential consequences of the withdrawals in the manuscript.

Missing primary outcome data in the randomised phase are not anticipated as most participants are expected to be hospitalised at the NHNN and participants who find the randomised condition they are allocated to difficult to tolerate before the end of the two weeks will be assessed for primary outcome data collection before being switched to the other treatment condition. Due to the nature of the intervention, loss-to-follow up is not expected in this group of participants. However, if a participant decides to withdraw consent from clinical investigation treatment and follow-up during the randomised phase, we will note the reasons for missingness and explore the potential consequences of the loss through threshold-based sensitivity analyses.

The mixed model approach allows us to use all data that are reported and does not require that all subjects have all data. We will also perform primary analysis limited to participants with all data available (complete case) as a supportive analysis.

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be convened which will include at least three individuals independent from the trial team who have experience with patients in TS.

The IDMC will review the clinical investigation results and make a recommendation to the Trial Steering Committee (TSC) regarding continuation/stopping of the clinical investigation based on

safety data. The Op-TICS Trial Statistician at CCTU will generate regular summaries of accumulating clinical investigation data for the IDMC to review.

Further details of the roles and responsibilities of the IDMC, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the Op-TICS IDMC Terms of Reference (ToR).

6.11.2 Interim Analyses

No formal interim analyses are planned, however IDMC members will convene at scheduled time points throughout the duration of the clinical investigation to review interim clinical investigation data and safety data.

6.11.3 Data Monitoring for Harm

All adverse events (AEs), adverse device effects and deficiencies and SAEs occurring during the clinical investigation observed by the investigator or reported by the participant, whether or not attributed to the investigational medicinal device, clinical investigation interventions or other clinical investigation-specific procedure will be recorded in the participant's medical records, and on the appropriate Op-TICS CRFs. CCTU will keep investigators informed of any safety issues that arise during the course of the clinical investigation.

The period for reporting of events directly related to the participant will be from the time the device is implanted until 30 days from visit 7.

Safety reporting procedures will be described in the Op-TICS Safety Management Plan.

6.11.3.1 Safety reporting

The following definitions have been adapted from MEDDEV 2.7/3 revision 3 (May2015): Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/EEC and 93/42/EEC.

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device. **Note 1**: This definition includes events related to the investigational medical device or the comparator **Note 2:** This definition includes events related to the procedures involved **Note 3**: This definition is restricted to events related to investigational medical devices
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. **Note 1:** this definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

	Note 2: this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE)	An AE that led to any of the following: A) death, injury or permanent impairment to a body structure or a body function B) serious deterioration in health of the subject, that either resulted in: – A life-threatening illness or injury*, or – A permanent impairment of a body structure or a body function, or – In-patient hospitalisation or prolongation of existing hospitalisation**, or – medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or – Chronic disease C) foetal distress, foetal death or a congenital physical or mental impairment or birth defect * the term life threatening here refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe **planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event
Serious Adverse Device Effect (SADE)	An ADE that has resulted in any of the consequences characteristic of a SAE.
Unanticipated Serious Adverse Device Effect (USADE)	A SADE which, by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report
Device Deficiency	Inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational medical device. **Note 1**: this includes malfunctions, use errors, and inadequate labelling

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease, condition or a laboratory abnormality present before treatment that does not worsen in frequency or intensity
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- the disease being studied, or signs/symptoms associated with the disease unless more severe than expected

6.11.3.2 Procedures to follow in the event of female participants becoming pregnant

Female participants with a positive pregnancy test at baseline 0 are not eligible for inclusion in this clinical investigation and should not have surgery. Eligible females of child-bearing potential will be advised to use an effective form of contraception whilst they are part of the clinical investigation.

If a participant should become pregnant any time after surgery a discussion will be held with the study team physicians as to the possibility of them remaining in the optimisation adjustment (open) phase of the clinical investigation. They will not be included in the double-blind, randomised cross-over phase of the clinical investigation. This phase could place additional stress on the participant in terms of tic severity, which could potentially increase during OFF-stimulation, and visit frequency.

If the pregnancy is detected during the double-blind, randomised cross-over phase unblinding will need to take place. If the participant is in the OFF-stimulation treatment group then they will have the assessments completed, by the blinded assessor, before the 2-day ON-stimulation break and cross-over to the ON-stimulation treatment group. This data will contribute to the primary end-point. If the participant is in the ON-stimulation treatment group, the clinician will discuss with the participant if they are willing to remain on the study. Assessments will be completed by the blinded assessor. They won't cross-over to the OFF-stimulation phase.

Once pregnancy is confirmed the study team, chief investigator and clinical team have decided that due to the severity of the tics, it is best to keep the pregnant female participants ON-stimulation for the protection of the mother and the unborn child. The clinical team has also confirmed this is safe and is supported by a study by Scelzo et al, 2015 (31).

Pregnancy is not a SAE. If pregnancy should occur the Pregnancy Notification and Follow Up form should be completed by the investigator at the site and forwarded to the Op-TICS trial team at CCTU, no later than 24 hours of the investigator becoming aware of the pregnancy. The pregnancy outcome may or may not be considered a SAE. Participants will be given a copy of the Op-TICS Pregnancy Monitoring Information Sheet and will be asked to sign the Op-TICS Pregnancy Monitoring Consent Form agreeing for data on the pregnancy to be collected. Pregnancy should be followed until the outcome is known (including any premature termination of the pregnancy) and information on the status of the mother and child. Pregnant participants will be followed up until birth, the Op-TICS Pregnancy Notification & Follow-Up Form (capturing information for up to 6 to 8 weeks after birth) should be completed and forwarded to the trial team at CCTU. Any congenital malformations and/or birth defects are reportable as an SAE.

6.11.3.3 Assessment of adverse events

All non-serious events, whether anticipated or not, should be recorded in the participant's medical notes and on the Op-TICS Adverse Events Log until 30 days after visit 7. Common Terminology Criteria for Adverse Events, version 5, will be used for the coding of adverse events.

Adverse events during the open adjustment phase, will be assessed by the unblinded programmers. Adverse events, during the randomised, double-blind phase will be assessed by blinded members of the site team.

Each adverse event will be assessed for the following criteria:

6.11.3.3.1 Severity or grading of Adverse Events

The severity of all AEs in this clinical investigation should be graded as follows:

Category	Definition
Mild	The adverse event does not interfere with the subject's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subject's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health **Note**: A severity rating of severe does not necessarily categorise the event as a SAE

6.11.3.3.2 Seriousness assessment

When an event occurs, the investigator responsible for the care of the participant must assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' (or is a DD that could have led to a SADE) then an SAE form must be completed and CCTU (or delegated body) notified immediately (no longer than 24hours), via the study database.

The minimum criteria required for reporting an SAE are the PIN and partial date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

If the database is not able to be accessed at the site then the paper SAE form must be scanned and sent by email to the trial team at CCTU:

cctu.optics@ucl.ac.uk

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or clinical investigation follow-up if necessary. CCTU should be informed of any further information as it becomes available. Additional information and/or copies of test results etc may be provided separately. The participant must be identified by clinical investigation number and partial date of birth only. The participant's name should not be used on any correspondence and should be blacked out and replaced with clinical investigation identifiers on any test results.

6.11.3.3.3 Causality

The assessment of relationship of AEs to the investigational medical device and study procedures will be a clinician decision, based on all available information at the time of the completion of the CRF, using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description
Not related	Relationship to the device or procedures can be excluded when:

	– The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; – The event has no temporal relationship with the use of the investigational device or the procedures; – The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; – The discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; – The event involves a body-site or an organ not expected to be affected by the device or procedure; – The serious event can be attributed to another cause (e.g. an underlying or concurrent illness / clinical condition, an effect of another device, drug, treatment or other risk factors); – The event does not depend on a false result given by the investigational device used for diagnosis when applicable; – Harms to the subject are not clearly due to use error; – In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the serious event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Related (Causal Relationship)	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: – the event is a known side effect of the product category the device belongs to or of similar devices and procedures; – the event has a temporal relationship with investigational device use/application or procedures; – the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; – the serious event follows a known response pattern to the medical device (if the response pattern is previously known); – the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

	– other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; – harm to the subject is due to error in use; – the event depends on a false result given by the investigational device used for diagnosis, when applicable; – In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

6.11.3.3.4 Expectedness

If causality is possible, probable, or related to the involvement of the investigational device or procedures (including any comparators), the investigator and sponsor must assess if it is an anticipated event. An unanticipated event is one that is not identified in the current version of the CIP.

6.11.3.3.5 Reporting of adverse events and device deficiencies: Investigator and Sponsor Responsibilities

The following events are considered reportable events in accordance with Directive 90/385/EEC and Directive 93/42/EEC, and Article 80 of Regulation (EU) 2017/745.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Adverse Events (AEs)	Investigator	Sponsor	Within **10 working days** on AE Log CRF
Serious Adverse Event (SAE) / Serious Adverse Device Effect (SADE)/ USADEs	Investigator	Sponsor	**Immediately**, but no later than 24hrs after becoming aware of the event
	Sponsor	MHRA	**Immediately, but not later than 2* calendar days** after awareness *For SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons This timeline will be adhered to wherever possible. CCTU is a non-commercial entity without 24-hour pharmacovigilance coverage. SAE/SADE reporting to the MHRA will occur on the next available working day. All other events immediately but not later than 7 calendar days following date of awareness.
	Sponsor	REC	**Within 15 days of awareness**

			Only reports of <u>related and unexpected</u> Serious Adverse Device Effects (i.e. USADEs - unanticipated serious adverse device effect) should be submitted to the REC.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Device Deficiency (DD)	Investigator	Sponsor	**Immediately**, no more than 24 hours of becoming aware of the event
	CI	MHRA	**7 calendar days** Only reportable if the event may have led to an SAE if: • suitable action had not taken • intervention had not been made • if circumstances had been less fortunate
Urgent Safety Measures	CI	REC	1. Immediately - By telephone 2. Within 3 days - Notice in writing setting out reasons for the USM and plan for further action

The Sponsor shall keep detailed records of all adverse events and device deficiencies relating to the clinical investigation, which are reported to them by the investigators. The Sponsor shall ensure that all relevant information about a reportable event, which occurs during the course of this clinical investigation in the United Kingdom, is reported as soon as possible to the relevant regulatory authorities as per their reporting requirements and according to the timelines in the above table. Any additional relevant information should be sent within the same time frame as the initial report. The CI is responsible for informing other investigators of any reportable events that have occurred with the study device in any clinical investigation according to the guidelines set forth by the REC of record where the clinical investigation is taking place.

6.11.3.4 Foreseeable adverse events and anticipated adverse device effects

The following are known risks with surgery and the use of deep brain stimulation(26):

	Related to Surgery			**Related to Presence of the Device**			**Related to Stimulation**		
	Very Likely >20%	**Less likely 2%-20%**	**Rare <2%**	**Very Likely >20%**	**Less likely 2%-20%**	**Rare <2%**	**Very Likely >20%**	**Less likely 2%-20%**	**Rare <2%**
• Allergic or immune system response			X			X			
• Anesthesia/neurosurgery risks, including unsuccessful implant, exposure to bloodborne pathogens			X						
• CSF leak			X						
• Death, including suicide			X			X			X
• Embolism, including air embolism and pulmonary embolism			X						
• Failure or malfunction of any of the device components or the battery, including but not limited to lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits and lead insulation breaches, whether or not this requires explant and/or reimplantion					X				
• Hemorrhagic or ischemic stroke, immediate or delayed, which could result in temporary or permanent neurologic deficits such as muscle weakness, paralysis or aphasia			X						

• Implant site complications such as pain, poor healing, wound reopening		X			X				
• Infection		X			X				
• Injury to tissues adjacent to implant or within surgical field, such as blood vessels, peripheral nerves, brain (including pneumocephalus), or pleura (including pneumothorax)			X						X
• Interference from external electromagnetic sources								X	
• Lead, extension (including extension header) and neurostimulator erosion or migration					X				
• Loss of adequate stimulation								X	
• Mentation impairment such as attention or cognitive deficits, memory disturbances, or confusion		X						X	
• Motor problems such as paresis, weakness, incoordination, restlessness, muscle spasms, postural and gait disorders, tremor, dystonia, or dyskinesias, and falls or injuries resulting from these problems		X						X	

• During an MRI examination, there are potential interactions with the implanted DBS lead, Extension, and Stimulator, and risk of patient harm. Make sure to follow the ImageReady MRI Guidelines for Boston Scientific DBS Systems, available on the website www.bostonscientific.com/manuals.						X If guidelines are followed			
• Musculoskeletal stiffness		X			X				
• Neuroleptic malignant syndrome or acute akinesia can occur very rarely			X						X
• New onset or worsening depression, which may be temporary or permanent, and suicidal ideations, suicide attempts, and suicide		X Depression	X Suicidal ideation, suicide attempt, suicide					X Depression	X Suicidal ideation, suicide attempt, suicide
• Overstimulation or undesirable sensations, such as paresthesia, transient or persistent								X	
• Pain, headache or discomfort, transient or persistent, including symptoms due to neurostimulation	X Short-term		X Persistent	X Short-term		X Persistent	X Short-term		X Persistent
• Poor initial lead location			X						

• Psychiatric disturbances such as anxiety, depression, apathy, mania, insomnia, suicide, or suicidal ideation or attempts		X Anxiety, depression, apathy	X Mania, insomnia, suicide, suicidal ideation or attempts					X Anxiety, depression, apathy	X Mania, insomnia, suicide, suicidal ideation or attempts
• Radiation exposure due to imaging (CT, fluoroscopy x-ray)			X Leading to harm						
• Seizures			X						X
• Sensory changes			X						X
• Seroma, edema or hematoma		X			X				
• Skin irritation or burns at neurostimulator site						X			
• Speech or swallowing problems such as dysphasia, dysarthria or dysphagia, as well as complications of dysphagia such as aspiration pneumonia		X Speech	X Swallowing					X Speech	X Swallowing
• Status dystonicus			X						X
• Systemic symptoms-autonomic (tachycardia, sweating, increased blood pressure, flushing, fever, dizziness), changes in renal function, urinary retention, sexual effects, gastrointestinal (nausea, bowel retention, bloating)			X						X
• Thrombosis			X						

• Visual disturbances or periorbital symptoms, such as diplopia, eyelid movement difficulty, oculomotor difficulties, transient flashes of light or other visual field effects			X						X
• Weight changes								X	

Participants will be instructed to seek medical advice in the routine way if adverse events occur. Participants will also receive a safety card at baseline 0 which will include a contact number in case of an emergency.

6.11.3.5 Progress reports

Progress reports will be submitted to the REC as per the REC requirements.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the Op-TICS clinical investigation are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the clinical investigation and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including clinical investigation design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the clinical investigation is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the clinical investigation related activities are fulfilled.

6.11.4.2 Central Monitoring at CCTU

CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The clinical investigation database will also be programmed to generate reports on errors and error rates. Essential clinical investigation issues, events and outputs, including defined key data points, will be detailed in the Op-TICS clinical investigation Data Management Plan.

6.11.4.3 On-site or Remote Monitoring

The frequency, type and intensity of routine and triggered on-site or remote monitoring will be detailed in the Op-TICS Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a clinical investigation site inspection by any regulatory authority UCL CCTU must be notified as soon as possible.

6.11.4.3.1 Direct access to patient records

Participating investigators must agree to allow clinical investigation related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other clinical investigation related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the clinical investigation.

6.11.4.4 Clinical investigation Oversight

Clinical investigation oversight is intended to preserve the integrity of the clinical investigation by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to clinical investigation groups; adherence to clinical investigation interventions and policies to protect participants, including reporting of harm; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent clinical investigation oversight complies with the CCTU trial oversight policy.

6.11.4.4.1 Trial Team

The Trial Team (TT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the clinical investigation, including budget management.

The membership, frequency of meetings, activity (including clinical investigation conduct and data review) and authority will be covered in the TT terms of reference.

6.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the clinical investigation. The membership, frequency of meetings, activity (including clinical investigation conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the clinical investigation in order to safeguard the interests of clinical investigation participants. The TSC provides advice to the CI, CCTU, the funder and sponsor on all aspects of the clinical investigation through its independent Chair. The membership, frequency of meetings, activity (including clinical investigation conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of clinical investigation participants, monitoring the accumulating data and making recommendations to the TSC on whether the clinical investigation should continue as planned. The membership, frequency of meetings, activity (including review of clinical investigation conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.11.4.4.5 Clinical investigation Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the clinical investigation. UCL is the clinical investigation sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

7 Ethics and Dissemination

7.1 Ethics Committee Approval

Before initiation of the clinical investigation at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective patient will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the clinical investigation at each additional clinical site, the same/amended documents will be submitted for local permissions.

The rights of the patient to refuse to participate in the clinical investigation without giving a reason must be respected. After the participant has entered the clinical investigation, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the clinical investigation for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This is considered a clinical investigation for a medical device and will be submitted for MHRA assessment.

This clinical investigation plan will be submitted to the MHRA in the UK for review .

The progress of the clinical investigation, safety issues and reports, including all serious adverse events, will be reported to the MHRA in accordance with relevant national and local requirements and practices.

7.3 Other Approvals

The protocol, patient information sheet (PIS) and informed consent forms on local headed paper, the REC/HRA approvals and MHRA notice of no objections, schedules of funding and activity (and other clinical investigation documentation as needed) will be submitted by those delegated to do so to the relevant NHS Trust R&D department of each participating site or to other local departments for approval as required in each country. The NHS Trust R&D department will conduct a local feasibility assessment to determine whether the NHS Trust has the capacity and capability to participate in the clinical investigation. No clinical investigation conduct can take place at a participating site until all approvals including the local capacity and capability approval are in place.

The protocol has received formal review and methodological, statistical, clinical and operational input from the CCTU Protocol Review Committee.

7.4 Protocol Amendments

The Sponsor will ensure that the clinical investigation protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by appropriate regulatory body (MHRA), REC and HRA prior to any patient recruitment. The protocol and all agreed substantial amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

7.5 Consent or Assent

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the patient is willing to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the patient is free to refuse to participate in all or any aspect of the clinical investigation, at any time and for any reason, without incurring any penalty or affecting their treatment.

In accordance with the UK Clinical Trial Regulations, the risk/benefit profile of the clinical investigation will be regularly monitored. Consent will be re-sought if new information becomes available that affects the patient's consent in any way. This will be documented in a revision to the patient information sheet and the patient will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use. A copy of the approved consent form is available from the CCTU trial team.

7.6 Confidentiality

Any paper copies of personal clinical investigation data will be kept at the participating site in a secure location with restricted access. Only non-identifiable data will be kept at the UCL CCTU office with only authorised UCL CCTU staff members having access. Only staff working on the clinical investigation will have password access to this information.

Confidentiality of participant's personal data is ensured by not collecting participant names on CRFs that will be sent to UCL CCTU and storing the data in a pseudonymised fashion at UCL CCTU. At clinical investigation enrolment the participant will be issued a patient identification code, and this will be the primary identifier for the participant, with secondary identifiers of month and year of birth.

The participant's consent form will carry their name and signature, but these will be kept at the clinical investigation site (participant's hospital) and not with the participant's data at the UCL CCTU. The patient consent forms will only be accessed by UCL CCTU staff for purposes of monitoring the consent procedure at the site.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the clinical investigation.

7.8 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical investigation. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical investigation is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical investigation. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical investigation without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical investigation shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

7.9 Finance

Op-TICS is fully funded by the Efficacy and Mechanism Evaluation (EME) programme grant number NIHR129340. It is not expected that any further external funding will be sought.

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of Op-TICS clinical investigation materials and records for a minimum of 5 years after the close of the clinical investigation unless otherwise advised by the CCTU.

7.11 Access to Data

Requests for access to clinical investigation data will be considered, and approved in writing where appropriate, after formal application to the TMG/TSC. Considerations for approving access are documented in the TMG/TSC Terms of Reference.

7.12 Ancillary and Post-clinical investigation Care

The DBS devices will remain in place and stimulation will continue, as per standard of care, after the clinical investigation, unless it is found to be ineffective or participants wish to have it removed. The type of device we are planning to use should last 25 years. After the clinical investigation, the device will be regularly monitored at routine NHS clinic visits. Patients will be managed jointly by their local Tourette Syndrome consultant and a DBS specialist, as per standard of care.

7.13 Publication Policy

7.13.1 Clinical investigation Results

The results of this clinical investigation will be submitted for publication in peer reviewed journals as well as in the NIHR EME journal, in addition to reports at appropriate conferences.

The results of the clinical investigation will be disseminated regardless of the direction of effect.

Results will also be communicated to participants with the assistance of the Op-TICS Patient and Public Involvement (PPI) group and the patient association – Tourettes Action.

7.13.2 Authorship

Authorship will be granted to individuals making a substantial contribution to the design, setup or conduct of the clinical investigation and/or analysis and interpretation of clinical investigation data.

7.13.3 Reproducible Research

The latest version of the clinical investigation protocol will be made available as supplementary material upon publication of the final clinical investigation report.

8 Ancillary Studies

There are no ancillary studies. Any proposal for ancillary studies will need to be approved by the TSC.

9 Protocol Amendments

Protocol version number	Protocol date	List of substantial amendments (for full description, refer to the 'Summary of changes to the protocol' document
1.0	04-Nov-2021	N/A
2.0	22-Dec-2021	Exclusion criteria 13 added as per MHRA advice following initial submission. Clinical Project Manager name changed. Date of first enrolment changed to Feb 2022

10 References

1. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. Spirit 2013 statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158:200–7.

2. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:1–42.

3. Barkley RA. Barkley Adult ADHD Rating Scale-IV (BAARS-IV). Guildford Press; 2011.

4. Beck AT; Steer RA; Brown GK. Manual for the Beck Anxiety Inventory. Psychological Corporation, San Antonio, TX; 1990.

5. Steer Robert A. BAT. The Beck Anxiety Inventory. In: Evaluating Stress: A book of resources. Scarecrow Press, Lanham, MD; 1997. p. 23–40.

6. Beck. Inventory for Measuring Depression. Arch Gen Psychiatry. 1961;4(6):561–71.

7. Cavanna AE, Schrag A, Morley D, Orth M, Robertson MM, Joyce FE, et al. The Gilles de la Tourette Syndrome-Quality of Life Scale (GTS-QOL) Development and validation. Neurology. 2008;71:1410–6.

8. Sheehan DV, Lecrubier Y, Harnett Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R DG. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 (suppl:22–33.

9. Goetz CG, Pappert EJ, Louis ED, Raman R, Leurgans S. Advantages of a Modified Scoring Method for the Rush Video-Based Tic Rating Scale. 1999.

10. Goodman WK. The Yale-Brown Obsessive Compulsive Scale. Arch Gen Psychiatry. 1989 Nov 1;46(11).

11. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity. J Am Acad Child Adolesc Psychiatry. 1989 Jul;28(4).

12. Groth C, Mol Debes N, Rask CU, Lange T, Skov L. Course of Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study. J Am Acad Child Adolesc Psychiatry. 2017 Apr;56(4).

13. Stern JS, Burza S, Robertson MM. Gilles de la Tourette's syndrome and its impact in the UK. Vol. 81, Postgraduate Medical Journal. 2005. p. 12–9.

14. Wilhelm S, Peterson AL, Piacentini J, Woods DW, Deckersbach T, Sukhodolsky DG, et al. Randomized trial of behavior therapy for adults with tourette syndrome. Arch Gen Psychiatry. 2012 Aug;69(8):795–803.

15. Pringsheim T, Holler-Managan Y, Okun MS, Jankovic J, Piacentini J, Cavanna AE, et al. Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology. 2019 May 7;92(19):907–15.

16. Krauss JK, Jankovic J. Severe motor tics causing cervical myelopathy in Tourette's syndrome. Mov Disord. 1996;11(5):563–6.

17. Fernández de la Cruz L, Rydell M, Runeson B, Brander G, Rück C, D'Onofrio BM, et al. Suicide in Tourette's and Chronic Tic Disorders. Biol Psychiatry. 2017 Jul;82(2).

18. Scharf JM, Miller LL, Mathews CA, Ben-Shlomo Y. Prevalence of Tourette Syndrome and Chronic Tics in the Population-Based Avon Longitudinal Study of Parents and Children Cohort. J Am Acad Child Adolesc Psychiatry. 2012 Feb;51(2).

19. Scharf JM, Miller LL, Gauvin CA, Alabiso J, Mathews CA, Ben-Shlomo Y. Population prevalence of Tourette syndrome: A systematic review and meta-analysis. Mov Disord. 2015 Feb;30(2).

20. Meier SM, Dalsgaard S, Mortensen PB, Leckman JF, Plessen KJ. Mortality risk in a nationwide cohort of individuals with tic disorders and with tourette syndrome. Mov Disord. 2017 Apr 1;32(4):605–9.

21. Brander G, Isomura K, Chang Z, Kuja-Halkola R, Almqvist C, Larsson H, et al. Association of Tourette Syndrome and Chronic Tic Disorder with Metabolic and Cardiovascular Disorders. JAMA Neurol. 2019 Apr 1;76(4):454–61.

22. Kefalopoulou Z, Zrinzo L, Jahanshahi M, Candelario J, Milabo C, Beigi M, et al. Bilateral globus pallidus stimulation for severe Tourette's syndrome: A double-blind, randomised crossover trial. Lancet Neurol. 2015 Jun 1;14(6):595–605.

23. Tisch S, Zrinzo L, Limousin P, Bhatia KP, Quinn N, Ashkan K, et al. Effect of electrode contact location on clinical efficacy of pallidal deep brain stimulation in primary generalised dystonia. J Neurol Neurosurg Psychiatry. 2007;78(12):1314–9.

24. Picillo M, Lozano AM, Kou N, Munhoz RP, Fasano A. Programming Deep Brain Stimulation for Tremor and Dystonia: The Toronto Western Hospital Algorithms. Vol. 9, Brain Stimulation. Elsevier Inc.; 2016. p. 438–52.

25. Welter ML, Houeto JL, Thobois S, Bataille B, Guenot M, Worbe Y, et al. Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. Lancet Neurol. 2017 Aug 1;16(8):610–9.

26. Vercise Deep Brian Stimulation Systems information for prescribers, MP92366226-02 REV A [Internet]. Available from: https://www.bostonscientific.com/content/dam/Manuals/eu/current-rev-de/92366226-02_VerciseTM_DBS_Systems_Information_for_Prescribers_multi-OUS_s.pdf

27. Holl EM, Petersen EA, Foltynie T, Martinez-Torres I, Limousin P, Hariz MI ZL. Improving targeting in image-guided frame-based deep brain stimulation. Neurosurgery. 2010;67:437–47.

28. Jeon S, Walkup JT, Woods DW, Peterson A, Piacentini J, Wilhelm S, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: A comparison of three methods. Contemp Clin Trials. 2013;36(2):414–20.

29. Tripoliti E, Limousin P, Foltynie T, Candelario J, Aviles-Olmos I, Hariz MI, et al. Predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease. Mov Disord. 2014;29(4):532–8.

30. Akram H, Georgiev D, Mahlknecht P, Hyam J, Foltynie T, Limousin P, et al. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. Neuroimage. 2017;158(January):332–45.

31. Scelzo E, Mehrkens JH, Bötzel K, Krack P, Mendes A, Chabardès S, et al. Deep brain stimulation during pregnancy and delivery: Experience from a series of “DBS babies.” Front Neurol. 2015;6(SEP):1–6.

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