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Optimizing epilepsy surgery

Submission date 17/09/2020	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 25/09/2020	**Overall study status** Ongoing	
Last Edited 19/02/2025	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Sixty million people have epilepsy and a third of them continue to have seizures despite medication, with risks of fatality, brain damage, physical harm and psychosocial disorders. Brain surgery (neurosurgery) can control epilepsy if the responsible part of the brain is removed. We have treated 1,074 individuals with epilepsy surgery since February 1990. In optimal circumstances, 80% have no seizures for 1 year or more after surgery, and 40% never have another seizure. There may, however, be adverse effects. After surgery 30% of individuals develop increased difficulty with memory and language, and 10-20% may lose part of their field of vision.

Over the next 4 years we will implement methods to improve epilepsy surgery, streamline the pathway and so improve access:
1. Systematic analysis of seizure symptoms to better understand the areas of the brain involved in each individual. This information is combined with results of brain imaging and other brain scans and electrical recordings from the scalp and viewed in 3-dimensions.
2. Use computer-assisted analysis of brain scans to define the best locations for recording electrodes in the brain at sites thought to be giving rise to seizures, avoiding blood vessels
3. Analyse the electrical signals recorded from electrodes in the brain, integrating this with analysis of MRI and other brain scans to determine which parts need to be removed to control the epilepsy
4. Plan surgery so that there is the best chance of stopping seizures, and minimized risk of other damage

Who can participate?
Individuals aged 18-70 under consideration for epilepsy surgery for drug-resistant focal epilepsy, at National Hospital for Neurology and Neurosurgery (NHNN), who are able to appropriately consent for involvement in the research as well as for surgery itself, and has no contraindications to undergoing neurosurgery.

What does the study involve?
The study will be part of the normal investigations and assessments made by the clinical teams as a part of the assessment for epilepsy surgery, and will involve clinical assessments and brain scans before surgery, and 3-4 months after the operation to determine whether the treatment was successful.

What are the possible benefits and risks of participating?
The possible benefits include a higher likelihood of seizure freedom and a lower likelihood of developing severe neurological deficits following the surgery.

Where is the study run from?
National Hospital for Neurology and Neurosurgery (UK)

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

Who is funding the study?
1. The Wellcome Trust (UK)
2. Epilepsy Research UK

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
278210

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 46471, IRAS 278210, WT 218380/Z/19/Z

Study information

Scientific Title
Optimizing epilepsy surgery

Study objectives
Computerised analysis of information from multiple brain scans will assist the neurosurgical treatment of epilepsy, at all steps along the pathway, particularly in designing the optimal surgical approach.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/09/2020, London - Queen Square Research Ethics Committee (HRA NRES Centre Bristol, 3rd floor, block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; no telephone number provided; queensquare.rec@hra.nhs.uk), ref: 20/LO/0966

Study design
Non-randomised observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Epilepsy

Interventions
This programme of research has been developed with the benefit of input from individuals who have had or are considering epilepsy surgery for themselves or a loved one. This is the BrainBuddyUK group that meets every 2-3 months at NHNN.

A key feature of the output of the research is to develop clinical decision support tools to enable better decisions to be made, faster, but with experienced consultants remaining in control of the process.

The different aspects of this research will be appropriate at different points along the pathway of considering epilepsy surgery. The pathway for considering epilepsy surgery, with all the steps considered, may extend over 2 years. 150-200 patients per year consider epilepsy surgery at NHNN. Of these, approximately 40 per year may be offered resection without intracranial EEG, another 30 will require intracranial EEG, and the remainder will not proceed past the initial phase 1 investigations of MRI, scalp video-EEG telemetry, neuropsychology and neuropsychiatry assessments.

Potential participants will be those 70-100 per year who are eligible to proceed past phase 1 investigations, and who wish to do so. They will be identified by the clinical team and informed of the study and asked if they wish to know more. If the individual is interested, they will be notified to the research team who will make contact and explain the research study, sending written information about the study and asked to contact the research team if they wish to participate. If, after discussion and asking questions they wish to do so they will be asked to indicate their consent in writing on a consent form.

Individuals at the start of the evaluation of their epilepsy for possible epilepsy surgery will be asked a structured questionnaire of the symptoms. This will be supplemented by the account of a witness and of video recordings of seizures in the Hospital, which is standard clinical practice.

The planning of the strategy of brain areas to be implanted with electrodes and the precise planning of trajectories is made at a weekly MDT involving neurophysiologists, neurosurgeons, neurologists and imaging processing specialists. The suggestions for implantation from the symptom analysis will be compared with the MDT recommendations made without this consideration. The MDT will then have the option to modify the strategic plan.

The planning of precise electrode trajectories is made when the strategy has been agreed. Clinical standard care is to implant the agreed targets, to not pass within 3mm of an identified blood vessel, within 10mm of another electrode or cross sulci, and to cross the skull within 15 degrees of orthogonal, if possible, and to enter the brain at gyral crowns. In this project we will enhance this process by using as a starting point trajectories that have been used in previous successful implantations. As is clinical standard care, the treating consultant neurosurgeon checks the safety of each and every trajectory. No patient involvement in this process. After implantation, it is clinical standard care for X-ray CT and MRI scans to be carried out to determine the precise location of electrodes in the brain, and for the brain's electrical activity to then be recorded.

We will link the standard EEG display with electrode contacts in the brain, so that the anatomical source of electrical activity and epileptic discharges can be visualized in 3D, superimposed on the anatomical MRI. This supplements the current standard of the EEG reader inferring the anatomical location of electrode contacts. We will also compute and present in 3D derived EEG signals such as high frequency ripples and Gamma power.

Clinical standard care is that the area of seizure onset and early spread is manually drawn onto a diagram of the brain to suggest the area to be resected, with estimates of the chances of achieving seizure freedom. The plan is then reviewed with the neurosurgeon who will constrain the plan to avoid damaging known critical areas. The proposed resection is then discussed with the patient, with estimates of achieving seizure control and the risks of causing new morbidity.

Clinical standard practice is that consultant neurophysiologists mark electrode contacts that are involved in seizure onset, early propagation and in interictal epileptic activity and decide which areas of brain around these contacts should be removed to try to control epileptic seizures. In this project, we will display the EEG contacts that detect epileptic activity in a 3D map of the brain and will use a seed growing algorithm to create a model of the putative volume to be resected.

This volume will be dilated up to the gyral surface, and then constrained by the individual anatomy of eloquent cortex visualized with functional MRI and with imaging representation of critical white matter tracts. The brain surface of the intended volume of resection is then overlaid with imaging of arteries and veins, and with a model of the skull and scalp so that the neurosurgeon may plan the detail of the operative approach and resection. At all times the image guidance offered is subordinate to the clinical opinion of the treating consultants.

The same process for planning a resection is used for individuals who do not need intracranial EEG to identify the sites of seizure onset.

In this study, we will have the conventional method used, to result in a resection plan, and this will then be compared with a resection plan produced by the EpiNav tools. The treating consultant will select the plan that they consider is optimal in terms of likely benefit and risk avoidance.

The 3D plan of the resection volume and the operative approach is then uploaded to the clinically standard neuronavigation system used in the operating rooms, so that the margins of the planned resection and critical structures that must be spared are displayed in the operating surgeon’s eye piece.

These steps do not require patient participation, beyond the resection plan being viewable by the patient in the discussion with the neurosurgeon when considering whether to proceed. Prior to and 4 months after a resection, we will carry out functional language MRI and diffusion MRI scans, to determine the effects of the surgical resection on eloquent language cortex, and white matter tracts in the brain. These will be carried out at the same appointment as clinically required scans, so the individual is not inconvenienced.

In studies of this nature, developing novel clinical decision support tools, conventional power calculations are not appropriate. We intend to invite the circa 70 patients per year who proceed past phase one investigations, over three years.

The proportions of investigated patients proceeding to surgery will be noted; the occurrence of any complications of surgery will be assessed 3 months after surgery. The long-term outcomes

of seizure freedom one year after resection will be determined 12 months after surgery. These rates will be compared with our recent rates for comparable patients, treated by the same multidisciplinary team.

By way of illustration, in an observational cohort study of anterior temporal lobe resections for mesial temporal lobe epilepsy using 3D imaging guidance to ensure inclusion of the piriform cortex in the resection and avoidance of language-related white matter tracts and of the optic radiation, 58 patients will give 90% power, $p<0.05$ one-tailed, to detect an increase in seizure freedom rate from 59% to 79%, compared to recent subjects operated upon by the same surgeons. In parallel we expect to reduce the incidence of word finding difficulties from 30% to 20% and of significant visual field defects from 15% to 0%.

Intervention Type
Other

Primary outcome measure
Seizure freedom following neurosurgical treatment for refractory focal epilepsy using the Engel classification at pre-operation (baseline), 3 months post-operation, 1 year post-operation

Secondary outcome measures
1. Symptom analysis – measured by the extent of change in the planned implantation of SEEG electrodes from the original clinical data without the symptom analysis (single timepoint)
2. Optimal electrode planning: The time taken to plan a study is measured, as is the safety of the planned implantation (proximity to blood vessels) compared to previous recent data of implantations planned without the use of prior trajectories as a starting point (single timepoint, comparator is historical data)
3. Resection planning: comparison of the resection plan derived from the conventional method used, with the resection plan produced by the image-guided methods (comparison of volume to be resected, single timepoint once both resection plans are made)
4. Complications, causing neurological deficit, following neurosurgical treatment for refractory focal epilepsy, particularly deficits of language and visual fields after temporal lobe resection (formally measured by visual fields testing and language and memory assessments pre-operatively and 3 months post-operatively)

Overall study start date
30/12/2019

Completion date
30/09/2025

Eligibility

Key inclusion criteria
1. Considering epilepsy surgery for drug-resistant focal epilepsy, at National Hospital for Neurology and Neurosurgery (NHNN)
2. Any gender, age 18-70 years
3. Has capacity to give informed consent
4. No contra-indication to neurosurgical intervention

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
70 Years

Sex
Both

Target number of participants
Planned Sample Size: 300; UK Sample Size: 300

Key exclusion criteria
1. Lack of capacity to give informed consent
2. Comorbidiites that would make neurosurgical intervention inappropriate (e.g., active neoplasia, cerebrovascular disease, dementia, coagulopathy)

Date of first enrolment
01/10/2020

Date of final enrolment
30/09/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
National Hospital for Neurology and Neurosurgery
University College London Hospitals NHS Foundation Trust
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Sponsor information

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Sponsor type
University/education

Website
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ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Epilepsy Research UK; Grant Codes: UK P1904

Alternative Name(s)
ERUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Wellcome Trust; Grant Codes: 218380/Z/19/Z

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/09/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version v3	07/02/2020	25/09/2020	No	No
HRA research summary			28/06/2023	No	No