**Observational Protocol Template: UCLH/UCL Sponsored Studies**

**UCL/UCLH Research Office**

**Optimizing epilepsy surgery**

**Chief Investigator:**

Prof JS Duncan MA DM FRCP FMedSci

Professor of Neurology

Queen Square Institute of Neurology

UCL

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**PROTOCOL VERSIONS**

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**DECLARATIONS**

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

**Chief Investigator:**

**Signature: Date: 10/07/2020**

**Print Name(in full):.....John Sidney Duncan.....**

**Position:..........Professor of Neurology....................**

**On behalf of the Study Sponsor:**

**Signature:  Date 10/07/2020**

**Print Name(in full): Pushpsen Joshi**

**Position: Research Governance Manager – Joint Research Office of UCL & UCLH**

**STUDY SUMMARY**

|  |  |
| --- | --- |
| **Identifiers** |  |
| IRAS Number | 278210 |
| REC Reference No |  |
| Sponsor Reference No |  |
| Other research reference number(s) (if applicable) |  |
|  |  |
| Full (Scientific) title | Optimizing epilepsy surgery |
| Health condition(s) or problem(s) studied | Epilepsy |
| Study Type i.e. Cohort etc | cohort |
| Target sample size | 300 |
|  |  |
| **STUDY TIMELINES** |  |
| Study Duration/length | 3 years |
| Expected Start Date | 01/04/2020 |
| End of Study definition and anticipated date | 31/03/ 2023 |
| Key Study milestones  | 01/04/2020: study submission, budget and contract to be finalised.01/08/2020: first patient recruitment31/12/2020: complete patient recruitment |
| **FUNDING & Other** |  |
| Funding  | Wellcome Trust, 215 Euston Rd, London NW1 2BEEpilepsy Research UK, CAN Mezzanine, 7-14 Great Dover St, London SE1 4YR |
| Other support  |  |
| **STORAGE of SAMPLES** **(if applicable)** |  |
| Human tissue samples | none  |
| Data collected / Storage | Not applicable |
| **KEY STUDY CONTACTS** | Full contact details including phone, email and fax numbers |
| Chief Investigator  | Prof JS Duncan |

**KEY ROLES AND RESPONSIBILITIES**

**SPONSOR:** The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

**FUNDER:** The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

**CHIEF INVESTIGATOR (CI):** The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the RE of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

**PRINCIPLE INVESTIGATOR (PI):** Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

**KEY WORDS**

Epilepsy Epilepsy surgery Brain imaging MRI

**LIST OF ABBREVIATIONS**

|  |  |
| --- | --- |
| AE | Adverse Event |
| AR | Adverse Reaction |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| DMC | Data Monitoring Committee |
| GAfREC | Governance Arrangement for NHS Research Ethics |
| HTA | Human Tissue Authority |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| MD | Medical Device |
| ISRCTN | International Standard Randomised Controlled Studies Number |
| PI | Principle Investigator |
| PIS | Participant Information Sheet |
| QA | Quality Assurance |
| QC | Quality Control |
| RCT | Randomised Clinical Study |
| REC | Research Ethics committee |
| SAR | Serious Adverse Reaction |
| SAE | Serious Adverse Event |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| SSI | Site Specific Information |
| TMF | Trial Master File |
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# INTRODUCTION

Sixty million people have epilepsy and a third continue to have seizures despite medication, with risks of fatality, brain damage, physical harm and psychosocial disorders. Neurosurgery can control epilepsy if the responsible part of the brain is removed. We have treated 1074 individuals with epilepsy surgery since February 1990. In optimal circumstances 80% have remissions of 1 year or more, and 40% never have another seizure. There may, however, be adverse effects. After temporal lobe surgery 30% of individuals develop increased difficulty with memory and language, and 10-20% may lose part of their field of vision.

Over the last decade we have worked to improve the outcome of epilepsy surgery: to increase the numbers of suitable individuals, improve the chances of remission and reduce risks of adverse effects, by using sophisticated brain imaging methods to guide neurosurgery.

Over the next 4 years we will implement methods to improve epilepsy surgery, streamline the pathway and so improve access by:

1. Implementing systematic analysis of seizure symptoms to better implicate the areas of brain involved in each

individual. This information is combined with results of MRI and other brain scans and electrical recordings from the scalp (EEG) and viewed in 3-dimensions to plan a resection or, if needed, the placement of recording electrodes in the brain to define the sites of seizure onset.

2. Use computer-assisted analysis of brain scans to define the best trajectories 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 optimal chance of stopping seizures, and minimized risk of collateral damage.

# BACKGROUND AND RATIONALE

Epilepsy affects over 450,000 people in the UK. Drug therapy does not control seizures in 30-40% of patients [1]. Epilepsy surgery is a cost effective treatment for medication refractory focal epilepsy, enhancing quality of life [2,3] and is underutilized in the UK [4]. In a randomised controlled trial of temporal lobe epilepsy surgery, 58% of patients were seizure free 1 year after surgery, compared with 8% after continued drug trials [5]. Resections outside the temporal lobe, which often require invasive electroencephalography (EEG), result in 40-60% seizure freedom [6-8]. Removal of a focal abnormality improves the chances of seizure freedom to 70% [9]. In 25% of surgical candidates, current in vivo structural MRI is unremarkable and other techniques are needed to infer the likely cause of the epilepsy. Defining the area to be removed depends on the integration of clinical, EEG and imaging data and may require placement of intracranial electrodes that must be precisely placed to sample relevant areas and avoid damaging veins.

The area giving rise to seizures is defined and the extent of the resection is constrained by the risk of damaging eloquent areas of the brain that are necessary for essential functions such as language, motor control, sensation and vision. As the threshold for epilepsy surgery decreases, the stakes in terms of risk of causing new deficits are higher than ever before.

Over the last six years, we have developed methods to analyse and visualize multimodality brain scan images in 3-dimensions and to use these to place electrodes in the brain to identify the sites of seizure onset, and to plan resections (10,11). We have developed new image analysis and visualization routines that we anticipate will be beneficial to the whole epilepsy surgery pathway.

**Anticipated impact**

1,000 persons per year are candidates for epilepsy surgery in the UK, but only half of these undergo treatment, largely because of concerns of causing neurological deficits. Simplifying the pathway, and improving the visualization of critical areas, veins and target areas will increase the precision and accuracy of surgery, resulting in improved outcomes, with resection of target areas, less post-operative morbidity and, in consequence, potentially curative treatment being offered to more individuals.

## Current state of the proposed methodology

We have an internationally respected epilepsy surgery programme [12-14]. We implemented in vivo MRI visualization of subtle cerebral abnormalities that may underlie refractory epilepsy [15], integrated with PET, SPECT and EEG-fMRI of epileptic activity.

Imaging modalities that may be included in the display include visualization of structural lesions, cortical veins, representation of critical white matter tracts using tractography (optic radiation, cortico-spinal tract, arcuate, uncinate, inferior lateral and inferior fronto-occipital fasciculi); eloquent cortex as indicated using functional MRI (motor, language, sensation, vision, memory) and measures of abnormal function that infer the location of the seizure onset zone (hypometabolism on fluoro-deoxyglucose PET, ictal hyperperfusion on SPECT, electrical and magnetic source imaging).

We pioneered integrating fMRI and tractography to visualize the white matter connections of eloquent cortex and probabilistic tractography of the optic radiation to predict and prevent visual field defects after temporal lobe surgery [17], and have refined methods for identifying other relevant tracts [18]. We have treated 1074 individuals with epilepsy surgery since February 1990. We established the integration of multimodal brain imaging data in 3-dimensions for planning surgery [19]. The National Hospital for Neurology and Neurosurgery (NHNN) has Medtronic Stealth neuronavigation systems in the operating rooms, for implanting electrodes, and BrainLAB interventional MRI for guiding resections.

# OBJECTIVES

The purpose of this research is to improve the chances of seizure freedom, and to reduce the risks of new deficits from neurosurgery for epilepsy. To achieve this, we need to identify in 3-dimensions the parts of the brain that generate seizures in each individual person, and map this onto an MRI scan of the brain structure, and include this information in the MRI scans used to direct neurosurgery, and at the same time show the operating surgeon the critical structures that must be preserved so that damage to important brain functions is avoided.

The four 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,20 of whom will subsequently be offered a resection. The remainder will not proceed past the initial phase 1 investigations of MRI, scalp video-EEG telemetry, neuropsychology and neuropsychiatry assessments.

**1. Symptom analysis.** To implement systematic analysis of seizure symptoms to better implicate the areas of brain involved in each individual. This information is combined with results of MRI and other brain scans and electrical recordings from the scalp (EEG) and viewed in 3-dimensions to plan a resection or, if needed, the placement of recording electrodes in the brain to define the sites of seizure onset.

**2. Optimal electrode planning.** To use computer-assisted analysis of brain scans to define the best trajectories for recording electrodes in the brain at sites thought to be giving rise to seizures, whilst avoiding blood vessels, based on prior successful trajectories.

**3. EEG analysis**. To analyse the electrical signals recorded from electrodes in the brain, visualising this in 3 dimensions in relation to the anatomical locations of the electrodes, and analysis of MRI and other brain scans to determine which parts of the brain need to be removed to control the epilepsy.

**4. Resection planning.** Integrate all previous information from imaging, symptoms, and EEG analyses to plan surgery so that there is the optimal chance of stopping seizures, and minimized risk of collateral damage.

# STUDY DESIGN

**Procedures**

**Symptom analysis.** We have identified the 50 major symptoms that may occur at the start of epileptic seizures and, from reports associating these symptoms with seizure freedom after resection of different parts of the brain, have built up a 3-dimensional map relating symptoms to areas of brain that are likely to be involved in generating seizures. With future patients we will analyse the symptoms that occur in their seizures and, by reference to the symptom map, will identify areas that are likely to be involved in the epilepsy and whether this is discrete or widespread and involving the left, right or both sides of the brain. Individuals at the start of the evaluation of their epilepsy for possible epilepsy surgery will be asked to complete a structured questionnaire of the symptoms. This will be supplemented by the account of a witness and review 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 multi-disciplinary team (MDT) involving neurophysiologists, neurosurgeons, neurologists and image processing specialists. The suggestions for implantation from the symptom analysis will be compared with the MDT recommendations already made without this consideration. The MDT will then have the option to modify the original strategic plan. The immediate endpoint will be the change in the planned implantation.

**Optimal electrode planning.** 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. As is clinical standard care, the treating consultant neurosurgeon will check the safety of each and every trajectory. There is no patient involvement in this process.

We have shown that computer-assisted guidance enables quicker and safer planning of precise trajectories of intracranial electrodes to record epileptic seizure onset and spread in the brain. In this project we will enhance this process by using as a starting point, the trajectories planned and successfully implemented and shown to be safe, in 70 previous patients, with 7-15 electrodes apiece. We will integrate additional patients into the prior experiences during the course of the study. As further experience accumulates, the prior experiences of intracranial electrode plans will be more comprehensive.

The immediate endpoint will be the time it takes to plan a study, and the safety metrics of proximity to blood vessels compared to recent data of implantations planned without the use of prior trajectories as a starting point.

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.A further outcome measure will be the occurrence of any complications from the electrode insertion.

**EEG analysis.** 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 3-dimensions and 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 3-dimensions derived EEG signals such as high frequency ripples and Gamma power and explore their concordance with other EEG makers of the sites of seizure onset.

**Resection planning.** In individuals who do not require intracranial EEG 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.

For individuals who have had intracranial EEG, 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. This plan 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.

In this project, we will display the EEG contacts that detect epileptic activity in a 3-dimensional 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. The suggested plan is then reviewed with the consultant neurosurgeon who will plan the detail of the operative approach and resection, and subsequently discuss the plan with the individual patient. At all times the image guidance offered is subordinate to the clinical opinion of the treating consultants.

The group of patients who are offered brain resections will be heterogeneous, as any part of the cerebral cortex may give rise to epilepsy. One of the most common operations is the anterior temporal lobe resection for medically-refractory mesial temporal lobe epilepsy. In this group in an observational cohort study we will use 3D imaging guidance to ensure inclusion of the temporal portion of the piriform cortex in the resection and avoidance of language-related white matter tracts and of the optic tract and radiation.

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

The 3-dimensional 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 eyepiece.

The immediate endpoint will be a comparison of the resection plan derived from the conventional method used, with the resection plan produced by the image-guided methods. Subsequent endpoints will be neurological and neuropsychological deficits following surgery, and those that are persistent at 4 months following surgery, compared with recent historical cases operated by same team.

### Outcome measures

**Symptom analysis**: change in the planned implantation from the original clinical plan without these data.

**Optimal electrode planning**: The time taken to plan a study, and the safety metrics of proximity to blood vessels compared to recent data of implantations planned without the use of prior trajectories as a starting point. A further outcome measure will be the occurrence of any complications from the electrode insertion.

**EEG analysis**: this is under development. Outcome measures will be usability. Subsequent studies would use seizure outcome as result of using methods to define epileptic focus and indicate extent of resection.

**Resection planning**: comparison of the resection plan derived from the conventional method used, with the resection plan produced by the image-guided methods.

Neurological and neuropsychological deficits following surgery, and those that are persistent at 4 months following surgery, compared with recent historical cases operated by same team.

Seizure freedom at 12 months following surgery, compared with recent historical cases operated by same team that will be derived from our epilepsy surgery database [13,14].

# STUDY SCHEDULE

All potential participants will be having evaluation for epilepsy surgery at NHNN. They will be identified by the epilepsy surgery administrator / coordinator at NHNN and if they express interest to learn more about the study, they will be introduced to the clinical research assistant

**Follow up**

The development of any new neurological deficit will be evident within days of surgery. As is standard clinical practice, all patients will have clinical, neuropsychological and MRI follow up at 3-4 and 12 months and then annual clinical follow up to determine outcome in terms of seizure control and neuropsychological changes.

Prior to surgery and 3-4 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.

As noted in the sections on procedures, outcome measures and analysis, there are a range of outcomes through the epilepsy surgery pathway, with post-operative status being determined at 3-4months after surgery, and then 12 months and then annually.

For analysis purposes the end of the study will be 12 months following surgery.

Participants will be at liberty to withdraw from the study without having to give any explanation and at any time, and will be assured that this will not impact on their future clinical care. Individual patient data that have been acquired up that point will be kept in the analysis.

# CONSENT

The research project will be explained verbally and in writing to potential participants and they will be given at least 24 hours in which to decide whether they wish to participate. If they have capacity to give informed consent, as evidenced by ability to understand what is involved, the implications of participating and of not participating, can remember the information and to indicate their choice, they will be asked to do so in writing.

# ELIGIBILITY CRITERIA

**Inclusion / exclusion**

An inclusion criterion is that participants will be being evaluated for epilepsy surgery at NHNN, will be fit for neurosurgery, and able to given informed consent to neurosurgery. Age limits will be 18 years to 70 years, this being the age range of epilepsy surgery at NHNN

# RECRUITMENT

All potential participants will be having evaluation for epilepsy surgery at NHNN. They will be identified by the epilepsy surgery administrator / coordinator at NHNN and if they express interest to learn more about the study, they will be introduced to the clinical research assistant, who will explain the research verbally and, if the individual patient is interested to participate, they will be sent written information and will be contacted after 1-7 days to see if they have questions and wish to participate. If they do, they will asked to indicate their wish to participate in writing. The study will not be presented by, or consent to participate taken by, the patients’ treating team.

# STATISTICAL METHODS

### Power calculation

We will recruit 70-100 patients per year who are candidates for epilepsy surgery evaluation at NHNN. Of these we estimate that 40 will proceed directly to resection without requiring prior SEEG. 30 per year will proceed to intracranial stereotactic EEG (SEEG), of whom 20 will proceed to cerebral resection.

Focal epilepsy is very diverse and heterogeneous, affecting any part of the brain. With a study of this nature, that seeks to develop software tools to assist clinical decision taking, formal power calculations are not appropriate and many aspects are regarded as pilot studies. If there is evidence of possible benefit we will then set up Randomised Controlled Trials (as we have recently done to evaluate the accuracy and speed of a robotic guidance device for the insertion of SEEG electrodes into the brain).

The component of the study to evaluate the benefits of increased precision for the surgical removal of the anterior temporal lobe for refractory mesial temporal lobe epilepsy is amenable to a power calculation.

Sample size of the anterior temporal lobe resection subgroup: 58 patients will suffice to detect a difference in the proportion of seizure-free patients one-year post-operation of 0.2, compared to historical one-year seizure freedom of 0.59, one sample Z-test (5% significance level, power=90%). This calculation includes allowance for an anticipated loss to follow-up rate of 2%.

**Statistical analysis**

**Symptom analysis**: We will use summary statistics to indicate the numbers and cerebral locations of changes in electrode implantations.

**Optimal electrode planning**: We will use summary statistics and linear regression models to compare time and electrode safety metrics (proximity to blood vessels) between the current and recent historical groups. Fisher’s exact test or a Pearson’s Chi-squared test will be used to compare incidence of complications between the groups.

**EEG analysis**: This is developmental. We will explore the spatial relationship between the location of parametric EEG features with other EEG measures of seizure onset and propagation with Dice scores.

**Resection planning**: We will use summary statistics of planned resection volumes, using traditional and image-guided methods, and of overlap with Dice scores.

**Statistical analysis of the anterior temporal lobe resection subgroup**

Seizure outcome: One sample Z-test of null hypothesis to detect a difference in the proportion of seizure-free patients one-year post-operation of 0.2, compared to historical one-year seizure freedom of 0.59 (5% significance level, power=90%). with calculation of 95%CI.

We will compare distribution of ILAE seizure outcome score at one-year post-operation between study and historical groups using Pearson’s Chi2. A logistic regression model will be fitted to estimate the proportion of seizure-free patients, with a group covariate (historical or current study) to compare proportions between groups. The odds ratio for seizure freedom at one year (with an associated 95%CI), comparing the ‘historical’ and ‘current’ study groups will be estimated.

Language: Post-operative word finding and vocabulary decreases will be summarised with scatterplots against an estimated percentage of the cut of parcellated white matter fasciculi. Multivariable regression model will use word-finding score as outcome variable and an estimated percentage cut through, tract type and language fMRI lateralization index as explanatory variables, to assess the effect of the proportion of fasciculi transected on word finding.

**Language fMRI**: activation maxima and functional connectivity will be compared pre and post-operatively using SPM12.

# PATIENT AND PUBLIC INVOLVEMENT (PPI)

We have engaged extensively with a cohort of individuals who are contemplating or have had epilepsy surgery at NHNN since 1990. This group “BrainBuddyUK” was formed in 2018 and meets every 3 months, with 50-80 attendees, to discuss their experiences, anxieties and aspirations and to interact with the clinical and research teams. Clearly expressed goals are to simplify the epilepsy surgery pathway and to improve access, to improve the selection of suitable patients, to increase the seizure freedom rate and to reduce surgical morbidity by making resections more precise and smaller.

Our suggestions to achieve this with image-guidance was strongly endorsed. The favoured design for the next stage of development was observational cohort studies, with the image guidance forming a decision support tool that was used at the discretion of the treating consultants and comparing outcome with recent cohorts treated by the same team.

We will keep the group updated with the progress of the research at the regular meetings and with the results. Results will also be shared with other Epilepsy NGOs: Epilepsy Society, Epilepsy Action, Epilepsy Research UK, International League against Epilepsy. We will work with the Communications Departments of UCL and UCLH to share the progress made with National and International written and transmitted Media.

# FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The research costs for the study have been supported by :

Wellcome Trust: Ref 218380/Z/19/Z £752,983. Awarded 06 January 2020

Epilepsy Research UK: Ref P1904 £163,573. Awarded 16 June 2019

# DATA HANDLING AND MANAGEMENT

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act’s core principles. UCL/UCLH is the data controller; the UCL/UCLH Data Protection Officer is Matthew Hall <matthew.hall@nhs.net. The data processor is Prof JS Duncan. The study will be collecting the following personal data:

Directly from patients’ history, UCLH clinical record and results of investigations. Patient identifiable data will only be stored on UCLH computers, backed up on the UCLH network. If data needs to be analysed on UCL networks for complex statistical analysis, they will be stored in the UCL "Data Safe Haven" for sensitive data. patient identifiers will be removed and the data pseudonymized with code numbers, with the key retained only in the secure UCLH network.

Access to these will be restricted to the data controller and clinical research assistant. Any data that is shared with others outside of UCL or UCLH, as a data-sharing agreement, will be anonymised so that individual patients will not be identifiable. Individual patients will not be identifiable from any publications emanating from this work.

The research team will access medical records after a patient has given informed consent to participate in the study. The research team will be employed by UCL and have honorary clinical contracts with UCLH NHS Foundation Trust (the parent NHS Trust for NHNN) that give authorisation to access patient identifiable data.

As is clinically standard, images that need to be transferred to the operative neuronavigation station will be sent via the secure NHS network. Encrypted NHS USB drives will be used to transfer imaging data to the operative neuronavigation station.

Patient identifiable data will be stored on UCLH computers, backed up on the UCLH network. If data needs to be analysed on UCL networks, they will be stored in the UCL "Data Safe Haven" for sensitive data. Patient identifiers will be removed and the data pseunonymized, with code numbers, with the key retained only in the secure UCLH network.

Any data stored on a laptop will be encrpyted according to NHS standards. Hard copy of papers relating to this study and participants, will be kept in a locked filing cabinet in a locked office, in a Department that has access controlled by swipe cards and combination key locks.

As is clinically standard, images that need to be transferred to the operative neuronavigation station will be sent via the secure NHS network. All data will be protected in accordance with the UCL Data Protection Policy and NHS Code of Practice on Confidentiality (2003). Members of the patient's care team also involved in the research will have access to this data.

We will follow GDPR principles, and the requirements of the NHS Code of Confidentiality. The study information leaflets given to patients prior to them giving informed consent will indicate what data may be accessed for this study and who will access these data. All members of the clinical and research team will have Information Governance training as part of the UCLH statutory and mandatory training for all those with substantive and honorary clinical contracts.

Any summary data that might be transmitted outside of UCL, for example if there was a meta-analyisis of data from many sites, would be fully an irreversibly anonymised.

After giving of informed consent, relevant personal data in the clinical file will be accessed by the research team. All access to clinical data is audited by UCLH.

The research team will be employed by UCL and have honorary clinical contracts with UCLH NHS Foundation Trust (the parent NHS Trust for NHNN) that give authorisation to access patient identifiable data. All members of the clinical and research team will have Information Governance training as part of the UCLH statutory and mandatory training for all those with substantive and honorary clinical contracts.

If internal or external audits are carried out, participants will be identified by an pseudonymised code. If staff from NHS R&D offices and/or regulatory inspectors require to see completed consent forms, these will be made available.

If a case report or small series in which it may be difficult to conceal an individual patient’s identity, was suggested to be published, this would only proceed with the individual’s written specific consent, having reviewed what was proposed to be included in the publication.

We will retain data for 6 years after the initiation of the study, as study enrolment will continue for up to 3 years, patients will spend 1-2 years having presurgical evaluation and post-operative follow-up is over 1 year after surgery. These are in accord with UCL and UCLH standards, as the whole dataset will need to be available for some analyses. These data will only be accessible to the data controller and clinical research assistant.

Research data are retained by UCL in their capacity as sponsor for 20 years after the research study has ended. Data are then securely destroyed.

# MATERIAL/SAMPLE STORAGE

There will not be any physical samples that require storage.

# PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCL/UCLH

The Sponsor considers the procedure for obtaining funding from Wellcome Trust and Epilepsy Research UK to be of sufficient rigour and independence to be considered an adequate peer review.

# ASSESMENT AND MANAGEMENT OF RISK

We have engaged with a cohort of individuals who are contemplating or have had epilepsy surgery at NHNN. This group “BrainBuddyUK” was formed in 2018 and meets every 3 months, with 50-80 attendees, to discuss their experiences, anxieties and aspirations and to interact with the clinical and research teams. The favoured design for the next stage of development was observational cohort studies, with the image guidance forming a decision support tool that was used at the discretion of the treating consultants and comparing outcome with recent cohorts treated by the same team.

The research involves the analysis of symptoms, brain imaging and EEG data and formulation of decision support tools that are designed to facilitate optimal clinical decision making.

A potential risk is that the research protocol implies a course of action that carries risk, such as an inaccurate trajectory for an intracranial electrode. We guard against this eventuality by, at every step of the way, all steps being under the direct manual control of, and checking by, treating consultants, as is the case for standard clinical care. All decisions concerning trajectories and resections will be checked using the conventional clinical CE-marked software. Thus, we are confident that the developments we make will offer improved solutions, with the safety net of consultants checking, and only using the data if they are in accord with their expert opinion.

# RECORDING AND REPORTING OF EVENTS AND INCIDENTS

## 16.1 Definitions of Adverse Events

|  |  |
| --- | --- |
| **Term** | **Definition** |
| Adverse Event (AE) | Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.  |
| Serious Adverse Event (SAE). | Any adverse event that:* results in death,
* is life-threatening\*,
* requires hospitalisation or prolongation of existing hospitalisation\*\*,
* results in persistent or significant disability or incapacity, or
* consists of a congenital anomaly or birth defect
 |
| \*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.\*\* Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE. |

## Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

* + 1. **16.2.1 Severity**

|  |  |
| --- | --- |
| **Category** | **Definition** |
| Mild | The adverse event does not interfere with the participant’s daily routine, and does not require further procedure; it causes slight discomfort |
| Moderate | The adverse event interferes with some aspects of the participant’s routine, or requires further procedure, 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 |

* + 1. **16.2.2 Causality**

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

If a differentiated causality assessment which includes other factors in the study is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this study to capture events related to the product application procedure, with image guidance as a decision support tool. The assessment of relationship of an adverse event to these additional safety issues will also be carried out as part of the study.

The differentiated causality assessments will be captured in the study specific AE Log and SAE form.

The following categories will be used to define the causality of the adverse event:

|  |  |
| --- | --- |
| **Category** | **Definition** |
| Definitely: | There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. |
| Probably: | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely |
| Possibly | There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant events). |
| Unlikely | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant’s clinical condition). |
| Not related | There is no evidence of any causal relationship. |
| Not Assessable | Unable to assess on information available. |

* + 1. **16.2.3 Expectedness**

|  |  |
| --- | --- |
| Category | Definition |
| *Expected* | An adverse event which is consistent with the information about the procedure defined in this protocol. |
| *Unexpected* | An adverse event which is not consistent with the information about the procedure clearly defined in this protocol. |

\* this includes listed events that are more frequently reported or more severe than previously reported

## Recording adverse events

All adverse events will be recorded in the medical records in the first instance.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded in the CRF until the participant completes the study

## Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor’s AE log.

All SAEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

Completed forms for unexpectedSAES must be sent within 5 working days of becoming aware of the event to the Sponsor

**Email forms to**

Research-incidents@ucl.ac.uk

**Flow Chart for SAE reporting**

**Was the event an Other Notifiable event?**

See section 16.5 for notifiable events which should also be reported as serious

**Submit SAE form to Sponsor within 5 working days**

Record in medical records, CRF (and AE Log if required)

**Complete an SAE report form**

No

Yes

Record in medical records,

And CRF in accordance with the protocol

**Is the event specified as an adverse event which does not require immediate reporting as an SAE?**

Yes

Yes

Record in medical records and CRF (if applicable)

No

No

**Was the event Serious?**

**AE occurs**

**Assign Severity Grade**

### 16.5 Serious Adverse Events that do not require reporting

You may choose not to report some particular SAEs to the sponsor, for example if they are expected to occur on a regular basis and offer no further new information to your safety profile or are related to the disease area of the participants. It should be specified that where the frequency or severity of these events is unusual they must be reported. These events must continue to be recorded in the medical records, CRF and the AE log (if required), however you may state that you will not complete an SAE form and forward it to the sponsor. Provide the rationale for doing so.

## Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

## Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

 A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

## Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.

b. It is contrary to specified or expected standard of patient care or service.

c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d. It puts the Trust in an adverse position with potential loss of reputation.

e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

1. It is an accident or other incident which results in injury or ill health.
2. It is contrary to specified or expected standard of patient care or service.
3. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
4. It puts the Trust in an adverse position with potential loss of reputation.
5. It puts Trust property or assets in an adverse position or at risk of loss or damage.

# MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

Every six months we will formally review the progress of all patients who have participated in the study and note whether there have been any adverse events. For those who have resections we will note whether they are free of seizures following surgery and whether there were any complications.

We will use a Cumulative summation analysis (CUSUM)analysis to determine whether there is any concern that adverse effects are more common than in recent historical controls. CUSUM is an early warning mechanism that has previously been employed to ensure quality and safety standards within clinical trials as well as learning curve

assessment. We intend to employ CUSUM to monitor outcomes from study patients using historical data to compare expected frequencies of complications such as visual field defect, language impairment, sensory-motor deficit, infection rate, haemorrhage rate and neuropsychological decline. CUSUM trends indicating increased complication

rates will be flagged to the chief investigator.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

#

# TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

# INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL.  Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights (“IPR”) to UCL and to disclose all such know-how to UCL. with the understanding that they may use know-know gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of UCL confidential information or infringement of UCL IPR.

# INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London 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 otherwise.

# ARCHIVING

UCL recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCL for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site’s study documents for [insert duration] and in line with all relevant legal and statutory requirements.

# PUBLICATION AND DISSEMINATION POLICY

We will submit papers on the results of this study to high-impact Journals and prestigious scientific conferences. All those contributing to the studies will be invited to co-author publications We will also share with Patients and Public and epilepsy NGOs: Epilepsy Society, Epilepsy Action, Epilepsy Research UK, International League against Epilepsy. We will work with the Communications Departments of UCL and UCLH to share the progress made with National and International written and transmitted Media.

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# APPENDICES