Clinical Investigational Plan (CIP) for Medical Device Studies

Full title of Investigation:	Single-blinded Randomised Case Control Parallel Group Single-site Investigation of Stereoencephalography Electrode Placement in Patients with Refractory Focal Epilepsy.
Short title:	A Randomised Control Trial of SEEG Electrode Placement methods
Version and date of Clinical Investigation Plan (CIP):	Version 3.0, 03 Jul 2017
Sponsor:	University College London
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1.0	**26 Oct 17**	First Version	

Signatures

The Chief Investigator (CI) and the JRO have discussed this Clinical Investigation Plan (CIP). The investigator agrees to perform the investigations and to abide by this CIP.

The investigator agrees to conduct the Investigation in compliance with the approved CIP, EU Good Clinical Practice (GCP) and UK Regulations for Devices (SI 2002/618; as amended) for regulated studies, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

J S Duncan

Signature Date

Sponsor Representative

Rajinder Sidhu

UCL Signature Date

This CIP template is intended for use with UK sites only.

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
CI	Chief Investigator
CIA	Clinical Investigation Agreement
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organisation
DCF	Data Clarification Form
DD	Device Deficiency
EC	European Commission
EU	European Union
EUDAMED	European Medical Devices Regulatory Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IMD	Investigational Medical Device
ISF	Investigator Site File
JRO	Joint Research Office

MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute of Clinical Excellence
NIST	National Institute of Standards and Technology
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UK	United Kingdom
USADE	Unanticipated Serious Adverse Device Effect

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A.1 Overall Synopsis of Clinical Investigation

Title:	Single-blinded Randomised Case Control Parallel Group Single-site Investigation of Stereoencephalography Electrode Placement in Patients with Refractory Focal Epilepsy.
Short title:	A Randomised Clinical Trial Of SEEG Electrode Placement methods
Device:	iSYS1 trajectory guidance system (iSYS Medizintechnik)- Class I
Objectives:	Primary: To compare the operative time of the iSYS1 trajectory guidance system (Medizintechnik GmbH) with the currently used frameless mechanical arm based technique for the placement of SEEG depth electrode bolts in patients undergoing pre-operative evaluation for drug resistant focal epilepsy. Secondary: To compare the accuracy and safety of iSYS1 trajectory guidance system (Medizintechnik GmbH) SEEG depth electrode placement with mechanical arm based insertion based on: a) Accuracy of SEEG depth electrode placement, as assessed by skull entry point, error of angle of implantation of intracranial bolt and distance of the actual electrode tip compared to the target point as defined by the preoperative plan and target region sampled. b) Incidence of clinically significant and non-clinically significant radiologically detected post-operative haemorrhages c) Infection rate d) New post-operative neurological deficits e) Operator (surgeon) based opinions for ease of use and perceived safety of the iSYS1 trajectory guidance system compared to conventional mechanical arm based insertion f) Routine clinical follow up

Type of Investigation:	Class I - Single-blinded Randomised Case Control Parallel Group Single-site Investigation of Stereoencephalography Electrode Placement in Patients with Refractory Focal Epilepsy.
Investigation design and methods:	Patients with refractory focal epilepsy who are considered for neurosurgery undergo a series of neurophysiological, neuropsychological, neuropsychiatric and multi-modal imaging investigations prior to review in a multi-disciplinary team setting. In individuals in whom the epileptogenic zone cannot be accurately determined or the investigations are not in agreement (non-concordant) then further 'invasive' testing is required, with stereoencephalography (SEEG) to provide continual video and EEG monitoring to determine the site of epileptic activity in the brain. A number of methods exist for the placement of SEEG electrodes and it is unclear which of these is best. A total of 32 patients requiring SEEG will be enrolled and undergo block randomization to undergo implantation with the use of a) the currently used mechanical arm based technique (using the precision aiming device) or b) iSYS1 trajectory guidance system (using the iSYS1, Medizintechnik GmbH) for aligning the trajectory of the electrodes to be placed. Patients will be blinded as to which of the SEEG techniques they undergo. As is routine clinical practice following electrode insertion patients will undergo a CT and MRI scan of the brain post-implantation to assess accuracy of electrode implantation and detection of complications.
Investigation duration per participant:	14 days (From consent to last Investigation assessment)
Estimated total Investigation duration:	18 months
Planned Investigation sites:	Single-site: National Hospital for Neurology and Neurosurgery (UCLH)

Total number of participants planned:	32
Main inclusion/exclusion criteria:	Inclusion criteria: • Age 18-80 years • Drug refractory focal epilepsy • Deemed to require SEEG placement as part of routine clinical care following multidisciplinary team meeting decision • Informed consent from patient to undergo intracranial SEEG investigation as part of routine clinical care Exclusion criteria: • Pregnancy • Uncorrectable coagulopathy • Lacking capacity to consent • Patients who are deemed unfit for general anaesthesia
Statistical methodology and analysis:	**Power calculation** A sample size of 11 patients in each arm (22 patients in total) will be sufficient to detect a change of at least 20% in the median electrode implantation time, using a two-sample t-test with a power of 90% and a significance level of 5%. Based on our pre-clinical testing and a recent study by Dorfer et al(1), we estimate the median electrode implantation time using the current conventional method to be 20 mins with an estimated standard deviation of 5 mins. We make the conservative assumption that an estimate of the time taken for SEEG electrode implantation time using the iSYS1 trajectory guidance system is 16 min with a standard deviation of 5 mins. We assume that the time taken for electrode implantation has a log-normal distribution and hypothesis testing shall be performed using log- transformed time values. We account for the clustering of electrodes within a patient through the assumption of an intra-class correlation coefficient of 0.2 and an average number of electrode implantations of 10 per patient. Due to the possibility of patient withdrawal from the study or loss to follow up we aim to recruit 16 patients in each arm (32 patients in total). Due to the higher estimated difference in secondary endpoints (entry and target point accuracy) this number of patients will provide a power of >95% for these factors.

Statistical analysis

Based on the above power calculations, random effects linear regression models, that account for clustering of electrodes within a patient, will be fitted to compare metrics by the study statistician Dr A O'Keeffe. Blinded data will also be provided for review by the data monitoring and ethics committee (DMEC) consisting of Dr S Eriksson (Chair), Pr S Wolfsberger and an independent statistician. Reviews will occur after randomization of 6, 12 and 18 subjects to determine whether the results of the study so far mandate premature termination.

Randomisation

Thirty-two patients will be enrolled and block randomized, by an independent statistician through the use of a computer generated system that contains a code assigning the patient to one or other arms of the study, with the use of a) the currently used Mechanical arm based technique (using the precision aiming device) or b) iSYS1 trajectory guidance system (Medizintechnik GmbH) for aligning the trajectory of the electrodes to be placed.

Blinding

The initial stage of the pre-operative model generation and electrode planning by the clinical team will occur prior to randomization. As such these investigators do not require blinding as this will not be affected by the surgical intervention arm.

Due to the nature of surgical interventions it is not possible to blind the operating surgeons or theatre support staff as to whether the implantation will be mechanical arm based or use the iSYS1 trajectory guidance system. This is because the procedures require different equipment, setup and operative techniques.

Patients will be blinded pre-operatively as to which intervention arm they will be randomized to. This is to prevent patient crossover and unequal recruitment to each intervention arm. Patients who find this unacceptable can withdraw from the study at any time and will undergo the current standard of care (mechanical arm based implantation technique). Patient blinding will be maintained until the end of the study.

A.2 Background

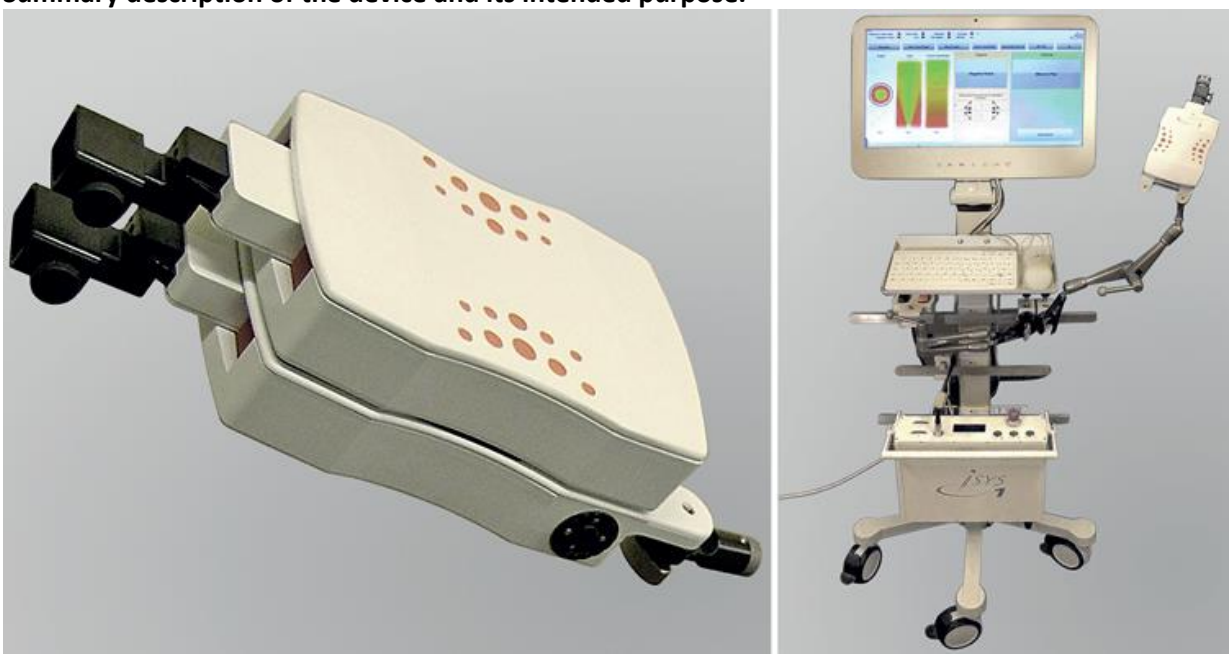
It is estimated 1% of the population suffer from Epilepsy(2,3). Between 30-40% of these patients do not achieve adequate seizure control despite a trial of two or more antiepileptic drugs(3). Seizures carry risk of morbidity and mortality and serious negative psychosocial impacts on patients. Surgical treatment offers a potential cure for these patients(4). To determine whether epilepsy surgery is possible a specialist evaluation is required including detailed clinical, neurophysiological, neuropsychological, neuropsychiatric and multi-modal imaging(5). If the evaluation identifies a defined surgical target as the cause resection can be performed.

In almost half of individuals, non-invasive data are not conclusive and intracranial electrodes are needed to determine the epileptic focus. These comprise subdural grids on the surface of the brain and electrodes implanted deep within the brain (Stereotactic EEG (SEEG) or depth electrodes)(6). Recordings during seizures using these techniques can precisely localize the site of seizure onset and define the resection margins. Depth electrodes carry a number of risks including bleeding, infection and neurological deficit due to damage to the brain as a result of misplacement, with a risk in large centres of 1.3% per patient (7). Electrode trajectories are therefore carefully planned to sample from the intended parts of the brain and to avoid blood vessels and important brain structures.

Currently, neuro-navigation systems are used in combination with a mechanical arm to manually align and insert electrodes along a predefined trajectory. This takes approximately 15-20 minutes per electrode, with 8-15 electrodes for each patient and an error to target of 3.2 +/- 2.2 mm (mean+/-SD)(8,9). A novel trajectory guidance system (iSYS1, Microguided systems, Medizintechnik GmbH) has recently been shown in a pre-clinical and clinical feasibility study to provide a statistically greater degree of accuracy and speed of implantation(1). We therefore aim to undertake a randomized controlled trial to compare the accuracy of trajectory guidance system-assisted electrode implantation in 16 patients, with the currently used mechanical arm based technique in 16 patients. In addition to the mean duration of electrode bolt insertion we will also assess the accuracy of implantation through entry point and target point error from plan, and safety: clinically significant and non-significant haemorrhage rates, infection rate, neurological deficit; and surgeon convenience and safety comments. The proportion of patients that go on to definitive surgical treatment and the subsequent outcome in terms of seizure freedom rate will take 1-2 years to be determined and will therefore be assessed during routine follow up and not directly as part of this randomised clinical control trial.

A.3 Identification and description of the Investigational Device

a) Summary description of the device and its intended purpose.



The iSYS1 is a trajectory guidance system that was initially developed for the implementation of invasive CT-guided interventions to prevent radiation exposure to the physician. The system consists of a control unit (CU) mounted to a computer work station, a mechanical 3-degrees of freedom (DOF) multifunctional arm (MFA), a 4-DOF robot positioning unit (RPU), a needle guide extension (NGE) and a hand control unit (HCU). Cable extensions are used to connect the RPU to the CU. The RPU consists of two flat modules that both have connected disposable sterile arms (see image). The modules are able to move independently of each other such that trajectory guidance can be provided through translation and angulation of the arms. On starting the computer workstation a series of internal verification steps are performed to ensure the integrity of the unit. Once complete this is then connected to the neuronavigation system (Stealth S7 workstation, Medtronic, CE marked device) via a single ethernet connection and the information regarding the trajectory of the electrode for insertion is relayed. The iSYS1 unit is connected securely to the MFA and fixed to the Mayfield clamp (head holding device). The MFA is used by the surgeon to ensure that all of the implemented trajectories are within reach of the iSYS1. When performing a procedure the unit is firstly covered with a sterile drape and the surgeon places the iSYS1 in rough proximity to the site in which the electrode is to be placed (+/- 20mm translation and +/-30 degrees angulation). A visual display on the screen shows when this has been achieved. Once fixed in a satisfactory position, the RPU provides precise submillimeter

alignment to the plan through a series of surgeon controlled iterative steps that take <10 seconds to complete. Instruments can then be passed through working channels that are connected to the disposable arms to provide trajectory guidance.

b) Details concerning the manufacturer of the investigational device.

iSYS Medizintechnik GmbH, Bergwerksweg 21, 6370 Kitzbühel, Austria

c) Name or number of the model/type, including software version and accessories, if any, to permit full identification.

Generic name of device: iSYS 1
Model name: iSYS 1
Model number: 4268

The classification is in compliance with Directive 93/42/EEC, Annex VII, rule 12 and with the Austrian Medical Devices Act (Austrian MPG). The product is **Class I**.
No other rule does apply.

d) Description as to how traceability shall be achieved during and after the clinical investigation, for example by assignment of lot numbers, batch numbers or serial numbers.

For the purposes of this study a single iSYS1 system has been provided by the manufacturer as part of a loan agreement for the duration. As such all procedures will be performed using the single iSYS1 system. For traceability purposes, the serial number of this system is 026, reference number 3908 and manufacturing date 08/2015.

e) Intended purpose of the investigational device in the proposed clinical investigation.

In this proposed randomised control trial the iSYS1 trajectory guidance system will be compared to the currently used, standard of care, frameless mechanical arm based technique for the implantation of SEEG electrodes(9). During the current mechanical arm based implantation technique the patient is firstly anaesthetised prior to registration to the neuronavigation system in which the electrode trajectory plans have been stored. A sterile mechanical arm is fixed to the Mayfield clamp and manual trajectory guidance is provided through alignment of a 'Precision aiming device' (Medtronic Inc.). All image guidance is provided by the Stealth S7 neuronavigation system through the use of infrared tracked positioning probes such as the 'Vertek probe'. Once the trajectory has been manually aligned to the entry point and target, the mechanical arm is tightened to lock the device in position. Drilling of the skull and placement of the securing bone anchored bolt can then proceed through the device if the alignment error provided by the Stealth S7 neuronavigation system is <1mm.

The current limitations with this system are the time it takes to manually align the 'Precision aiming device' to the trajectory, and the error introduced in alignment during tightening of the mechanical arm and any deviation of trajectory that occurs during the course of drilling.

In the current study we propose substituting the step involved with manual alignment of the precision aiming device with the iSYS1 trajectory guidance system to determine if this provides more rapid and accurate alignment to the predefined electrode trajectory plan as has previously been claimed(1). The drilling and electrode insertion will all be performed by the surgeon, as is routine, using the iSYS1 trajectory guidance system solely as a working channel. The iSYS1 trajectory guidance system does not perform or control any instruments or insert any devices into the brain, this remains under the control

of the operating surgeon at all times. The iSYS1 trajectory guidance system works in unison with the S7 stealth station (CE marked) and receives all plan and target alignment information from this system.

f) The populations and indications for which the investigational device is intended.

Patients with refractory focal epilepsy who are considered for neurosurgery are referred to a specialist epilepsy clinic for assessment by a neurologist with specialist expertise in Epilepsy management. If the patient is deemed eligible for epilepsy surgery then a series of neurophysiological, neuropsychological, neuropsychiatric and multi-modal imaging investigations are performed and reviewed in a multi-disciplinary team setting. Following these investigations if the area in which the seizures arises (epileptogenic zone) can be accurately determined and all of the different tests are concordant, then the patient may proceed to surgery. This is the case in roughly half of the patients who undergo assessment(5). In individuals in whom the epileptogenic zone cannot be accurately determined or the investigations are not in agreement (non-concordant) then further 'invasive' testing is required, with intracranial EEG. This may comprise recording electrodes that are placed on the surface of the brain (subdural grids) or within the brain (depth electrodes) to measure the electrical activity arising from different parts of the brain. With the electrodes in place the patient has continual video and EEG monitoring to determine the site of epileptic activity in the brain. If a focal onset is determined that is distant from eloquent cortex (primary motor, sensory, language) then surgery can be recommended.

Intracranial EEG recording is preceded by a series of imaging studies, including but not limited to: magnetic resonance imaging (MRI), Computed tomography (CT) to visualise the skull, angiography and venography, functional MRI (fMRI), diffusion tensor imaging (DTI), positron emission tomography (PET) and ictal single positron emission tomography (SPECT). These investigations are reviewed in a weekly multidisciplinary team meeting and the areas for depth electrode placement are determined. A safe trajectory for the placement of the depth electrodes to ensure accurate recordings without injuring vital parts of the brain or coming in close contact with blood vessels, to prevent risk of bleeding, is paramount. We intend to recruit patients who have already been through the above-mentioned investigations as part of their routine care and now require SEEG to determine if definitive resection of the epileptogenic zone is possible.

g) Description of the investigational device including any materials that will be in contact with tissues or body fluids.

The iSYS trajectory guidance system is not in contact with tissues or body fluids. A bone fixated guide for the implantation of depth electrodes (GIDE), various reduction tubes, drills and bolts are all passed through the sterile needle guide adapter by the surgeon and it is these tools that are in contact with the patient's skull. This is in accordance with the current standard of care where the surgeon controls all aspects of drilling and electrode insertion.

h) Summary of the necessary training and experience needed to use the investigational device.

All SEEG and manual electrode implantations during the clinical trial will be performed by two Consultant neurosurgeons working simultaneously. Manuals have been provided (included within the technical file) for use of the iSYS1 trajectory guidance system. Pre-clinical implantation tests on phantom skulls (as outlined in section A4) have been performed to gain experience in the use of the device in accordance with the manufacturer's recommendation. To gain clinical experience the surgeons had travelled to Vienna, Austria to learn how to use the system and discuss this with a surgeon who uses the iSYS1 trajectory guidance system routinely(1) . No certification has been issued

for this training as no courses are currently provided by the manufacturer. Through a series of quality assurance analyses the accuracy of standard of care (manual) implantations with our frameless implantation technique is 3.66+/-2.21 mm (mean+/-SD)(9). To reduce the risk to patients and determine the accuracy of the iSYS1 insertion method a series of pre-clinical studies have been performed. 3D printed phantoms were generated from three patients who had previously undergone manual implantations of 21 SEEG electrodes in total. The phantom skulls were 3D printed in Duraform PA (3D systems Inc.) following a series of drill tests in which this was found to closely replicate the properties of skull bone. The phantoms were then registered to the patient CT scans of the skull using the Stealth S7 neuronavigation station and a high level of registration accuracy (<0.4mm) was achieved in all cases showing the high anatomical replication accuracy of the phantoms. Using the same electrode trajectory plans as performed in the patients, the procedure was repeated on the phantom skulls using the iSYS1 trajectory guidance system. These results are included in section A.4 and have shown that the surgeons are adequately trained to achieve implantation accuracies superior to the current standard of care (manual) implantations.

i) Description of the specific medical or surgical procedures involved in the use of the investigational device.

The iSYS1 trajectory guidance system will be used for SEEG electrode placement. Following general anaesthesia and accurate registration of the patient to the Stealth S7 workstation the iSYS1 is attached to the Mayfield clamp, in the same way as the precision aiming device, using a mechanical arm. An initial check is performed by the surgeon to ensure that the iSYS1 trajectory guidance system can reach all of the proposed trajectories. The electrode trajectories are then implemented one by one by placing the device in rough proximity to the site on the scalp in which the electrode will be inserted. The system will then use the pre-planned trajectories inputted into the S7 stealth station to automatically and precisely align a working channel in the correct position and trajectory as the pre-planned electrode. A skin incision is then made by the surgeon over the defined site and the electric hand drill is placed through the working channel to drill the skull in the defined location and trajectory. A bolt will then be screwed through the working channel into the drilled pilot hole. A stylet is placed through the bolt to pierce the dura mata and create a channel through the brain for the electrode to follow. On removal of the stylet the electrode will then be passed through the working channel to the predefined target point. The electrode is secured in place by tightening the collar of the bolt. The subsequent electrodes are then placed in the same fashion. On average 10-15 electrodes may be placed in a single patient to provide comprehensive sampling of the brain regions that may be involved with seizure onset or propagation to define the area for surgical resection.

A.4 Justification for the design of the clinical investigation

Preclinical and clinical testing of the iSYS1 trajectory guidance device for SEEG placement and related procedures have been published in an open study by authors in Vienna, Austria (1). We have also undertaken extensive pre-clinical testing to ensure the previously published results are achievable in our centre and that implantation accuracies are superior to the currently used methods.

The first publication of preclinical and clinical use of the iSYS1 for intracranial procedures was by Minchev et al(12). In this study preclinical testing was undertaken in the form of phantom and

cadaveric testing. Accuracy of targeting was performed on a human model skull phantom in which 9 screws had been placed. The screw heads were used as biopsy targets. Following this a comparison of manual and iSYS1stereotactic biopsies were performed by 9 neurosurgeons of varying experience in cadaveric specimens. In total 162 biopsies (81 manual and 81 iSYS1) were performed. This study showed that iSYS1 guided biopsies significantly reduced the mean target error from 1.2mm to 0.6mm when compared with the manual method ($p = 0.001$). In addition, time for the biopsy procedure reduced from 3.7 minutes to 2.6 minutes when using the iSYS1 system ($p<0.001$). Based on these results approval was granted from the Ethics Committee of the Medical University of Vienna and the Austrian Agency for Health and Food Safety for a clinical feasibility study to be performed. Twenty-five consecutive patients were then recruited for tumour biopsy, ventricular catheter placement or stereotactic cyst drainage. In these patients 24 of 25 underwent successful biopsy without complication. In the remaining case, due to a technical error unrelated to the iSYS1 system, the pre-operative registration imaging was incorrectly registered to the plan on the Stealth S7 neuronavigation system. This therefore led to inaccurate information being relayed to the iSYS1 computer workstation. The procedure was therefore abandoned and performed manually. Of the 24 patients enrolled 16 had stereotactic biopsies, 5 had ventricular shunt placement and 3 had stereotactic cyst drainage. Twenty-one patients were operated on in the supine position, 3 prone and one sitting. Initial targeting error during the alignment of the iSYS1 to the pre-planned trajectory was between 0.0 and 0.1mm in all cases. Post-operative CT and MRI images revealed a mean entry point error of 1.3 mm and mean target point error of 0.9 mm. Set up time of the neuronavigation system and iSYS1 in combination was 11.8 minutes and time for biopsy and catheter placement was 15.7 minutes and 11.6 minutes respectively. The procedure for stereotactic biopsy, catheter placement and cyst drainage are in many ways similar to SEEG placement.

The same authors have published an open study in which they used the iSYS1 to perform SEEG electrode placement(1). In the first instance a preclinical phantom study was repeated in order to optimise the theatre workflow and ensure the accuracy of the technique was non-inferior to the manual implantation. Here 5 electrodes placed with the iSYS1 robot were compared with 5 manual implanted electrodes on post-operative CT scans. The mean entry point error was found to be 1.4 mm with the manual technique and 0.6 mm with the iSYS1, whilst target point error was 1.4 mm and 0.8 mm respectively. Sixteen patients were then recruited for a clinical study in which 93 SEEG electrodes were implanted. Electrodes were implanted into perilesional regions throughout the brain (47%), mesial temporal lobe structures (39%) and the insula (14%). The authors reported a mean entry point error of 1.3 mm and target point error of 1.5 mm using the iSYS1. Prospective comparison to manual implantations was not performed during this study, but retrospective comparison to a historical cohort from the same centre revealed a 60% reduction in mean entry point error from 3.5 mm and a 40% reduction in target error from 3.0 mm. It is important to note, during the consecutive study the instrumentation used during the technique was modified to further increase the accuracy of the procedure. The authors introduced the use of a ‘K-wire’, which is used as a bone spike prior to drilling. This spike produces a notch in the bone into which the drill can engage to prevent it from slipping on the cortical bone surface of the calvarium. This statistically reduced the entry point target error from a mean 1.54 mm to 1.18 mm ($p = 0.021$). The use of a bone fixated guide for implantation of depth electrodes (GIDE) has previously been described and was utilised to increase the construct stability by

anchoring the iSYS1 system to the skull thereby preventing any translational and leverage forces from drilling. Time for electrode insertion was a mean of 15.7 minutes using the iSYS1 compared to a mean 19.1 minutes in the historical cohort suggesting a 20% reduction in operative time. To date, no prospective randomised study has been performed comparing the iSYS1 trajectory guidance system with the currently employed frameless mechanical arm based technique.

UCL preclinical testing

Following the implantation of the phantom using the iSYS1 trajectory guidance system a CT scan of the implanted bolts was performed and the same above mentioned quality assurance tests were undertaken to ascertain the entry point, target point and insertion angle accuracies. We have shown that surgeons performed more accurate implantations using the iSYS system in the phantoms than in the prior manual implantations in the patients (Figure 1). Furthermore, time for alignment of the trajectories was significantly faster using the iSYS1 system.

Figure 1: Preclinical testing accuracy of iSYS1 trajectory guidance system phantom implantation compared with historical manual patient implantations

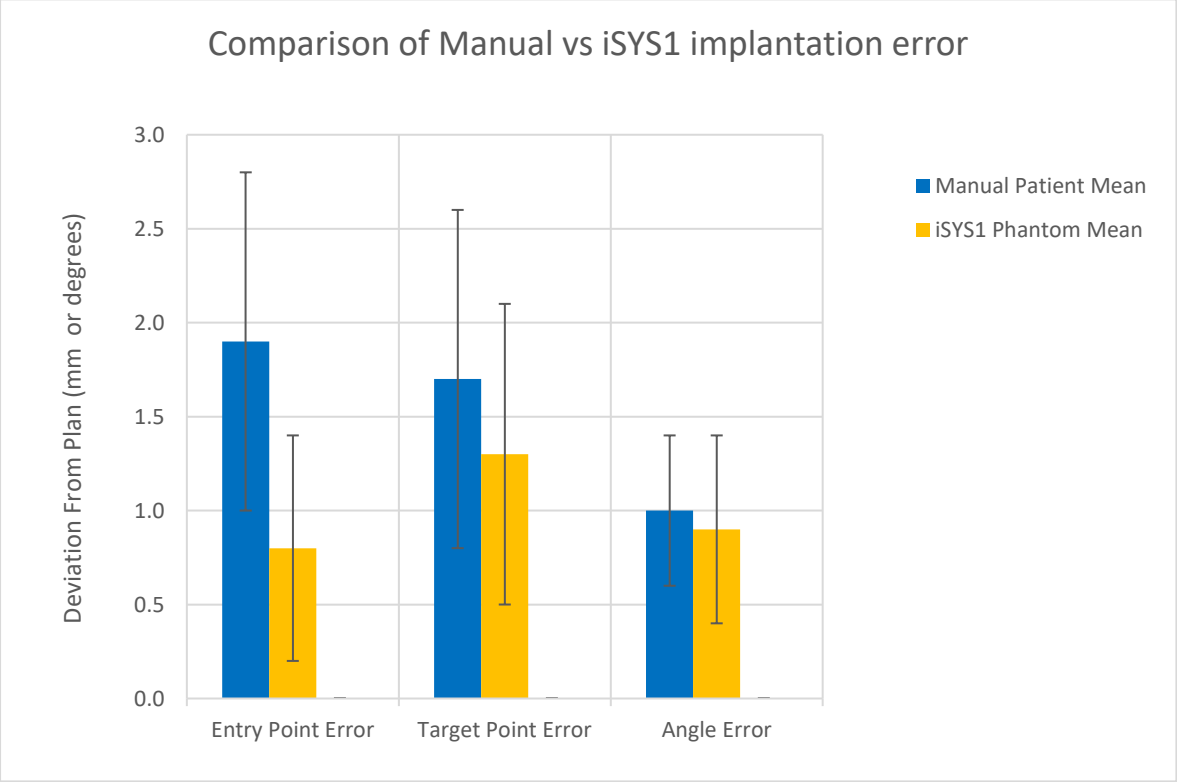


Figure 1 is a summary of the results of the phantom testing undertaken in comparison to the same electrode trajectories inserted into patients. The mean entry point error reduced from 1.9 +/- 0.9 mm SD to 0.8 +/- 0.6 mm SD ($p < 0.001$) whilst the mean target point error reduced from 1.7 +/- 0.9mm SD to 1.3 +/- 0.8mm SD ($p=0.08$). There was no significant difference in angle to plan.

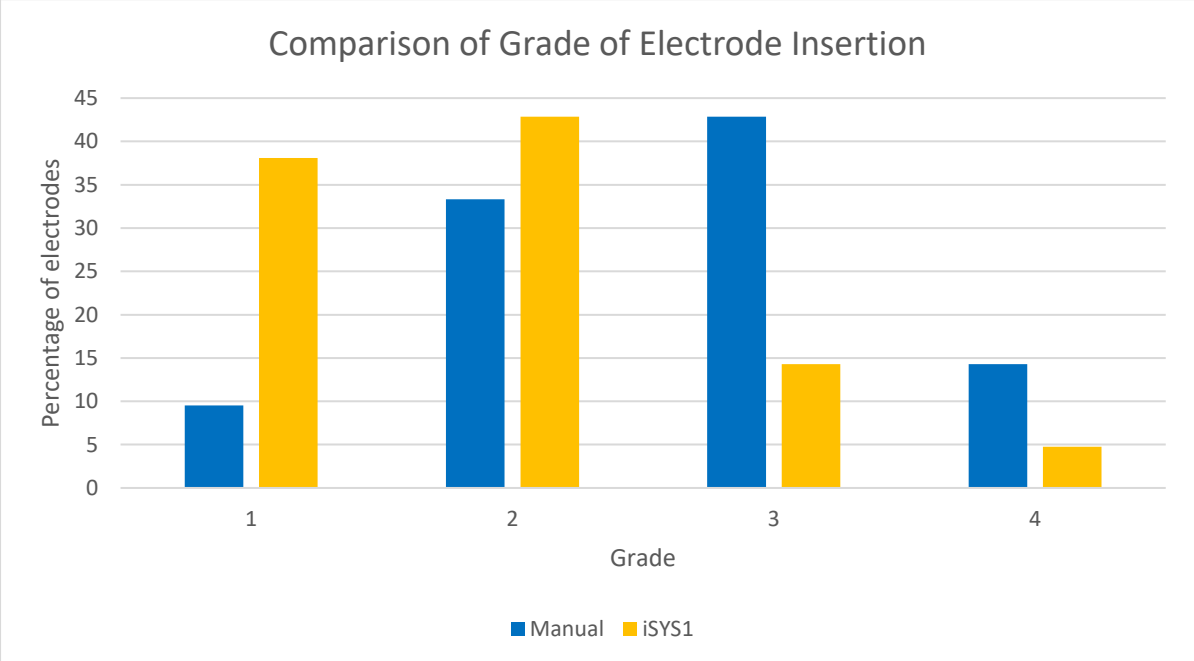
There are no unified grading criteria for the accuracy of electrode placement. We have therefore developed a grading system based on both radiological and clinical criteria. Assessment is based on the greatest error (either at the entry point or target) from the planned trajectory.

Proposed Unified Grading system:

Grade	Deviation from plan (Greater of EP or TP)
1	<1 mm
2	<2 mm
3	<3 mm
4	>or = 3 mm
A	No radiological haemorrhage
B	Clinically insignificant haemorrhage
C	Clinically significant haemorrhage

Comparison of the iSYS1 trajectory guidance system with mechanical arm based electrode insertion using the above grading system is shown in figure 2. This shows an increase in Grade 1 and 2 and fewer grade 3 and 4 electrodes when using the iSYS1 trajectory guidance system.

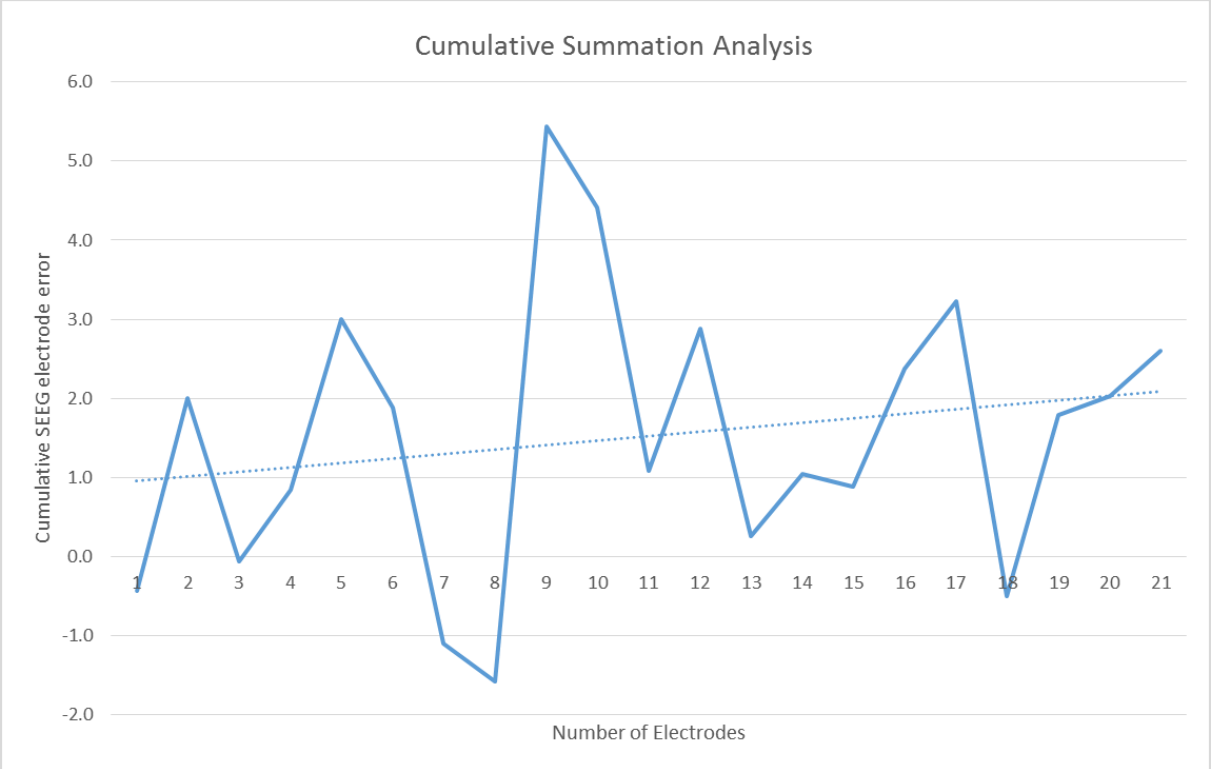
Figure 2: Comparison of SEEG electrode implantation based on proposed grading system:



Given that the surgeons had not used the iSYS1 system prior to the clinical testing we longitudinally analysed the consecutively inserted electrodes to determine if there was any improvement in the accuracy. Figure 3 reveals a Cumulative Summation (CUSUM) Analysis of consecutive iSYS1 phantom

SEEG electrode insertions in comparison to the patient manual electrode technique (solid blue line). CUSUM analyses have been utilized in a number of surgical specialties such as cardiothoracic and orthopedic surgery(10) where the continuous assessment and quality assurance of operative outcomes is paramount. The analysis is used in a prospective fashion and acts as an early warning scheme when new / novel techniques are introduced to ensure deterioration of patient outcomes are detected and corrective measures are put into place. CUSUM analyses also allow the effect of surgeon learning curves to be assessed. In general, surgical techniques which have outcomes similar to the conventional technique to which they are being compared, oscillate about the baseline(11). Thresholds are set based on the acceptable variance around the baseline which is intervention / disease specific. When the CUSUM line is within these boundaries the test intervention can be said to be as good as the conventional technique and the new intervention does not pose any greater risk to the patient. If the line falls above or below the boundaries, then in comparison to the conventional method the new technique is better or worse respectively. The solid blue line represents a CUSUM analysis of the sum of the entry and target point errors. The gradient of the dashed blue line indicates the learning curve of the surgeon as the number of SEEG electrode insertions increases. This would suggest that over the 21 electrodes inserted using the iSYS1 for SEEG placement, the sum of the entry point and target point errors reduced by 1mm and use of the iSYS1 is as accurate, if not more so, than the manual implantations even without the effect of learning. Put in other words, the surgeons were able to perform SEEG electrode insertion using the iSYS1 more accurately than the manual implantation without any previous experience of using the system.

Figure 3: CUSUM analysis of consecutive electrode insertions



The results from previous clinical studies using the iSYS1 trajectory guidance system very closely match the pre-clinical phantom testing that we have undertaken and show that the iSYS1 is more accurate at aligning to the pre-defined electrode plan compared to the currently used manual implantation method. A randomised control trial is therefore required to provide the highest level of evidence to determine if the use of the iSYS1 trajectory guidance system can:

1) Reduce operative time (as defined by average time for intracranial bolt insertion) and

2) Improve the accuracy and safety of SEEG depth electrode placement based on:

a) Accuracy of SEEG depth electrode placement, as assessed by skull entry point, error of angle of implantation of intracranial bolt and distance of the actual electrode tip compared to the target point as defined by the preoperative plan and target region sampled.
b) Clinically significant and non-clinically significant radiological post-operative haemorrhage rate
c) Infection rate
d) New post-operative neurological deficits
e) Operator (surgeon) based opinions for ease of use and perceived safety of the iSYS1 trajectory guidance system compared to conventional mechanical arm based insertion

We propose a single blinded block randomised control trial comparing SEEG electrode placement between the iSYS1 trajectory guidance system and the manual implantation technique using the 'precision aiming device'. Based on the preclinical and clinical data available from our institution and Vienna, Austria we feel there is sufficient evidence to show that the iSYS1 trajectory guidance system is not inferior and will not result in increased patient risk. The CUSUM analysis performed (Figure 3) as part of preclinical phantom testing has shown that when compared to the same implantations in patients using the manual technique, surgeons were able to achieve superior entry and target point accuracies. Only adult patients who have capacity to consent will be enrolled into the study. Patients under the age of 18 years old will not be enrolled as we are not a paediatric epilepsy centre and therefore do not evaluate paediatric patients for epilepsy surgery.

A.5 Risks and benefits of the Investigational device and clinical Investigation

a) Anticipated clinical benefits

Based on the outcomes of previous clinical publications surrounding the use of the iSYS1 trajectory guidance system it is claimed that compared to manual implantations it can:

1) Reduce operative time (as defined by average time for intracranial bolt insertion) and

2) Improve the safety of SEEG depth electrode placement based on:

a) Accuracy of SEEG depth electrode placement, as assessed by skull entry point, error of angle of implantation of intracranial bolt and distance of the actual electrode tip compared to the target point as defined by the preoperative plan and target region sampled.
b) Clinically significant and non-clinically significant radiological post-operative haemorrhage rate
c) Infection rate

d) New post-operative neurological deficits
e) Operator (surgeon) based opinions for ease of use and perceived safety of the iSYS1 trajectory guidance system compared to conventional mechanical arm based insertion

b) Anticipated adverse device effects associated with device

To date, based on the published literature and preclinical testing we do not anticipate any adverse effects associated with the device outside of that which would be related to an electric device, such as failure during a loss of power etc. The device has been CE marked for stereotactic biopsy purposes within interventional radiological purposes and the proposed use for SEEG implantation follows a very similar workflow. In such an instance where there is a power failure, as in any other surgical procedure, the operation will be stopped until the back-up power supply (generator) has restored power. A clinical decision will therefore be made if the operation is to continue based on the best interests of the patient. If the device is damaged in any way during an implantation, then the iSYS1 trajectory guidance system will be withdrawn immediately and the manual technique will be used to complete the surgery. If the device is found to be damaged outside of surgery then the device will be returned to the manufacturer for repair or replacement and recruitment to study will be stopped until this has been resolved.

Improper use of the device outside of the manufacturer's guidelines has the potential to result in patient and operator injury. Potential sources of improper use surround the fixation of the device to the Mayfield clamp and to image registration. The multifunctional arm can be attached to the table via a table adapter or the Mayfield clamp. In all instances we will attach to iSYS1 trajectory guidance system to the Mayfield clamp so that any movement of the patient is translated through the Mayfield clamp (3 point rigid fixation to the skull) to the iSYS1 trajectory guidance system. This therefore improves the rigidity of the system and reduces inaccuracy. At our institution only two surgeons perform the SEEG implantations and both are aware not to use the table top adapter. To mitigate the risk of this being used in error the table top adapter will be removed from the operating room set. The potential risk of incorrect image registration is not specific to the iSYS1 trajectory guidance system and can equally occur with any image guided intervention including the manual implantation technique. The registration image in all cases is the navigation CT scan performed on the day of surgery following bone fiducial implantation. The other images potentially transferred to the S7 stealth station include the T1-weighted gadolinium enhanced MRI image and if clinically indicated a FLAIR MRI image. In this situation it is possible that the reference image (on the S7 stealth system) is incorrectly chosen by the operator. Given that the registration image is a CT and the other potential options are MRI scans it is extremely unlikely to be the case. To mitigate this risk however, as is recommended by the manufacturer of the S7 Stealth neuronavigation system, both surface landmarks and bone fiducial positions will be checked to ensure the accuracy of registration.

c) Residual risks associated with study procedures (provide details in table 1 below)

The technical file provided by the manufacturer includes a detailed risk assessment based on ISO 14791:012 "Medical Devices – Application of risk management to medical devices". The lifecycle of the device defined by manufacturer is 10 years based on use of 10 hours per day at 280 days per year provided the device is serviced every year after the third year of use. The device that has been loaned by the manufacturer for the purpose of the randomised control trial is new and aside from the preclinical testing will not have been used for surgeries previously. Given that the trial is projected to last 18 months it will not require a service within the lifetime of the study. The usability of the device has been examined on the basis of the main operating functions in accordance with ISO62366 and

ISO60601-1-6. The following figure provides an overview of the risk assessment pre and post mitigation (see: page 34 of the document PD_73_3450 in Technical file for detailed information)

pre mitigation

Probability \ Severity	1	2	3	4
6				
5				1
4	19	3	29	
3	2	5	11	
2	7	8	25	
1	2	3	3	

post mitigation

Probability \ Severity	1	2	3	4
6				
5				
4				
3				
2	6	4		
1	34	21	54	

Following hazards have been mitigated to an acceptable risk level:

- H_P3 Burning
- H_P4 Mechanical Injury
- H_O2 Infection
- H_O3 Burning
- H_O4 Mechanical Injury
- H_O5 Ergonomics
- H_X1 Interference with other medical devices
- H_X2 Malfunction of other devices
- H_X3 Environmental hazards

The following hazards have been mitigated to the ALAP region:

- H_P1 Electrical Shock
- H_P2 Infection
- H_P5 Mistreatment
- H_O1 Electrical shock

The remaining hazards concerning the **electrical shock** derive from the general danger of electrical components. Any measure that is reasonable has been taken and the system is tested according to the IEC 60601-1 for electrical safety. Nevertheless, an electric system in an operation theatre bears a remaining risk.

d) Risks associated with participation in the clinical investigation (provide details in table 2 below)

The risk with any operative procedure surrounds that of general anaesthesia and surgery specific risks. The risks of general anaesthesia within the cohort of patients is not elevated as the patients undergoing presurgical evaluation with SEEG implantation are relatively young and the disease does not result in associated co-morbidities. Surgery specific risks have been estimated based on a recent meta-analysis (7) and include haemorrhage (0.3-1%) and general infection (0.3-1.2%). The consequence of haemorrhages secondary to SEEG placement can vary from being small and clinically insignificant to large and life-threatening. The risk of haemorrhage is associated with poor placement accuracy resulting in damage to a nearby blood vessel. Planning in our institution incorporates a 3 mm safety margin around segmented vasculature based on our quality assurance analysis of previous implantations.

Given that both preclinical and clinical data has revealed more accurate implantations with the iSYS1 trajectory guidance system, we do not feel patients are at any higher risk of haemorrhage than that in standard of care setting. Surgical sterility is of utmost importance during implantation procedures and as such the iSYS1 trajectory guidance system will be draped using manufacturers specified sterile drape. To maintain sterility new disposable needle guide inserts will be used for every procedure. Based on previous clinical studies there is no increased risk of infection, but surgical sterility will be strictly maintained throughout.

All electrical devices have an electrical risk element associated with them. Figure 1 (below) and the document PD_73_3450 within the technical file on page 35 highlights the electrical risks associated with this device and the risk mitigation steps that have been undertaken to reduce this to as low as possible (ALAP). The device is Class 1 and the electrical components do not come in contact with the patient. The risk mitigation steps include but are not limited to testing of the device by the manufacturer to IEC 60601-1-2, reinforcement and/or double insulation and/or class 1 housing, testing against cleaning and disinfecting agents.

f) Possible interactions with concomitant medical treatments

Some medications that epilepsy patients are taking can result in an increased tendency to bleed, such as sodium valproate. As such, as is routine in surgical procedures, a coagulation profile will be checked pre-operatively. Surgery will not be performed until any coagulopathy has been corrected and re-checked.

g) Steps that will be taken to control or mitigate the risks. (add information in respective table below)

See below

h) Risk-to-benefit rationale.

Previous studies outlined above have revealed a significant reduction in operative time, entry point and target point errors without any increased reported risks. We have corroborated these claims with pre-clinical phantom testing. The direct implication of reduced operative time is both clinical and economic. Clinically a reduced operative time results in shorter general anesthetic time and fewer anaesthesia related complications. Economic benefits of shorter operating times include the ability to maximize theatre usage and the potential of increasing the number of cases that can be performed in one day. The implications of reduced entry and target point errors are safer implantations with less haemorrhagic complications and the ability to more accurately sample regions of the brain. This will ultimately allow a more precise estimation of the seizure onset zone and potentially better patient selection for epilepsy surgery.

The table below summaries the risks and mitigations of **the investigational procedures** that are being performed:

Table 1 (see Risk Management document PD_73_3450_PD-B06 for details)

Name of IMD	Potential risk	Risk Frequency	Risk Management
Energy Hazard	Electric shock	Acceptable risk / As low as possible	Cables tested according to IEC 60601-1-2 Correct power supply to be used

			Class 1 housing of control unit to prevent shock due to water condensation or spilling on device. Device checked by clinical engineering department prior to use
Biological and chemical Hazards	Harm due to infection	As low as possible	Use of sterile covers and disinfectable of multifunctional arm prior to each use
Operational Hazards	Incorrect functionality	As low as possible	All navigation information derived from S7 stealth and checked with anatomical landmarks clinically prior to use
Environmental Hazards	Interference with other medical devices Toxic materials Mistreatment / mechanical damage	As low as possible	Designed to comply with IEC 60601-1-2 Avoidance of highly toxic materials Device will be locked away securely when not in use
Usability Hazards	Harm due to ergonomics	Acceptable risk	Test of mechanical stability
Information Hazards	Instructions for use	As low as possible	Manufacturer's instructions for use will be adhered to and experience with use of the device has been gained through preclinical testing.

Table 2: Summary of the risks and mitigations of all test above standard care that are being performed:

Intervention	Potential risk	Risk Management

iSYS1 trajectory guidance system implantation	System stability through fixation to bed and not Mayfield clamp	Removal of bed fixation adaptor from set so device can only be fixed to Mayfield clamp

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC (as amended). There are four classes, ranging from low risk to high risk.

Class I

Class IIa

Class IIb

Class III

The Medical Device used in this investigation is classified as **Class 1**

The risk management process, which includes risk analysis, risk-to-benefit assessment and risk control as described in ISO 14971 is outlined in Risk management document PD-73-3450_PD-B06 within the technical file.

A.6 Objectives and hypotheses of the clinical investigation

A6.1 Hypotheses

The use of the iSYS1 trajectory guidance system (Medizintechnik GmbH) in comparison to the conventional mechanical arm based technique (using the precision aiming device) will:

1. Reduce the operative time taken for target alignment and electrode insertion
2. Improve the accuracy of bolt entry point position at the skull compared to the pre-operative plan
3. Improve the accuracy of electrode target point position compared to the pre-operative plan
4. Improve accuracy of angle of bolt insertion at the skull compared to the pre-operative plan
5. No increase in clinically significant and non-clinically significant radiological post-operative haemorrhage rate
6. No increase in infection rate
7. No increase in new post-operative neurological deficits

A6.2 Primary Objective

To compare the operative time of the iSYS1 trajectory guidance system (Medizintechnik GmbH) with the currently used frameless mechanical arm based technique for the placement of SEEG depth electrode bolts in patients undergoing pre-operative evaluation for drug resistant focal epilepsy.

A6.3 Secondary Objective(s)

To compare the accuracy and safety of iSYS1 trajectory guidance system (Medizintechnik GmbH) SEEG depth electrode placement with mechanical arm based insertion based on:

a) Accuracy of SEEG depth electrode placement, as assessed by skull entry point, error of angle of implantation of intracranial bolt and distance of the actual electrode tip compared to the target point as defined by the preoperative plan and target region sampled.
b) Incidence of clinically significant and non-clinically significant radiologically detected post-operative haemorrhages
c) Infection rate
d) New post-operative neurological deficits
e) Operator (surgeon) based opinions for ease of use and perceived safety of the iSYS1 trajectory guidance system compared to conventional mechanical arm based insertion
f) Routine clinical follow up

A.7 Design of the clinical investigation

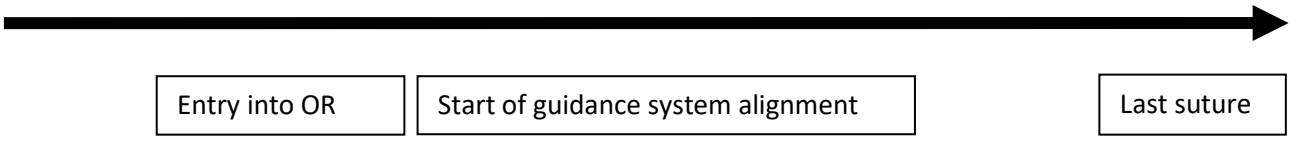
A.7.1 General

Type of investigation

We intend to undertake a Class I - Single-blinded Randomised Case Control Parallel Group Single-site Investigation of SEEG Electrode Placement in Patients with Refractory Focal Epilepsy.

Single blinding (patient only) has been chosen as the nature of a surgical intervention requires the surgeon and surgical support staff to be aware of which intervention is being performed in advance of the procedure so the appropriate equipment can be prepared.

a) **Primary endpoint**
The primary outcome measure of the study will be the operative time for intracranial bolt insertion as defined by Steps 1-6 of the total operative time table below. The following timeline outlines the sequence of events during the procedure:



Setup time is common to both study arms and starts from the time of entry into the OR from the anaesthetic room and ends once the trajectory guidance system is used to mark the entry points of the electrodes for insertion. The set up time consists of:

1. Transfer and positioning of patient on operating table
2. Connection of anaesthetic monitoring equipment
3. Placement of Mayfield clamp
4. Registration of patient to stealth S7 neuronavigation system including accuracy check
5. WHO checklist
6. Surgeon scrubbing and gowning
7. Prep and draping of patient
8. Connection of sterile iSYS1 trajectory guidance system and check to ensure all trajectories can be reached by initial position

Total operative time starts from the time of initial use of either trajectory guidance system to mark the entry points until the placement of the last suture. Total operative time consists of:

Mechanical arm system:	iSYS1 trajectory guidance system:
1. Free hand marking of entry points	1. Free hand marking of entry points
2. (A) Alignment of mechanical arm to first electrode trajectory	2. (A) Rough alignment of iSYS1 trajectory guidance system to satisfactory position
3. (B) Achievement of trajectory with target point accuracy of <0.7mm (current clinically accepted threshold)	3. (B) Precision alignment of iSYS1 trajectory guidance system to final position defined by system (between 0.0-0.1 mm)
4. Skin incision at defined entry point	4. Skin incision at defined entry point
5. Drilling of trajectory	5. Drilling of trajectory
6. Accuracy of trajectory checked with Vertek probe	6. Accuracy of trajectory checked with Vertek probe
7. Insertion of intracranial bolt	7. Insertion of intracranial bolt
8. Accuracy of trajectory checked with Vertek probe and new entry point set	8. Accuracy of trajectory checked with Vertek probe and new entry point set
9. Removal of mechanical arm	9. Removal of iSYS1 trajectory guidance system
10. Repeat steps 2-5 depending for each electrode to be inserted	10. Repeat steps 2-5 depending for each electrode to be inserted

11. Measurement of electrode trajectory length (from top of intracranial bolt to target point)	11. Measurement of electrode trajectory length (from top of intracranial bolt to target point)
12. Insertion of stylet to predefined length	12. Insertion of stylet to predefined length
13. Insertion of electrode to predefined length	13. Insertion of electrode to predefined length
14. Repeat steps 7-10 for each electrode to be inserted	14. Repeat steps 7-10 for each electrode to be inserted
15. Placement of sutures to close incision	15. Placement of sutures to close incision

There are a number of times that will be noted during the operative procedure outlined in the trial data collection sheet with defined start and ends points which are uniform in both arms of the trial. During the procedure each of the intracranial bolts are inserted according to the predefined trajectories. Only after all of the bolts are inserted are the electrode lengths to the target measured. Using a probe measuring device a rubber collar is then placed on the stylet at a length determined by the surgeon. This prevents the stylet from being inserted too deep and injuring critical structures past the target point. Following the stylet insertion the electrodes are then inserted to the predefined depth. The rationale for performing the procedure in this way is to prevent electrode leads interfering with the field in which subsequent electrodes are to be inserted. It is therefore not feasible or possible to measure the time for each individual electrode insertion from alignment to final electrode placement. Due to this we have decided to use the primary outcome as the time taken for intracranial bolt insertion. The time for the insertion of the electrode (steps 8-12 in the above table) is not affected by the type of trajectory guidance system used so, although recorded, does not form part of the primary outcome. All times during the procedure will be recorded by the rater using a digital clock placed above the Stealth S7 machine and documented contemporaneously on the trial data collection form. A video recorder will used to record both the digital clock and the Stealth station S7 screen. No patient filming will be undertaken. The footage video can then be used to independently verify and check the recorded times for the individual steps should any discrepancies arise.

b) Secondary endpoints

The secondary outcome measures include electrode accuracy (entry and target points), incidence of clinically and non-clinically significant haemorrhages, infection rate, new post-operative deficits, operator (surgeon) based opinion and routine clinical follow up. The methods by which the data will be collected and recorded are outlined individually:

i) Electrode accuracy: following the implantation patients undergo a CT on the same night as surgery as part of their routine care for the detection of any intracranial complications. The positions of the electrodes will then be segmented from the post-operative CT image and fused with the pre-operative MRI scan. An appropriately trained independent rater will be blinded to which intervention arm was undertaken and will define the entry and target points of each of the electrodes. The coordinates of the electrode entry and target points will then be extracted. The difference in the

actual (implemented) entry and target points will be compared with the preoperative planned trajectory. The entry and target point accuracies will be measured using a lateral shift technique i.e. the distance between the planned entry or target point measured perpendicular to the implemented entry or target point. The measurements will be recorded in the eCRF.

ii) Incidence of clinical and non-clinically significant haemorrhages: will be based on the post-operative CT and MRI scans. As per routine care the CT scan is performed on the evening of surgery and MRI scan on the following day. If the clinical team are concerned about a potential intracranial haemorrhage or evidence of which is found on the post-operative imaging, then the research team will be informed of this and documented in the eCRF. Interpretation of the imaging will be undertaken by a blinded independent neuro-radiologist. Clinically significant haemorrhages include those that result in neurological deficit, depressed conscious level or if there is a requirement for evacuation of the haematoma. All other haemorrhages that are found incidentally on imaging alone will be defined as non-clinically significant. As an example, a haemorrhage leading to a transient or permanent motor weakness would both be deemed clinically significant, whilst a small visual field deficit not detected by the patient or on clinical confrontation testing (only detectable on formal visual field assessment) would be clinically insignificant.

iii) Infection rate: following electrode implantation patients are transferred to the video telemetry unit so that intracranial electrical recordings can be performed when the patient undergoes a seizure. The duration of time which recordings are taken over is dependent on the frequency of the patient's seizures and the different types of seizures they may have. This is clinically driven and not part of the research study. Whilst an inpatient on the video telemetry ward, the patients will have routine care provided by the clinical neurosurgical and neurology teams (overseen by the study CI Prof. Duncan). If any infection is noted the clinical teams will institute appropriate management and the research team will be informed. Post-operative infection will be defined as the need for therapeutic antibiotic administration based on clinical and/or radiological evidence of infection. Infections will be classified as either superficial (external to skull) or deep (deep to the bone). It is likely that deep infections will require the removal of both the electrode and intracranial bolt as part of the treatment. In extremely rare cases, if an intracranial abscess occurs, further surgery for drainage of the abscess may be required. It is possible for a delayed infection to occur i.e. after the patient has been discharged. This is rare, but will either be detected by the patient calling the clinical team for advice or during the routine clinical follow up (see below). Based on data from previous studies, there is no reason to believe that the rate of infection (either superficial or deep) will be increased following the use of the iSYS1 trajectory guidance system. Treatment decisions will be made independently of the research team, who will note the documentation of any infection and prescription of antibiotics in the clinical record. This will be noted in the eCRF.

iv) New post-operative deficit: the patient will be examined following surgery by the clinical team as part of routine clinical care. The research team will be informed of any neurological deficit (transient or permanent) and this will be recorded in the eCRF.

v) Operator (surgeon) based opinion: will occur during surgery after each electrode and at the end of implantation of the all of the electrodes. This will give the surgeons the opportunity to comment on any factors that they feel may affect the accuracy of the specific electrode being inserted or any systemic factors affecting all of the electrodes.

vi) Routine clinical follow up: following removal of the electrodes patients are discharged home. As per routine clinical care all patients are then followed up by the clinical teams after 3 months of surgery for the detection of any late complications of the surgery and to discussion further management i.e. whether resection neurosurgery can be recommended on the basis of the electrode recordings. The clinical team will inform the research team of any delayed complications and/or recommendations for further management and this will be noted on the eCRF.

c) Replacement of subjects

We do not propose to replace subjects. We will enrol 32 patients, so that we will retain sufficient power for the intended outcome, even if there are drop-outs prior to SEEG implantation.

A.7.2 Investigational device and comparators

a) Description of the exposure to the investigational device(s) or comparator(s), if used.

Investigational device: iSYS1 trajectory guidance system

Comparator: Precision aiming device (Medtronic Inc.)

b) Justification of the choice of comparator(s).

The current clinical standard of care for the frameless insertion of SEEG electrode insertion in our institution uses the Precision aiming device, which is part of the Vertek passive biopsy instrument set 9733936 (Medtronic Inc.). Other possible comparators would include frame-based and other robotic guidance systems such as the Renishaw Neuromate and the ROSA. Frame-based techniques are used during deep brain stimulation procedures in which few electrodes are placed to a very restricted range of targets. Due to the need for SEEG to access any part of the cerebral hemispheres, with multiple electrode placements frame-based techniques have serious limitations in flexibility and most hospitals that implant SEEG have adopted frameless or robotic assistance techniques. There have been no class 1 studies directly comparing the outcomes from frame-based and frameless techniques, although comparisons to historical cohorts have shown no worse outcomes with frameless techniques.

In the United Kingdom, the ROSA robotic system is not used in any institution and would therefore make for a poor comparison choice, as it would have little clinical applicability. The Renishaw Neuromate is used within a small number of mainly paediatric institutions. The Neuromate system is extremely large, weighing 180 kg and requires a significant footprint within the operating room. Furthermore, these systems cost in the region of £300,000 greatly reducing their applicability. The iSYS1 trajectory guidance system is a novel and compact device that does not require the use of large amounts of space within the operating room (see section A3 for image). Furthermore, the device

directly links to the Stealth S7 neuronaviation system (Medtronic Inc.) which are found within almost all neurosurgical centres in the United Kingdom. This therefore immediately opens up the number of institutions that the results of this study can be clinically translated to.

The current frameless system used in our institution to which the comparison will be made utilises the Vertek passive biopsy instrument set, which consists of the following components:

1. Vertek probe (for use with the Stealth S7 neuronavigation system)
2. Precision aiming device (for precision alignment to the trajectory)
3. Reducing tube (through which drilling an intracranial bolt insertion is performed)
4. Vertek articulating arm (for stable connection of the precision aiming device to the Mayfield clamp via the use of the dual Mayfield attachment)
5. Dual Mayfield attachment (required to allow attachment of both the Vertek articulating arm and the neuronavigation system passive star to the Mayfield clamp.

c) List of any other medical device or medication to be used during the clinical investigation.

Other medical devices used during the clinical trial include:

Routine anaesthetic equipment: anaesthetic machine

Routine equipment associated with SEEG in general: surgical bed, diathermy machine, Mayfield clamp (Integra), S7 neuronavigation system (Medtronic), bone fiducials, AdTech intracranial bolt and electrodes, Colibri drill and drill bits.

Additional equipment associated with trial: Digital clock and digital video camera.

d) Storage of the investigational device

A single iSYS1 trajectory guidance system, loaned by Medtronic, will be used. In the event of failure of the iSYS1 trajectory guidance system the device will be returned for repair. In this unlikely event a replacement device will be provided for the remaining cases. The iSYS1 trajectory guidance system is stored within a bespoke case that was used for delivery of the device to ensure it is not damaged in any way during storage. The device will be taken to the operating theatre before use by the trial research associate, if randomization of a patient to be implanted indicates the device is to be used. Following the procedure the device will be returned to its secure storage area.

A.7.3 Subjects

a) Inclusion criteria

1. Age 18-80 years
2. Drug refractory focal epilepsy as determined by the clinical epilepsy team , and as defined by the international league against epilepsy as 'failure to achieve sustained seizure freedom following the adequate trial of two tolerated and adequately chosen anti-seizure medications'
3. Deemed to require SEEG placement as part of routine clinical care following multidisciplinary team meeting decision

4. Informed decision by patient to undergo intracranial SEEG investigation

b) Exclusion criteria

1. Pregnancy
2. Uncorrectable coagulopathy
3. Lacking capacity to consent
4. Patients who are deemed unfit for general anaesthesia

c) Criteria and procedures for subject withdrawal or discontinuation.

As per HRA guidance, patients are eligible to withdraw consent from inclusion in the clinical trial at any point. The patient's clinical care will not be affected by the decision to withdraw consent and will continue to receive routine treatment as is standard for the institution (mechanical arm based electrode implantation). If a competent adult withdraws consent and subsequently becomes unable to give informed consent then the refusal is legally binding. In the setting of SEEG electrode placement for the investigation of drug resistant focal epilepsy we do not envisage that patients will lose capacity in the interval between time of consent and SEEG electrode placement. However should a competent adult provide informed consent and subsequently becomes incapacitated it is unlikely that the clinical need for SEEG implantation will remain. However, if the clinical need exists then the consent previously given when competent remains legally valid unless there is a clinical indication or personal legal representative that finds this unacceptable. If this is the case then the patient will be treated as having withdrawn consent.

d) Point of enrolment

As per the current clinical pathway, patients who are referred for specialist epilepsy assessment are discussed in an Epilepsy surgery MDT after noninvasive investigations including MRI, functional MRI, scalp video-EEG, neuropsychology and neuropsychiatry evaluations. Those patients who are deemed to require SEEG recordings to define the site of seizure onset are referred to the intracranial EEG MDT for review of the investigations to date by the team including neurologists, neurophysiologists and neurosurgeons. Those patients who are deemed to require SEEG placement and eligible for inclusion in the study are identified, and the proposal, including discussion of potential benefits and risks is made to the patients in neurology and neurosurgery clinics. Patients are sent a written description of the procedure, risks and benefits and indicate their wish to proceed in writing, and only than are placed on the waiting list for SEEG implantation.

Those eligible patients who have indicated their wish to proceed with SEEG placement will then be contacted by the clinical trial team by both telephone call to confirm they are eligible for enrolment. Patient information sheet will be posted to serve as a reminder of the telephone conversation and provide any additional information. The patients then have the ability to consider if they would like to be enrolled in the trial and be able to contact the research team either in person, by telephone or email should they have any further questions. As part of the current standard of care patients are required to attend the National Hospital for Neurology and Neurosurgery for a digital subtraction angiogram. This investigation occurs 1-4 weeks prior to SEEG implantation surgery. At the time of attendance for the digital subtraction angiogram the PI or qualified member of the research team will then take a written consent from the patient if they wish to be included in the trial. We aim for the PIS to be sent to the patient no later than 2 weeks prior to written consent being taken to allow the patient to have sufficient time to make an informed decision regarding enrolment in the trial and

adequate opportunity to discuss this with the research team. On receipt of the signed consent form the patient will be defined as enrolled and randomization to a surgical intervention arm will occur.

e) Total expected duration of the clinical investigation.
The primary outcome of the study, duration of time taken to implant the intracranial bolts will be measured during the surgical procedure. The secondary outcomes of haemorrhage and accuracy of electrode placement (entry point, target point, angle error) in relation to the preoperative plan will be identified from the post-operative CT and MRI scans. We perform post-operative CT scans on the same day of surgery. Post-operative MRI scans usually performed the following day. The duration of the clinical investigation from the point of the trial is 48 hours therefore. After implantation patients then go to the video-EEG telemetry unit where they undergo continuous recordings for a variable period of time (usually one week) depending on the frequency of seizures. This is part of the patient's routine clinical care and therefore not included in the trial duration. Other secondary outcome factors such as infection rate will be monitored as part of the routine clinical follow up.

f) Expected duration of each subject's participation.
For the purposes of the randomised control trial the primary and secondary outcomes will be known within 48 hours of SEEG implantation. The only secondary outcome which will not be detected within this period is infection rate, as this may take weeks to manifest. All patients will undergo video-EEG telemetry assessment following SEEG implantation and any infection that occurs will be detected during the routine clinical follow up.

g) Number of subjects included in the clinical investigation.
Based on the power calculation performed by the trial statistician a minimum of 22 patients (n=11 in each arm) are required to detect a 20% difference in median electrode insertion time with a 5% significance level of and a power of 90%. Due to the potential for patient withdrawal we aim to recruit 32 patients in total (n = 16 in each arm). Due to the higher estimated difference in secondary endpoints (entry and target point accuracy) this number of patients will provide a power of >95% for these factors.

h) Estimated time needed to select this number (i.e. enrolment period).
Based on the current rate of SEEG implantation at our institution of 2 per month, we aim to recruit the required 32 patients within 18 months of trial onset.

Subject Eligibility

Eligibility for inclusion within the study will be confirmed via review of the clinical record and MDT discussion, followed by telephone conversation with a member of the research team prior to inviting patients for enrolment.

Once a written informed consent has been obtained, an electronic Case Report Form will be completed using the ReDCAP system to formally document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will be documented and the signed consent form and completed inclusion/exclusion criteria retained by the Principal Investigator. The subject will not be advanced any further into this clinical investigation.

Subject Identification

When a potential subject is identified and considered eligible for entry into this clinical investigation, the subject will be allocated the next available investigation number (subject ID number).

For subjects enrolled, this number will consist of 01 for the first subject, 02 for the second subject and so on. This number will be the unique identifier of the subject and written on each page of the paper/electronic Case Report Form booklet and all other documentation relating to that subject.

Each subject that is enrolled into the study will have their study participation recorded and details of the device recorded in their hospital notes, a copy of their signed consent form and patient information sheet will also be placed on his/her hospital notes to identify the subject as participating in a Clinical Investigation.

A7.4 Recruitment

This study will involve a small number of patients at a single site. As outlined previously, epilepsy patients who are eligible for enrolment in the study are a select group that have undergone a significant number of investigations and following discussion in the appropriate multidisciplinary team meetings. Once a patient has been identified as requiring SEEG investigation, the patient is reviewed in neurology and neurosurgical clinics at which the risks and benefits of SEEG placement is discussed. Only after a patient has indicated that they wish to proceed with SEEG electrode placement will they be eligible for recruitment. Patients will then receive an initial telephone consultation by a member of the trials research team prior to surgery to confirm eligibility and to explain the trial. Patients will then be sent a copy of the patient information leaflet (PIS) and then be offered the option of a face to face, telephone or email contact to discuss the trial in more detail and give the opportunity to ask further questions. As part of the current standard of care patients are required to attend the National Hospital for Neurology and Neurosurgery for a digital subtraction angiogram. This investigation occurs 1-4 weeks prior to SEEG implantation surgery. At the time of attendance for the digital subtraction angiogram the PI or qualified member of the research team will then document written consent from the patient if they wish to be included in the trial. We aim for the invitation letter and PIS to be sent to the patient no later than 2

weeks prior to written consent being taken to allow the patient to have sufficient time to make an informed decision regarding enrolment in the trial and adequate opportunity to discuss this with the research team.

A7.5 Randomisation Procedures

Given this is a single centre study, participant randomisation will be undertaken centrally by the coordinating trial team using a computer based randomization program via an independent statistician in UCL JRO Biostatistics Group.

Participants are considered to be enrolled into the trial following receipt of the signed consent form. Following enrolment and formal confirmation of eligibility on the eCRF using the ReDCAP system, the randomisation procedure described below will be carried out:

Coordinated registration and allocation of participant trial numbers will be assigned to each enrolled participant. At the time of enrolment the generated randomization code will be used to provide the assignment to either the iSYS1 trajectory guidance system or mechanical arm based insertion technique. Randomisation will not occur outside of normal working hours as the surgical intervention is only performed electively (i.e. within working hours). The randomisation list will be kept securely and maintained by the trial research associate Vejay Vakharia.

Participants will be assigned to treatment groups via a block randomization process and a Trial Subject Enrolment Log will be maintained to record which intervention arm patients received.

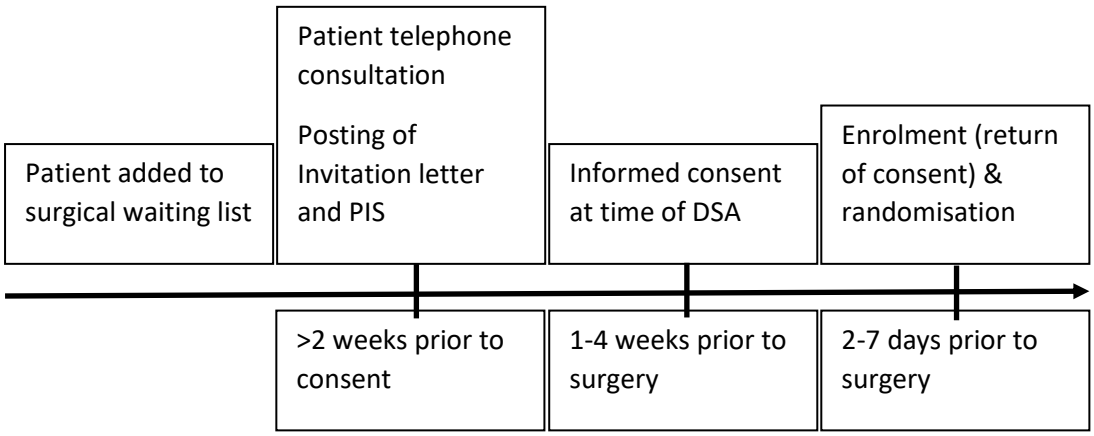
A.7.6 Procedures

No further examinations or investigations outside of the routine clinical care are required for enrolment into the trial. Baseline characteristics of age and gender will be documented. Given that age and gender are not factors that will affect the primary or secondary outcomes we do not feel stratified randomisation based on these characteristics is required.

a) Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation.

All investigations will be undertaken prior to enrolment and randomisation into trial. Following surgery a CT and MRI scan of the patient will be undertaken to detect any complication of the surgery and detect electrode placement accuracy. This is part of the routine care of patients following SEEG.

A.8 Informed Consent Process



Informed consent will occur in a staged manner. Once the patient has provided a written indication that they would like to be put on the waiting list for SEEG implantation they will provided with an operation date as part of their routine care. Patients will be contacted at this point by telephone consultation to confirm eligibility and to explain the study. Patient information sheet will be posted to them. Patients will then have the ability to contact the research team in person, by telephone or email (details provided on the patient information sheet) to ask any further questions As part of the current standard of care patients are required to attend the National Hospital for Neurology and Neurosurgery for a digital subtraction angiogram. This investigation occurs 1-4 weeks prior to SEEG implantation surgery. At the time of attendance for the digital subtraction angiogram the PI or qualified member of the research team will then take a written consent from the patient if they wish to be included in the trial.. On receipt of the consent form the patient will be enrolled in the study and randomisation will occur as per section A7.5. Randomisation will therefore occur between 2-7 days prior to surgery to allow sufficient time to prepare the necessary surgical equipment.

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each subject prior to participation in the Investigation, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. This will usually be undertaken by consultation by trial research associate Vejay Vakharia.

The person taking consent is GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI/PI on the delegation log.

“Adequate time” will be given for consideration by the patient before taking part. We will record when the patient information sheet (PIS) has been given to the patient and intend for this to be as soon as the patient returns written confirmation that they would like to be placed on the waiting list for surgery. In exceptional circumstances if the amount of time between the PIS being given and the date of consent are less than 24 hours, the PI will explain the rationale for this. Once the patient has signed the consent form they will be defined as enrolled within the study. Randomisation to a surgical intervention arm can then occur. A copy of the dated letter sent to the patient with invitation for enrolment and participant information sheet (PIS) will be stored in the patient’s electronic medical notes (CDR).

The Investigator or designee will explain to the patients that they are under no obligation to enter the Investigation and that they can withdraw at any time during the Investigation, without having to give a

reason. It is also clearly explained in the patient information sheet that withdrawal from the study will not affect the patients routine care and they will therefore undergo the current standard of care in the form of manual implantation with the precision aiming device utilising the Vertek arm. If a patient withdraws prior to treatment, their data will not be used in the trial.

No clinical Investigation procedures outside of routine care will be conducted prior to taking consent from the participant. Consent will denote enrolment into Investigation. A copy of the signed Informed Consent Document will be given to the participant. The original signed form will be retained at the study site and a scanned electronic copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate

The Investigation does not include children or adults unable to consent for themselves.

A.9 Schedule of assessments and interventions by visit

Please refer to Appendix A for schedule of assessment

A9.1 Laboratory Assessments and Procedures

Local laboratories – no laboratory investigations will be performed as part of the clinical trial outside of those required for routine standard of clinical care.

Central laboratories - no laboratory investigations will be performed as part of the clinical trial outside of those required for routine standard of clinical care.

A.10 Device accountability

A single iSYS1 trajectory guidance system device 4268 has been provided on a loan agreement by Medtronic Inc. The device has already been received so that pre-clinical studies (outlined above) can be undertaken. Sterile consumables for each procedure comprise a 'Universal Cover Robotic Positioning Unit Sterile' (Article no. 11720EU). This is a disposable sterile cover for the RPU and part of the multifunctional arm / cables. This also includes two needle guide joints that are sterile and attach to the end effectors of the RPU. This will be provided by the manufacturer for use during the clinical trial. Other sterile covers e.g. for the handheld control unit are not required as these will not be used by the surgeons. Needle guide markers or inserts are not needed for this procedure.

A.11 Monitoring Plan

The monitor will be responsible for ensuring the compliance of the Principal Investigators to the signed agreement, the Clinical Investigation Plan, the requirements of the European Standard EN ISO 14155:2011 a Clinical Investigation of Medical Devices for Human Subjects- Good clinical practice, or conditions of approval imposed by the reviewing ethics committee or regulatory authorities.

A Trial specific monitoring plan will be established for studies. The trial will be monitored with the agreed plan.

eCase Report Forms (CRFs) will be completed by the investigator and/or his/her delegates within 2 working days of the study visit. All data from the examinations and investigations listed in section A.9 will collected in the eCRF.

The sponsor will perform interim monitoring visits at least once a year during the study. The site will allow access to the study patients' records for [100%] source verification. The sponsor will schedule interim monitoring visits with advance notice and confirm the scheduling of the visit with the study site. The sponsor representative should meet with the investigator at each monitoring visit.

The investigator(s)/ institution(s) will permit Investigation-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Investigation participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

The sponsor representative shall perform the following activities at each monitoring visit;

- [100%] source verification
- Essential document review
- Deviation review
- Adverse event review

At the conclusion of the monitoring visit, the sponsor representative shall write a monitoring report detailing the activities performed during the visit with recommendations for action items and study site action. A follow-up letter to the study site detailing these recommendations and actions will be sent to the investigator.

The sponsor representative shall perform the following activities at each monitoring visit;

- [100%] source verification
- Essential document review
- Deviation review
- Adverse event review

At the conclusion of the monitoring visit, the sponsor representative shall write a monitoring report detailing the activities performed during the visit with recommendations for action items and study site action. A follow-up letter to the study site detailing these recommendations and actions will be sent to the investigator.

a) Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. The CRFs will not bear the subject's name or other personal identifiable data. A pseudo-anonymisation in the form of the first three letters of the surname and the first letter of the first name (e.g. Joe Bloggs = bloj) will be used along with the date of birth and Investigation identification number, will be used for identification. Subjects will be assigned an Investigation identification number by the study site sequentially starting with NHNN/01 upon enrolment into the study. The study site will maintain a master Subject Identification Log.

b) Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Chief Investigators are responsible for the secure archiving of essential Investigation documents as per their Trust policy. All essential documents will be archived for at least 20 years after completion of Investigation. Destruction of essential documents will require authorisation from the Sponsor.

A.12 Statistical Considerations

Statistical design and analytical procedures

This is a prospective, single-blind, randomised control trial comparing two neurosurgical techniques for SEEG electrode implantation.

The primary outcome is to compare the operative time (minutes / seconds) of the iSYS1 trajectory guidance system (Medizintechnik GmbH) with the currently used frameless mechanical arm based technique for the placement of SEEG depth electrode bolts in patients undergoing pre-operative evaluation for drug resistant focal epilepsy.
Secondary: To compare the accuracy and safety of iSYS1 trajectory guidance system (Medizintechnik GmbH) SEEG depth electrode placement with mechanical arm based insertion based on:

a) Accuracy of SEEG depth electrode placement, as assessed by skull entry point (mm), error of angle (degrees) of implantation of intracranial bolt and target point error (mm) of the actual electrode tip compared to the planned target point as defined by the preoperative plan and target region sampled.
b) Incidence of clinically significant and non-clinically significant radiologically detected post-operative haemorrhages (%) based on the post-operative imaging (within 48 hours of implantation).
c) Infection rate (%)
d) New post-operative neurological deficits (%)
e) Operator (surgeon) based opinions for ease of use and perceived safety of the iSYS1 trajectory guidance system compared to conventional mechanical arm based insertion

f) Routine clinical follow up to include proportion of patients that are offered resective surgery and seizure freedom following resective surgery if performed.

Sample size and Power calculation

A sample size of 11 patients in each arm (22 patients in total) will be sufficient to detect a change of at least 20% in the median bolt implantation time, using a two-sample t-test with a power of 90% and a significance level of 5%, with log-transformed time as the outcome. Based on our pre-clinical testing and a recent study by Dorfer et al(1), we estimate the median bolt implantation time using the current conventional method to be 20 mins with an estimated standard deviation of 5 mins. We make the conservative assumption that an estimate of the time taken for SEEG electrode implantation time using the iSYS1 trajectory guidance system is 16 min with a standard deviation of 5 mins. We assume that the time taken for electrode implantation has a log-normal distribution and hypothesis testing shall be performed using log- transformed time values. In addition, we account for the clustering of electrodes within a patient through the assumption of an intra-class correlation coefficient of 0.2 and an average number of electrode implantations of 10 per patient. Due to the possibility of patient withdrawal from the study or loss to follow up, together with the possibility of a variable cluster size, we aim to recruit 16 patients in each arm (32 patients in total). Due to the higher estimated difference in secondary endpoints (entry and target point accuracy) this number of patients will provide a power of >95% for these factors.

Procedures for reporting any deviation(s) from the original statistical plan,

Any deviations from the original **statistical** plan will be discussed with the study statistician, and documented in the exceptions log.

Randomisation

32 patients will be enrolled and block randomized, by an independent statistician through the use of a computer generated system that contains a code assigning the patient to one or other arms of the study, with the use of a) the currently used Mechanical arm based technique (using the precision aiming device) or b) iSYS1 trajectory guidance system (Medizintechnik GmbH) for aligning the trajectory of the electrodes to be placed.

Blinding

The initial stage of the pre-operative model generation and electrode planning by the clinical team will occur prior to randomization as to which operative technique of electrode insertion will be used. These clinical team members do not require blinding as this will not be affected by the subsequent surgical intervention arm.

Due to the nature of the surgical interventions it is not possible to blind the operating surgeons or theatre support staff as to whether the implantation will be mechanical arm based or use the iSYS1 trajectory guidance system. This is because the procedures require different operative equipment, setup and operative techniques.

Patients will be blinded pre-operatively as to which intervention arm they will be randomized to. This is to prevent patient crossover and unequal recruitment to each intervention arm. Patients who find this unacceptable can withdraw from the study at any time and will undergo the current standard of care (mechanical arm based implantation technique). Patient blinding

will continue until after the end of the trial and patients will be informed of which surgical intervention was performed on request after this point. The trial statistician shall remain blinded to treatment allocation until the end of the trial.

Expected drop-out rates

Given the nature of the study and the selected patient group, we do not anticipate patient drop-outs. In view of the nature of the study, we will analyze data in patients in whom implantation of any SEEG electrodes is carried out, discounting data from patients who dropped out prior to this step. The reasons for any drop outs will be documented and the characteristics of drop outs will be compared with those patients who completed the study.

Statistical Analyses

The primary outcome (operation procedure time) shall be analysed using a random effects linear regression model, accounting for the clustering of electrodes within patients that compares outcomes for the mechanical arm based technique and the iSYS1 trajectory guidance system. The patient-level operation times shall be log-transformed and checked for normality. Other appropriate transformations shall be considered if necessary.

Where secondary outcomes are collected for each electrode, clustered within a patient (e.g. bolt entry angle accuracy) multi-level regression models that account for within-patient clustering shall be used to compare outcomes between randomized groups.

For other, patient-level secondary outcomes (e.g. presence of neurological defects, intracerebral haemorrhage incidence) suitable methods such as linear regression (for continuous outcomes) or generalized linear models or categorical data analysis (for non-continuous outcomes).

A detailed, formal, statistical analysis plan will be produced by the trial statistician at a later stage, prior to the collection of data and with the approval of the trial investigators. Any deviations from this statistical analysis plan will be described and justified, either as a protocol amendment or in the final report, where appropriate.

Interim analysis and Premature study termination.

Data will be reviewed by a data monitoring and ethics committee with review after randomization of 6, 12 and 18 subjects to determine whether the results of the study so far mandate premature termination. Criteria for termination would be if the complication rate of one arm is significantly higher than the other, if the primary outcome has achieved statistical significance prior to the end of the study or if it becomes apparent during the study that achieving the primary objective is futile.

A.13 Data Management

Data Management procedures will be detailed in trial specific Data Management Standard Operating Procedure.

Some information (e.g. name and birthdate of the patient) will be retained with the images on the secure MR computer system at NHNN, but images will be anonymised electronically before use for research. Imaging data from individual scans and some recorded data will be shared with other organisations including those outside of the EU, but this will be fully anonymised. Any information that might allow individual patients to be identified (either in connection with their images or separately) will always be removed before exporting them onto any computer system outside the NHNN or to any other organization. Imaging data will be stored on a secure computer system, only accessible to individuals with suitable authorisation from UCLH NHS Foundation Trust. 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. Following image data anonymisation, access to the mapping between unique scan identifiers, patient data and to the archive of consent forms will be restricted. Dr Roman Rodionov, lead image integration specialist at the NHNN, acting under the direct supervision of the CI, will act as custodian of this data; he will provide limited access where needed by other individuals named for consent and record keeping on this application. Access to archived (identifiable) scans will be within the clinical computer system and subject to the normal access controls and policies of UCLH Trust. All images used for research will be anonymised; only the research scientists, who hold UCLH Hospital contract sand hospital staff involved in the scan itself will be aware of who has been imaged. Individual researchers will retain anonymised data on their own computer systems, and act as custodians for their data.

Most data (excluding large raw measurements) will also be archived within the Neuroradiology Department on the secure imaging network by computers configured specifically for data storage and anonymisation. Backups will normally be held on the same network in another secure room elsewhere at NHNN.

In accordance with the UCL Records Management Policy, findings from UCL research projects will be stored for 20 years after the research has finished.

The handling of all data on the CRFs will be the responsibility of UCL and UCLH.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

A13.1 Procedures for data review, database cleaning, and issuing and resolving data queries.

Data entered on the CRFs will be 100 % source verified by a sponsor representative trained on the CIP and who has current GCP training. Data Clarification Forms (DCF) will be issued to the Investigator should a discrepancy be found between the source and CRF. The Investigator will be required to verify and correct all errors or provide an explanation for the discrepant data. Sponsor representatives will re-verify the corrected data and mark the clarification as resolved at the next monitoring visit.

A13.2 Procedures for verification, validation and securing of electronic clinical data systems

All data from the examinations and investigations listed in Appendix A will be transferred to media provided by the sponsor and collected at the time of CRF collection.

The CI will manage and maintain the study database throughout the Investigation. At the conclusion of the Investigation, the database will then be locked and data transferred for analysis. A final copy of the database will be provided to the study site. Where data is transferred electronically, this will be in accordance with the UK Data Protection Act 1998 as well as Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer.

The database maintained by the CI, shall be validated and secured according to the [sponsor] standard operating procedures. Access to the data shall be limited to sponsor representatives directly involved in the collection, analysis, maintenance or safety monitoring of the data. Any study data released shall be done according to the publication policy and in accordance with the UK Data Protection Act 1998.

A13.3 Data retention

Archiving will be authorised by the Sponsor following submission of the end of study report. Chief Investigators are responsible for the secure archiving of essential Investigation documents and the Investigation database as per their trust policy. All essential documents will be archived for at least 20 years after completion of Investigation. Destruction of essential documents will require authorisation from the Sponsor.

A13.4 Clinical quality assurance

The Clinical Investigators will meet as required to discuss any issues with data quality and any concerns will be discussed with the Sponsor.

A13.5 Completion of Case Report Forms

The Principal investigator or delegated personnel will be responsible for the timing, accuracy and completeness of the eCRF for each individual subject. All entries will be electronic and there will be a clear audit trail in place for input and corrections of entered data. The personal data recorded on all documents will be regarded as confidential.

The Principal investigator or delegated personnel must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the Principal investigator must keep a separate list of all subjects entered into the clinical investigation showing each subject's name, date of birth and assigned subject number (for identification purposes). A Subject Identification Log will also be provided in the Investigation Site File to record the subject's initials and assigned subject number.

All data will be handled in accordance with the UK Data Protection Act 1998.

The eCRFs will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

A13.6 Review and Return of Completed Documentation

The Principal investigator will make the electronic Case Report Forms available to the Sponsor's designated monitor at each visit. At the conclusion of the clinical investigation, completed Case Report Forms will be electronically signed by the Principal investigator and a printed copy returned to the Sponsor.

A13.7 Retention of Documentation

The Principal investigator will retain all copies of the records for a period of 20 years from the discontinuation of the clinical investigation. In all cases, the Principal investigator must contact the Sponsor prior to disposing of any records related to the clinical investigation. Included in records to be maintained are signed Clinical Investigation Plan, copies of the eCRFs, signed consent forms, ethics committee approval letters, product accountability records, correspondence concerning the clinical and any other documents to identify the subjects.

In addition, if the Principal investigator moves/retires, etc., he should provide University College London with the name and address of the person who will look after and be responsible for the clinical investigation related records.

A13.8 Training

During the initiation of the investigation site, the sponsor will ensure the investigators and the site study staff are trained on the device. The investigator is then responsible for ensuring that the investigation staff uses the device in the same way. All training will be documented in a Site Training Log provided by the sponsor.

The monitor will also ensure that the investigator and investigation site team have received and understood the requirements and content of:

* CIP (Clinical Investigation Plan)
* IB (Investigators Brochure)
* The informed consent forms
* CRFs (Case Report Forms)
* IFUs (Instructions For Use)
* All written clinical investigation agreements as appropriate

A.14 Amendments to the CIP

Amendments to this CIP may be necessary to protect the safety of the patients and integrity of the data. In collaboration with the Investigator(s), the CIP amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per sponsor SOPs. Amendments will be considered implemented after all ethical and regulatory approvals (as required) are received and all key sponsor and site staff has been trained. This process does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

A.15 Deviations from clinical investigation plan

A deviation is considered a departure from the conditions and principles of GCP in connection with that Investigation; or the CIP relating to that Investigation, as amended from time to time.

The Investigator shall not deviate from this CIP except in situations that affect the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

A.15.1 Procedures for recording, reporting and analysing CIP deviations

If possible, prior approval from the sponsor and REC, if appropriate, shall be obtained by the investigator. All spontaneous CIP deviations shall be recorded and reported to the sponsor as agreed. A deviation log shall be maintained by the study site. Deviations shall be reported to the REC and the regulatory authorities if required by national regulations. All deviations will be included, as required in the final study report.

Notification requirements and time frames.

Requests for deviations by the investigator will be responded to within 24 hours of receipt.

Corrective and preventive actions and principal investigator disqualification criteria.

Refer to the Monitoring Plan (as applicable) for corrective and preventative actions and principal investigator disqualification criteria.

A.15.2 Procedure for reporting any protocol deviations

Any deviation from the protocol that has not been previously approved by the sponsor (JRO at University College London), must be reported to the sponsor within 2 working days of the deviation occurrence. Any deviations from the clinical investigation plan that are identified during routine monitoring visits will be reported to the sponsor (JRO, University College London) within 24 hours of being identified.A.16 Statements of compliance

The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO standard 14155 and all other applicable device and UK regulations.

The clinical investigation shall not commence recruitment until all REC, regulatory (if applicable) and local (NHS permission) is received. All additional requirements imposed by the REC or regulatory authority will be followed.

A.16 Insurance

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

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London 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 the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial 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 University College London, upon request.

An indemnity arrangement is in place, with the manufacturer, to cover the malfunction and breakdown of the device. In such an event, a repair or replacement of the device will be provided.

A.17 Adverse events, adverse device effects and device deficiencies

a-c) Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, 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:** For users or other persons, this definition is restricted to events related to investigational medical devices
Adverse Device Effect (ADE)	Adverse Event related to the use of an investigational 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 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)	Any adverse event that:
	• Led to death,
	• Led to serious deterioration in the 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 or prolonged hospitalisation, or
	  • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
	• Led to foetal distress, foetal death or a congenital anomaly or birth defect

Serious Adverse Device Effect (SADE)	An ADE that has resulted in any of the consequences characteristic of an SAE
Unanticipated Serious Adverse Device Effect (USADE)	An SADE, which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report.
Device Deficiency (DD)	Inadequately of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note 1:** this includes malfunctions, use errors, and inadequate labeling

An adverse event does not include:

- Medical or surgical procedures; the condition that leads to the procedure is an adverse event.
- Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);
- The disease being studied or signs/symptoms associated with the disease unless more severe than expected for the subject's condition.
- Expected post-operative course (see section x)

d) Reporting requirements and timelines

AEs and ADEs are not considered reportable.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Adverse Event (AE)	Investigator	Sponsor	As agreed with sponsor. CI to record fully all AEs.
Adverse Device Effect (ADE)	Investigator	Sponsor/Manufacturer	As agreed with sponsor. CI to record fully all ADEs.

The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of DIRECTIVES 90/385/EEC AND 93/42/EEC respectively.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Serious Adverse Event (SAE)**/ Serious Adverse Device Effect (SADE)	Investigator	Sponsor	Immediately, but no more than 3 calendar days after becoming aware of the event
	CI	MHRA aic@mhra.gsi.gov.uk	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 All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	N/A
Unanticipated Serious Adverse Device Effect (USADE)	Investigator	Sponsor	Immediately, but no more than 3 calendar days after becoming aware of the event
	CI	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. All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	Within 15 days of the chief investigator becoming aware of the event. Only reports of related and unexpected Serious Adverse Events (SAEs) 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	(i) Immediately-By telephone (ii) Within 3 days-Notice in writing setting out reasons for the USM and plan for further action

** **Note** Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

e) Assessments of adverse events

Each adverse event will be assessed for the following criteria:

Severity

Category	Definition
Mild	The adverse event does not interfere with the subjects daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subjects 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 an SAE.

Seriousness

Seriousness as defined for an SAE in section a) above.

Causality

The assessment of relationship of adverse events to the study procedure and the investigational device will be a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Yes	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 procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
No	There is no evidence of any causal relationship.

Expectedness

Category	Definition
Expected	An adverse event that is consistent with the information about the device listed in the Investigator Brochure or clearly defined in this CIP.
Unexpected	An adverse event that is not consistent with the information about the device listed in the Investigator Brochure

The reference document to be used to assess expectedness against the intervention is the IB. The CIP will be used as the reference document to assess disease related and/or procedural expected events.

f) Procedures for recording and reporting Adverse Events and Device Deficiencies

Investigator responsibilities:

All adverse events and SAEs will be recorded in the medical records and CRF following consent.

The Chief or Principal Investigator will complete the serious adverse event form and the form will be faxed/ emailed to the sponsor at sae@ucl.ac.uk, within 3 working day of his/her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

The Investigator will report to the MHRA and REC (as applicable) all reportable events within the specified timeframes as per section d above.

Patients recruited to the study are expected to continue to have Epileptic seizures and drug reduction or seizure inducing procedures such as sleep deprivation may be performed to elicit these to aid with the SEEG recordings. This is part of the routine clinical care of these patients. Any injury associated with a seizure including transient neurological deficits, fractures and soft tissue injuries would be expected as part of the disease and therefore would not be reported as an SAE. Sudden unexpected death in epilepsy (SUDEP) has an incidence of 3-9/1000 person-years and may therefore affect patients in this study.*"All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the device, or an unrelated event".*

All SAEs and UADEs should be reported to the following;

Phone: 020 7679 6594

Fax: 020 3108 2312

e-mail: sae@ucl.ac.uk

Reporting of all Adverse Events and Device Deficiencies: Investigator and Sponsor responsibilities

Investigator responsibilities shall be as per section d). 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 Investigation 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 MHRA, and the relevant ethics committees per their reporting requirements and according to the timelines in section d. Any additional relevant information should be sent within the same time frame as the initial report. The CI is responsible for informing the appropriate regulatory authorities, ethics committees and other investigators of any reportable events that have occurred with the study device in any clinical investigation according to the guidelines set forth by either the REC of record or regulatory authority in the country where the clinical investigation is taking place.

Progress reports

Progress reports will be submitted to the REC as per the REC requirements. The chief investigator will prepare the annual progress reports.

Foreseeable adverse events and anticipated adverse device effects

Patients recruited to the study are expected to continue to have Epileptic seizures and drug reduction or seizure inducing procedures such as sleep deprivation may be performed to elicit these to aid with the SEEG recordings. This is part of the routine clinical care of these patients. Any injury associated with a seizure including transient neurological deficits, fractures and soft tissue injuries would be expected as part of the disease and therefore would not be reported as an SAE. Sudden unexpected death in epilepsy (SUDEP) has an incidence of 3-9/1000 person-years and may therefore affect patients in this study. Seizures that occur in hospital will be managed in line with the routine standard care of the patient. The recording of seizures following the placement of the SEEG electrodes is fundamental to the procedure to identify the source of the seizure activity to guide further surgical management. As is the routine standard of care the risk of injury / harm from a seizure will be

minimized by the nursing staff on the wards. The risk of SUDEP is mitigated by continual observation and positioning and stimulation at the end of seizures.

A.18 Oversight Committees

Trial Management Group (TMG)

The TMG will include the Chief and Principal Investigators and experts from relevant. The TMG will be responsible for overseeing the trial. The group will meet at least twice per year and all members will sign a TMG charter. The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA.

Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and the Sponsor. All Trial Steering Committee Members will sign a TSC charter.

Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held annually to review the safety data generated by the study or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC. All IDMC members will sign an IDMC charter.

A.19 Suspension or premature termination of the clinical investigation

Both the Sponsor and the Principal investigator reserve the right to terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual basis after review and consultation by both parties. In terminating the clinical investigation, the JRO at University College London and the Principal investigator will assure that adequate consideration is given to the protection of the subject's interests. Data will be reviewed by a trial steering committee with review after randomization of 6, 12 and 18 subjects to determine whether the results of the study so far mandate premature termination, if the complication rate of one arm is significantly higher than the other. Subject follow up following suspension / premature study termination will be as part of routine standard of care as the intervention arm of the procedure occurs on a single day and the CT / MRI scans from which the majority of the primary and secondary outcomes measures are derived from occurs within 48 hours of the surgery.

A20.1 Subject Withdrawals and Discontinuation

During the course of this clinical investigation, subjects may elect to withdraw from further treatment through any of the following reasons:

- Subject's rescission of consent.
- Any unexpected adverse device effect which is, in the opinion of the Principal investigator, related to the device and will endanger the wellbeing of the subject if the treatment is continued.
- The development of any undercurrent illness(es), infection or condition(s) that might interfere with the Clinical Investigation Plan.
- Any problem deemed by the Principal investigator and/or the JRO at University College London to be sufficient to cause discontinuation.

All subjects discontinued from the clinical investigation due to an unexpected adverse device effect, directly related to the clinical investigation, will be treated until the effect resolves. The Principal investigator will clearly document the date and reason(s) for subject withdrawal in his/her CRF and the monitor must be notified.

Subjects who are withdrawn prior to receiving investigational device will be replaced.

A.21 Definition of End of Trial

The expected duration of the trial is 20 months from recruitment of the first participant.

The end of trial is 48 hours following the date of the last SEEG implantation.

A.22 Publication policy

All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings.

All proofed publications, including conference abstracts will be reviewed by Wellcome Trust and Medtronic, 20 days prior to publication or presentation. Please refer to UCL publication policy.

A.23 Bibliography

List of bibliographic references pertaining to the clinical investigation.

List of the literature and data that are relevant to the trial, and that provide background for the trial. Please ensure the text contains appropriate cross references to this list

1. Dorfer C, Minchev G, Czech T, Stefanits H, Feucht M, Pataraia E, et al. A novel miniature robotic device for frameless implantation of depth electrodes in refractory epilepsy. J Neurosurg. 2016;1–7.

2. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: A meta-analytic approach. Epilepsia. 2010;51(5):883–90.

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4. De Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: A cohort study. Lancet [Internet]. Elsevier Ltd; 2011;378(9800):1388–95. Available from: http://dx.doi.org/10.1016/S0140-6736(11)60890-8

5. Fois C, Kovac S, Khalil A, Tekgöl Uzuner G, Diehl B, Wehner T, et al. Predictors for being offered epilepsy surgery: 5-year experience of a tertiary referral centre. J Neurol Neurosurg Psychiatry [Internet]. 2015;(1):jnnp – 2014–310148 – . Available from: http://jnnp.bmj.com/content/early/2015/05/02/jnnp-2014-310148.long

6. Enatsu R, Mikuni N. Invasive Evaluations for Epilepsy Surgery: A Review of the Literature. Neurol Med Chir (Tokyo) [Internet]. 2016;1–7. Available from: https://www.jstage.jst.go.jp/article/nmc/advpub/0/advpub_ra.2015-0319/_article

7. Mullin JP, Shriver M, Alomar S, Najm I, Bulacio J, Chauvel P, et al. Is SEEG safe? A systematic review and meta-analysis of stereo-electroencephalography-related complications. Epilepsia. 2016;57(3):386–401.

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http://linkinghub.elsevier.com/retrieve/pii/S1878875016305022

9. Nowell M, Rodionov R, Diehl B, Wehner T, Zombori G, Kinghorn J, et al. A novel method for implementation of frameless stereoeeg in epilepsy surgery. Neurosurgery. 2014;10(4):525–34.

10. Lee Y-K, Biau DJ, Yoon B-H, Kim T-Y, Ha Y-C, Koo K-H. Learning curve of acetabular cup positioning in total hip arthroplasty using a cumulative summation test for learning curve (LC-CUSUM). J Arthroplasty. United States; 2014 Mar;29(3):586–9.

11. Kim H-J, Lee SH, Chang B-S, Lee C-K, Lim TO, Hoo LP, et al. Monitoring the Quality of Robot-Assisted Pedicle Screw Fixation in the Lumbar Spine by Using a Cumulative Summation Test. Spine (Phila Pa 1976) [Internet]. United States; 2015 Jan;40(2):87–94. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00007632-201501150-00005

12. Minchev G, Kronreif G, Martínez-Moreno M, Dorfer C, Micko A, Mert A, et al. A novel miniature robotic guidance device for stereotactic neurosurgical interventions: preliminary experience with the iSYS1 robot. J Neurosurg. 2016;1–12.

Appendix A:		

Need to list all the planned baseline assessments that will be performed once the patient has been entered into the Investigation and before their first exposure to the device

	Screening	***Baseline [a]***	***Treatment Phase [b]***		***Follow Up [c]***
Visit #	*1*	*2*	*3*	*4*	*5*
	Day – X	*Day-1*	*Day 0*	*Day 1*	*48 hours*
Informed Consent	*X*				
Medical History/Physical exam	*X*	*X*		*X*	*X*
Vital Signs	*X*	*X*	*X*	*X*	*X*
Eligibility determination	*X*				
Pre-surgical blood tests (routine care)	*X*	*X*			
Randomisation	*X*				
Device/Treatment			*X*		
Adverse Events review			*X*	*X*	*X*
Post-operative CT and MRI			*X*	*X*	*X*

Appendix A:		

scans (routine care)					
Physician's Withdrawal Checklist				*X*	*X*