SEMMELWEIS UNIVERSITY
Neurosurgery and Neurointerventional Clinic

clinic director
DR. HABIL. LORÁND ERŐSS

Clinical Investigation Protocol

Document title: **Clinical trial data and documents**

The name of the study: **Changes in brain activity as a function of scalp and subcutaneous electrical stimulation parameters in epileptic patients**

Original permission number: **OGYÉI/9674/2021**
Date of original acceptance: **04/06/2021**

Permission number of revised protocol: **NNGYK/4245/2025**
Date of last revision: **01/13/2025**

Name of the sponsor/investigation manager: **Dr. habil Erőss Loránd**

Address: 1145 Budapest, Amerikai út 57.
Postal address: 1085 Budapest, Üllői út 26.; 1428 Budapest, Pf. 2.
E-mail: titkarsag.amerikaiut@semmelweis.hu
Tel: (+36-1) 467-9301
semmelweis.hu

Clinical Investigation Protocol

In case of a multicenter investigation, a resolution from the relevant Ethics Committee of the State party to the EEA Agreement (if applicable).

The study is not multicentric, so this point is not applicable.

15) The clinical trial plan, which includes

a) **Purpose of the study (testing effectiveness)**

The objective of this study is to evaluate the effects of spatially and temporally targeted transcranial stimulation—specifically, Intersectional Short Pulse (ISP) stimulation administered via extracranial and subgaleal electrodes—on epileptic brain phenomena, [redacted] and EEG activity in subjects with epilepsy. We aim to assess the tolerability, safety, and preliminary effectiveness of ISP stimulation by systematically optimizing stimulation parameters. In patients participating in the extended three-phase study design, we will evaluate the practicality and effectiveness of closed-loop automatic stimulation. This stimulation will be precisely controlled by a fine-tuned seizure detection algorithm, with efficacy determined primarily by the reduction in the frequency of clinically observable epileptic seizures.

Furthermore, we aim to refine the precision of deep brain targeting for transcranial stimulation by employing individualized MRI and neuronavigation-based localization techniques.

b) Accurate, objective definition of the goals to be achieved

First objective is to determine the accuracy and feasibility of electrode placement under the scalp. We will perform patient-specific MRI-based estimations of current distribution in epileptic patients. These estimations, combined with neuronavigation positioning, will inform the precise placement of implanted electrodes.

Our second aim is to investigate the dose-response and tolerance relationships:

- [redacted]

- i**n epileptic patients**. Targeted ISP stimulation will be applied to cortical areas using standardized parameters to evaluate its efficacy and safety.

During the study, subjective sensations experienced by the patients will be systematically recorded, both to identify potential side effects and to evaluate sensory experiences induced by the stimulation. [redacted] Additionally, changes in epileptic spike frequency on EEG recordings will be monitored.

Our third objective is to determine whether stimulation triggered very early in seizure onset, via an automated seizure detection algorithm, is more effective in terminating seizures or preventing their generalization compared to stimulation initiated at later stages of the seizure.

This involves the detection of epileptic seizures in patients and customization of the seizure detection algorithm to their individual EEG patterns. The accuracy of this seizure detection will be validated using EEG segments from both seizure-free intervals and intervals with artificially introduced EEG artifacts.

An additional objective of this study is to modulate epileptic seizures through spatially and temporally targeted transcranial stimulation delivered via implanted electrodes. Seizure episodes will be recorded through the stimulation electrodes and automatically detected. Detected seizures will then be targeted for intervention using timed ISP pulses delivered at previously established safe intensities. The effectiveness of stimulation will be evaluated by comparing the duration of seizures treated with ISP stimulation to untreated seizures. For patients enrolled in the three-phase experimental protocol, we will further compare clinically observed seizure frequencies during periods of active stimulation and control periods without stimulation.

c) Description of study method (e.g. double-blind, randomised, etc.)

Interventional, open label observational clinical trial.

d) Description of the investigation procedure

We will use a previously developed electronic system capable of delivering precisely controlled Intersectional Short Pulse (ISP) stimulation. This device can simultaneously record EEG signals from electrodes placed externally on the scalp or subgaleally, without significant

distortion due to its wide dynamic range. Recorded signals will undergo real-time adaptive signal processing to remove stimulation-related electrical artifacts, thereby preserving the integrity and clinical relevance of the EEG data.

In the current study, we will employ our validated (1) signal processing system to investigate the impact of transcranial stimulation on resting-state and pathological brain activities, [redacted]

Address: 1145 Budapest, Amerikai út 57.
Postal address: 1085 Budapest, Üllői út 26.; 1428 Budapest, Pf. 2.
E-mail: titkarsag.amerikaiut@semmelweis.hu
Tel: (+36-1) 467-9301
semmelweis.hu

[redacted]

Procedures for Patients with Epilepsy

Patients will primarily be recruited from the epilepsy outpatient clinic at SEINK. Eligibility includes drug-resistant epilepsy patients who have been determined unsuitable for resective surgery based on established clinical criteria (as detailed in the inclusion criteria).

Upon providing informed consent after thorough explanation of the study, participants will undergo assessments conducted at the SEINK facilities. Patients will be enrolled based on the availability of resources in the Video-EEG testing laboratory.

The investigation consists of multiple sequential stages:

Stage I: MRI Scanning and Neuronavigation

Patients will first undergo an MRI scan to guide precise electrode placement using neuronavigation technology. The MRI protocol, lasting no more than 60 minutes, will include routine clinical sequences (3D MPRAGE T1, FLAIR) to obtain high-resolution anatomical images necessary for creating individualized neuronavigation maps.

Stage II: Electrode Positioning and Planning

The exact electrode positions will be determined based on patient-specific 3D head models derived from MRI images. Neuronavigation (Neural Navigator, Brain Science Tools BV) will ensure accurate and reproducible placement of electrodes at predefined cortical targets.

[redacted]

[redacted]

Stage III: Electrode Implantation and ISP Stimulation

Electrode implantation and subsequent neurophysiological and cognitive assessments, including ISP stimulation, will be performed in the Video-EEG laboratory at SEINK's Neurology Department.

Two alternative protocols are available for conducting the investigation:

In the first protocol, patients will participate for a maximum duration of 30 days, during which hospitalization is continuous, under the following conditions:

1) Seven days after electrode implantation, a surgical assessment of wound healing is performed to ensure proper healing and the absence of infection risk. If the outcome of this evaluation is satisfactory, the investigation may continue.

2) Fourteen days after implantation, the wound check described in point 1 will be repeated. If results are satisfactory, the investigation period may be extended for two additional 7-day intervals. Thus, the total duration of participation can reach up to 30 days, including 2 days dedicated to preparatory examinations, surgery, and system installation, followed by up to 28 days allocated for EEG monitoring, seizure recording, and ISP stimulation.

During rapid, pulse-like electrical stimulation, the risk of potential tissue damage is not determined solely by stimulation intensity, power density, or duration individually, but rather by the total charge density transferred to cellular membranes over the stimulation period—

essentially, the combination of these parameters. In practice, this means that a longer, low-intensity stimulus and a shorter, high-intensity stimulus can produce equivalent effects. For example, intraoperative cortical stimulation often uses a short duration of 0.1 ms at approximately 100 mA intensity, whereas transcranial stimulation typically involves several milliseconds at lower intensities (1–2 mA), both potentially resulting in similar charge densities. For our electrical stimulation experiments, instruments specifically developed by Neunos ZRt will be utilized. During ISP stimulation, electrodes with a surface area of 19.6 mm² will be implanted subgaleally (beneath the scalp) to reduce charge density, thereby minimizing patient discomfort and avoiding potential injury. Standard subdural electrode strips (Ad-Tech Medical Instrument Corporation, WI, USA; models MS08R-IP10X-0JH and MS08R-IP10X-000) will be used.

Electrode insertion will be carefully planned and performed by an experienced neurosurgeon under general anesthesia. Electrodes will be inserted subcutaneously through small skin incisions. [redacted]

Electrodes will be positioned beneath the scalp but superficial to the skull bone. The electrode strips remain stable once positioned subgaleally, secured only by absorbable sutures. Electrode cables will be externalized percutaneously using a tunneling needle, exiting away from the primary skin incision site to minimize infection risk.

[redacted]

[redacted]

Following electrode insertion, externalisation of electrode leads, layered closure of the skin, and recovery from anesthesia, a CT scan is performed to verify the exact positioning of the electrodes. The patient is then transferred to the video-EEG unit. After a brief postoperative recovery period, the externalised electrode leads are connected to the Neunos SeizureSTOP™ system. [redacted]. The subgaleal electrodes are simultaneously connected to both the clinical EEG recording system and the Neunos system, allowing concurrent monitoring.

[redacted] Although the stimulation parameters used in the proposed paradigms differ, the charge density transferred during a single stimulation cycle at any electrode does not exceed the safe limit used by commercially used and already approved stimulation methods . (3)

Before, during and after the stimulation, EEG measurements will be performed to investigate the spectral properties of brain activity and, through them, the electrophysiological efficacy of the stimulation. EEG analysis will be performed off-line, [redacted]

The planned 3+1 stimulation paradigms are as follows:

III./1. ISP Parameter Dependence of Subjective Tolerability of Stimulation

The tolerance test will be performed on the morning following electrode implantation, or—in the case of patients enrolled in the three-phase (ambulatory) protocol—the morning after hospital admission. This timing ensures adequate recovery of the surgical site, patient comfort, and minimizes the potential influence of residual anesthetic effects on test outcomes.

The objective of this test is to evaluate how individual ISP stimulation parameters, beyond stimulation intensity alone, influence subjective tolerability. The results obtained will guide the optimization of ISP stimulation parameters for subsequent clinical use, aiming to achieve maximum therapeutic efficacy while minimizing patient discomfort.

[redacted]

[redacted]

[redacted]

[redacted]

Clinical Investigation Protocol

[redacted]

Address: 1145 Budapest, Amerikai út 57.
Postal address: 1085 Budapest, Üllői út 26.; 1428 Budapest, Pf. 2.
E-mail: titkarsag.amerikaiut@semmelweis.hu
Tel: (+36-1) 467-9301
semmelweis.hu

[redacted]

III./2. Measurement of Patient-Specific ISP Sequence Tolerance

Therapeutic stimulation is delivered by rapidly connecting specific groups of electrodes, forming a tailored ISP sequence. Based on the outcomes of the previous test (III./1), we identify the electrode pairs within the sequence capable of safely delivering the highest stimulation intensity without causing discomfort. Spatial targeting is guided by directing stimulation specifically towards the patient's presumed seizure-triggering cortical area. When creating the ISP stimulation sequence, preference is given to electrode pairs demonstrating higher tolerability to ensure optimal spatial selectivity.

Prior to initiating therapeutic stimulation, we determine the maximum tolerable stimulus intensity for the finalized ISP sequence. This determination accounts for the patient's individual anatomy and the tolerance thresholds identified for each electrode pair.

Procedure: Subjects are positioned comfortably, either seated in a reclining chair or lying in their hospital beds during the measurement.

After programming the selected ISP stimulation sequence, stimulation is initiated at an intensity of 5 mA. The amplitude is incrementally increased in steps of 0.5–2 mA, and the patient's reported sensory experiences and subjective discomfort levels are digitally recorded using a Visual Analog Scale (VAS). A pause of at least 5 seconds is maintained between each stimulus. Stimulation parameters match those used for seizure management: [redacted]

The stimulation intensity continues to be gradually increased until the patient reaches an painful level (VAS = 10), which the patient deems higher than acceptable for anti-seizure treatment or until the maximum safe charge density is achieved. The highest intensity level associated with acceptable discomfort (VAS = 9) immediately preceding intolerable pain is designated as the subject's individual tolerance threshold and represents the maximum allowed therapeutic stimulation intensity for seizure control in that ISP sequence.

In cases involving multiple ISP sequences (e.g., multifocal epilepsy), individual tolerance thresholds are determined separately for each sequence. The tolerance assessment procedure typically requires up to 5 minutes per ISP sequence.

[redacted]

SEMMELWEIS UNIVERSITY
Neurosurgery and Neurointerventional Clinic

clinic director
DR. HABIL. LORÁND ERŐSS

Clinical Investigation Protocol

[redacted]

Address: 1145 Budapest, Amerikai út 57.
Postal address: 1085 Budapest, Üllői út 26.; 1428 Budapest, Pf. 2.
E-mail: titkarsag.amerikaiut@semmelweis.hu
Tel: (+36-1) 467-9301
semmelweis.hu

Clinical Investigation Protocol

[redacted]

Address: 1145 Budapest, Amerikai út 57.
Postal address: 1085 Budapest, Üllői út 26.; 1428 Budapest, Pf. 2.
E-mail: titkarsag.amerikaiut@semmelweis.hu
Tel: (+36-1) 467-9301
semmelweis.hu

[redacted]

III./6. The Ability of Closed-Loop Administration of ISP to Stop Pathological (Epileptic) Brain Rhythms

One desired outcome of this study is to investigate that accurately parameterized and precisely timed ISP stimulation can effectively modulate pathological brain activity. As demonstrated previously in animal models,(1) such stimulation may impact epileptic activity by arresting seizures, shortening seizure duration, preventing seizure propagation (including bilateral spreading), and modifying seizure spectral composition. According to existing literature, these effects strongly correlate with long-term therapeutic efficacy of this method (35).

The Measurement Procedure:

1**. To assess changes in seizure frequency and severity,** a paper-based seizure diary is maintained by the patient starting at least 30 days prior to electrode implantation (if available), and continuing for at least 60 days after implantation. This diary records the daily number and type of seizures, patient comments, and medication usage. The three-phase study design (ambulatory) also enables detailed analysis of changes in electrophysiological activity through continuous EEG monitoring data.

2. **Examination of the effects of ISP stimulation on neurophysiological properties of epileptic seizures.** The primary objective of this set of measurements is to statistically compare seizure durations with and without ISP stimulation, thereby evaluating the efficacy of the intervention. An additional goal is to validate and refine the performance of the automatic

seizure detection algorithm. *Together, these objectives will further establish the feasibility and safety of the closed-loop stimulation method.*

In the first protocol (**the maximum 30-day, in-hospital-only study**), EEG monitoring is conducted using the Neunos system employed in previous studies, alongside standard clinical EEG equipment. During the monitoring period, patients will be housed within the SEINK Video-EEG monitoring unit. They will be permitted mobility consistent with standard clinical procedures, allowing them to move within the hospital as directed by clinicians. The total monitoring period—from implantation to hospital discharge—is limited to 30 days and is divided into the following phases:

1. **Initial (Control seizure recording) Phase:** Lasting at least 5 days (including the implantation day), this phase involves continuous EEG recording without stimulation. Spontaneous seizures and resting EEG activity are documented, and individual tolerance assessments [redacted] are conducted as detailed previously. Collected EEG data, combined with clinician-annotated seizure onset and offset times, serve as training data for the automated seizure detection algorithm.

2. **Semi-Automatic Stimulation Phase:** After completing the detector training, the semi-automatic ISP stimulation mode is activated. Here, when the seizure detector triggers an alert, the investigator initiates stimulation manually after verifying seizure onset through real-time EEG and video monitoring. If a seizure occurs without detector activation, the investigator may manually trigger stimulation based on clinical judgment. ISP stimulation intensity settings are based on patient-specific tolerance thresholds established in prior testing phases. During this phase, the accuracy of seizure detection (specificity, sensitivity, false detection rate) is evaluated against clinician-defined seizure epochs, and detection parameters are adjusted accordingly.

3**. Automatic Closed-Loop Stimulation Phase:** Once the clinician confirms reliable seizure detection performance (specificity >90%, sensitivity >90%, false detection rate <1/h), the ISP system proceeds to automatic closed-loop stimulation. EEG and video streams continue to be closely monitored by the investigator, who retains the ability to manually intervene and stop or initiate stimulation to address any false positives or negatives.

4. **ISP Stimulation Procedure During Seizures**: When seizure activity is identified—either automatically by the detector or manually by the supervising clinician—the pre-configured ISP stimulation sequence is activated. Post-stimulation, EEG signals are momentarily obscured by stimulation artifacts (lasting 1-2 seconds). Once the artifact period passes, the seizure detector

resumes EEG analysis. If ongoing seizure activity is detected, the clinician visually confirms and may repeat stimulation.

Multiple stimulation sequences (each consisting of three half-sine pulses) can be administered per seizure, with sufficient intervals between sequences to enable clear EEG analysis post-artifact. Individual stimulation pulses are [redacted]

The cortical target for stimulation is initially set by the clinician, based on the identified epileptic focus and with careful consideration of minimizing side effects to adjacent deep brain structures. ISP stimulation sequences are always individually tailored to patient-specific tolerance thresholds.

In the second protocol, in the three-phase study design, patients will participate for a maximum of 90 days (3 days in hospital; up to 30 days at home with EEG recording without stimulation; up to 30 days at home with EEG recording and seizure detection without stimulation; up to 30 days in hospital with stimulation) to evaluate longer-term efficacy. The objectives of the two at-home phases are: firstly, to record sufficient baseline EEG and seizure data required to train the seizure detection algorithm and collect non-stimulated control seizures; secondly, to fine-tune the seizure detection algorithm and validate its performance
(sensitivity and false-positive rate). These preparations will ensure safe and effective closed-loop ISP stimulation during the final hospital phase.

The test phases are conducted under the following conditions:

1) Three days after electrode implantation, the patient remains hospitalized, the system is installed, and the hospital staff assesses wound healing (proper healing, no infection risk). If the evaluation is positive, the study continues.

2) If the wound condition is satisfactory, the hospital and technical staff prepare the patient and, if necessary, their relatives for the home phase of the study:

a. The patient receives thorough instructions on using the system at home, including guidance on daily activities, comfort, hygiene, sleep, and mobility.

b. The patient is provided with necessary equipment: modular device storage bag, external batteries, battery charger, and a waterproof bag.

c. The patient receives detailed instructions on maintaining cleanliness of the cable exit site and symptoms requiring immediate staff notification.

d. Patients and relatives are provided with immediate contact details for technical and medical support.

3) The patient spends the registration phase (up to 30 days) at home under the following conditions:

a. The system operates only in EEG recording mode, without stimulation or seizure detection, recording EEG signals continuously (24/7).

b. The modular neurostimulator is stored in a dedicated backpack, with externalized cables connected directly to the device inside. The patient replaces the external battery daily based on audible device notifications. A factory-designed, mechanically safe connector cable is used, which disconnects safely under excessive tension, avoiding damage to cables or scalp stitches.

c. Electrode cables may be temporarily disconnected for activities such as cleaning or washing. In such cases, the head unit collecting cables must be placed in a provided waterproof bag. Upon reconnection, EEG recording automatically resumes.

d. Hospital staff conduct phone check-ins every other day to confirm patient wellbeing and address any concerns. If feedback is positive, the study continues.

e. A qualified healthcare professional inspects the wound condition every 7 days (or more frequently if clinically required), either at home or hospital, assessing for proper healing and absence of infection risk (mild inflammation may be acceptable). Dressings are changed, and the wound area treated accordingly. If the outcome is positive, the study continues.

f. If signs of wound infection are detected, the patient is immediately examined by the surgical team at the hospital and treated according to medical guidelines. Patient safety remains the priority; the team may decide to continue with conservative treatment (topical or systemic antibiotics) or immediately terminate the study and explant electrodes.

g. The study must also be terminated immediately if the patient experiences discomfort, pain, or any other issues that prompt withdrawal, even without visible complications.

h. To adequately train a highly reliable seizure detection algorithm, recording an adequate number of seizures with good-quality data is essential. The duration required for this phase

depends on the individual patient's seizure frequency. When sufficient data is obtained, this phase may be shortened, subject to investigator review and agreement.

4) During the initial registration phase, technical staff review EEG recordings daily, annotating seizure activity and any EEG artifacts. Annotated data is used to train the seizure detection algorithm. The trained algorithm is activated during a scheduled hospital visit without delivering stimulation at this stage. During the same visit, wound status is assessed again (proper healing, no risk of infection, mild inflammation acceptable). If this check is satisfactory, the study continues.

5) In the following seizure detector tuning phase, the patient spends another period at home under conditions described in point 3. During this up-to-30-day phase, EEG signals and automated detector decisions are continuously recorded. This data allows long-term monitoring and further tuning of detector performance as needed. Detector efficacy is evaluated offline through recorded data analysis (sensitivity, specificity, false detection rate).

6) Upon reaching a sufficient number of detected seizures and statistically acceptable detector accuracy (>90% specificity, >90% sensitivity, false detection rate <1/h), the study may proceed earlier to the next phase, shortening the 30-day duration. The final decision on study pipeline progress is made collaboratively by the clinical investigators.

7) Following the second home phase (seizure detector tuning), the patient returns to the hospital for up to 30 days for the final stimulation phase, similar to the first case described above. During this phase, stimulation-related testing is performed. Unlike the first case, no additional control seizure recordings or detector training are required, as these steps were completed previously. The stimulation phase begins immediately following the determination of individual tolerance thresholds.

IV) The conclusion of the will occur no later than 30 days after implantation. The exact duration of participation is determined jointly by the patient and the clinical team. At the end of the study period, the implanted electrodes are removed under local scalp-blockade, and the skin is closed in anatomical layers.

After participation in the three-phase study, slight scarring may develop around the implanted electrodes, which can make atraumatic removal of the electrode strips more difficult. In such cases, and based on the neurosurgeon's judgment, a pulsed radiofrequency (RF) dissection device may be used. This technique allows the strips to be removed without causing tissue damage and without damaging the explanted device, ensuring that no part of the implant remains under the skin (36).

V) During the follow-up phase, any delayed adverse effects or medium-term changes in epileptiform activity will be monitored and recorded to provide additional safety data. The follow-up plan is detailed in Chapter 16g).

e) Factors Affecting the Outcome of the Test (e.g., Other Diseases)

Patients eligible for inclusion in the study may present with comorbidities, such as memory or mood disorders, depending on their specific epilepsy type. The etiology of epilepsy in the patient population is expected to be heterogeneous; however, autoimmune etiologies are strictly excluded. Each patient will serve as their own control, and all results will be analyzed individually prior to any pooled analysis. Therefore, the presence of comorbidities in a participant is not expected to introduce bias into the study results. Additionally, patients with severe internal medicine conditions or progressive brain pathologies will be excluded from the study.

Data sheet sample, algorithm, written instructions for the evaluation of the study

Data recorded during electrophysiological measurements are analyzed using commercially available [redacted] software [redacted] and [redacted]. EEG signals during stimulation are cleaned and pre-processed using a proprietary signal filtering algorithm(1). Statistical tests are performed using [redacted]

1. Planned Statistical Analysis

The following statistical analyses are planned to evaluate the results of the study. The primary endpoint is the feasibility and safety of the method. Secondary endpoints include determining the effect of stimulation on epileptiform activity.

1.1. 1.1. Incidence of adverse events during the study

[redacted]

In patients with epilepsy, side effects/adverse events will be closely monitored. Patients will be instructed to report any adverse effects throughout the study. Additionally, side effects will

be assessed and recorded twice daily (morning and evening) during hospitalization, and every other day during home visits. Surgical- and stimulation-related adverse events will be recorded separately. Although the likelihood of unexpected events after discharge is low, patients will be actively queried during follow-up visits (see Chapter 16g) for any such occurrences.

1.2. Tolerance Testing of Individual Stimulus Intensity

[redacted]

Tolerance Analysis in Epileptic Subjects

For epilepsy patients, we will assess intra- and inter-subject variability in stimulus tolerance for each electrode sublocation. The dependence of tolerable intensity on the anatomical site of stimulation will be analyzed at both individual and group levels.

Because ISP sequences are uniquely customized for each patient and vary significantly, their tolerance levels are not comparable across subjects; therefore, no statistical analyses will be conducted for ISP sequence tolerance data.

1.3. Statistical Analysis of the Effect of ISP on Epilepsy

The primary therapeutic goal of ISP stimulation is to reduce or terminate seizures by modulating their onset through electrical stimulation. While a statistically significant therapeutic effect is not expected during the study period (given that neuromodulation effects often manifest over weeks or months), we expect to observe trend-level changes. The following variables will be tracked and analyzed:

1.3.1. Change in Seizure Rate

1.3.1.1. Seizure Rate Change Calculated from the Seizure Diary

Seizure frequency will be tracked using a patient-maintained seizure diary for 30 days before implantation (if available) and for at least 60 days post-implantation. In cases of

long-lasting stimulation effects observed during hospitalization, a reduction in seizure frequency may be noted. The diary will include details on seizure types and frequencies, enabling tracking of total seizure burden as well as changes in specific seizure types—offering insight into potential long-term effects of ISP stimulation.

1.3.1.2. Seizure Rate Variation Calculated from Video-EEG Analysis (In-Hospital Only)

During hospitalization, continuous video-EEG monitoring from implanted electrodes will be reviewed. The clinician annotates all observed epileptic events. [redacted] The number and types of seizures in the control phase will be compared to those during the stimulation phase, allowing inference of acute effects.

1.3.1.3. Epileptiform EEG Activity and Seizure Rate Variation Calculated from Continuous EEG Recording Analysis in the Three-Phase Study

Continuous EEG data collected during the up to 60-day pre-stimulation period (registration + seizure detector tuning) and during the stimulation phase (up to 30 days in hospital) will be analyzed. This data allows for a comparison of interictal and ictal phenomena over a longer timeframe, enabling a more statistically robust assessment than the shorter video-EEG analysis described in 1.3.1.2.

1.3.2. Investigation of the Effect of ISP Stimulation on the Length of Electrographic Seizure Patterns

The duration of electrographic seizures recorded via EEG will be measured, and the effect of ISP stimulation on seizure duration will be evaluated. Two experienced clinicians will independently identify seizure onset and offset, reaching a consensus on duration. Focal and generalized phases will be analyzed separately, and total seizure duration will also be assessed. A reduction in seizure duration will indicate potential long-term therapeutic benefit.

1.3.3. Investigation of the Effect of ISP Stimulation on the Spectral Composition of Electrographic Seizure Patterns

Changes in the spectral profile of seizure activity are a sensitive indicator of neuromodulatory impact. Spectral analysis will be conducted [redacted] Spectral features of control (non-stimulated) and stimulated seizures

will be compared for each patient. Clinician-annotated timestamps will define baseline and seizure windows for spectrogram generation.

1.3.4. Examining the Impact of ISP Stimulation on Seizure Severity and Propagation

We will analyze whether ISP stimulation alters the severity or progression of seizures. Seizures will be classified by two clinicians in consensus into: Focal aware seizures, Focal seizures with impaired awareness, Focal to bilateral tonic-clonic seizures (secondary generalized seizures). The analysis will determine whether ISP stimulation can acutely prevent seizure generalization.

1.4. Evaluating the Performance of the Seizure Detector

Post-recording, the automated seizure detector's performance will be benchmarked against expert clinician annotations, [redacted]

g) **Follow-up plan**

Follow-up will be conducted through a combination of in-person visits and remote consultations (telephone or video call), as follows:

- Control 1 (10–14 days after explantation): In-person neurosurgical follow-up visit, including suture removal.
- Control 2 (10–14 days after explantation): In-person epileptological follow-up, recording of any side effects, and review of the seizure diary.
- Control 3 (first month after explantation): Telephone epileptological follow-up, recording of side effects, and review of the seizure diary.
- Control 4 (second month after explantation): Telephone epileptological follow-up, recording of side effects, and review of the seizure diary.
- Control 5 (third month after explantation): Telephone epileptological follow-up, recording of side effects, and review of the seizure diary.
- Control 6 (sixth month after explantation): In-person epileptological follow-up, recording of side effects, and review of the seizure diary.

Clinical visits for study participants will be conducted according to standard medical practice. As outlined in the patient information leaflet (provided prior to study participation and at hospital discharge), patients are instructed to report any adverse events to the investigating clinician by phone—even between scheduled visits—and especially during the first 30 days following study completion.

h) Scientific, Medical, and Technical Justification for Carrying Out the Study

Modification of brain function through electrical stimulation—commonly referred to as electrical neuromodulation—is a well-established treatment for several neuropsychiatric conditions, including depression, movement disorders (e.g., Parkinson's disease), epilepsy, and obsessive-compulsive disorder (5)(6)(7). One of the key advantages of neuromodulation is its ability to deliver targeted, systemic treatment with minimal side effects. Both the stimulation site and parameters can be adjusted, allowing for highly individualized treatment planning.

In many of these conditions, the electric field is applied directly to selected deep brain structures in a method known as deep brain stimulation (DBS) (8). DBS has been approved by both U.S. and European regulatory authorities for various indications, and hundreds of thousands of patients have undergone this therapy, with the number continuing to rise (9). In DBS, electrodes are surgically implanted into the brain and cannot be repositioned without another invasive procedure. While the method offers high targeting precision, it is inherently invasive and restricts target flexibility.

Non-invasive neuromodulation methods that avoid neurosurgery also exist. Transcranial electrical stimulation (TES) (10) and transcranial magnetic stimulation (TMS) (11) have both been investigated and applied clinically. However, these techniques offer limited penetration to deep brain structures or require complex and bulky equipment (12).

Neuromodulation therapies rely on two main mechanisms of action. The first involves direct modulation of neuronal function through the applied electric field, typically by increasing neuronal firing rates and synchronizing activity to the stimulation frequency (13). Depending on the frequency, this can result in excitation or functional inhibition of the target area (14). These effects persist only during stimulation, and abnormal brain activity typically returns shortly after the stimulus ends.

The second mechanism leverages plasticity: changes in neural firing patterns activate long-term plastic processes that can lead to sustained inhibition of pathological activity and a lasting return to normal function (15). This true neuromodulation is exemplified in TMS therapy for depression, where patients often experience long-term improvement—even

months after receiving thousands of stimulation pulses (11). Achieving such effects requires repetitive stimulation, which implies the need for portable or implantable systems the patient can use regularly.

However, current TMS systems are large and non-portable, requiring repeated visits to clinical facilities. A promising alternative is electrical stimulation, yet its main limitation is the poor penetration of electric fields into the brain. For instance, with the commonly used transcranial direct current stimulation (tDCS) at therapeutic levels (1–2 mA), most of the current is shunted outside the skull (Liu, 2018). Increasing current or frequency can cause discomfort or pose a risk of inducing epileptic seizures at certain frequencies (16).

Prior research conducted at the University of Szeged has shown that Intersectional Short Pulse Stimulation (ISP) can safely and effectively stimulate the cortex using low extracranial charge densities (17). This method applies extremely brief electrical pulses distributed in space and time at several kHz to the target region, creating a modifiable electrical field with controlled frequency and minimal scalp current—making it tolerable for patients. Additionally, by employing a specialized signal filtering algorithm, EEG activity can be recorded even during stimulation. Studies have shown that ISP above 4.5 mA selectively modulates continuous brain rhythms, such as the posterior alpha oscillation (1).

The goal of the current study is to further refine the technical parameters for precise brain targeting using the ISP technique and to define the optimal design and stimulation conditions for delivering effective and safe deep brain stimulation. We specifically aim to evaluate stimulation frequencies comparable to those used in high-frequency DBS therapy.

e) Selection criteria of study participants

[redacted]

Epilepsy patients:

Potential study subjects will be selected from among epilepsy patients treated at the epilepsy outpatient clinic of the National Institute of Clinical Neuroscience (SEINK). Only adult patients aged 18 years or older will be considered.

Eligible participants will include individuals with drug-resistant epilepsy, specifically those diagnosed with generalized or focal epilepsy, who have undergone comprehensive clinical assessments—including non-invasive or invasive EEG monitoring, neuropsychological testing, and epilepsy protocol-compliant cranial MRI, FDG-PET/CT, FDG-PET/MRI, and/or ictal SPECT scans—and have been deemed unsuitable for resective epilepsy surgery by a multidisciplinary epilepsy surgery team. Patients with a confirmed autoimmune etiology will be excluded. In cases where the cause of epilepsy is unknown, autoimmune processes must be ruled out through serological testing if not already completed. The neurologists participating in the study will be responsible for identifying potential participants and informing them about the research. Final eligibility is determined based on clinical findings and the patient's specific epilepsy type. Importantly, all diagnoses will be established independently—prior to any consideration of study participation—and solely in the best interest of the patient's health, in alignment with the Hippocratic Oath.

Selection Criteria

- Age between 18–65 years
- Diagnosis of drug-resistant focal epilepsy, with unsuitability for resective epilepsy surgery confirmed by an interdisciplinary team based on:
  - Non-invasive or invasive EEG
  - Neuropsychological assessment
  - Brain MRI (epilepsy protocol)
  - FDG-PET/CT or FDG-PET/MRI and/or ictal SPECT
- Diagnosis of focal epilepsy or idiopathic generalized epilepsy
- On antiepileptic treatment
- ≥4 focal seizures per month, or
- Frequent spike-wave activity on EEG (minimum 10 seconds per hour)
- Patient must be capable of caring for the surgical wound, and the home environment must support study requirements in terms of hygiene and compliance

Exclusion Criteria

- Age under 18 years
- Patient is eligible for resective epilepsy surgery or has unclear surgical candidacy
- Autoimmune epilepsy etiology
- The presence of therapy-resistant or untreated psychiatric symptoms at the time of inclusion (e.g., depression, severe anxiety), as well as a history of suicide or psychotic episodes.
- Progressive brain lesions (MRI), serious internal medical conditions, or clinically significant coagulopathies
- Presence of electrically active implanted medical devices, including:
    - Pacemakers
    - Implantable cardioverter defibrillators
    - Any other electrical energy-transmitting medical device
    - Pregnancy
- All women of childbearing potential must have a negative pregnancy test
- History of traumatic brain injury, skull injury, or stroke not automatically exclusionary, but such cases require consultation with both the investigating physician and the Neunos technical support team
- Metal implants generally contraindicated; all such cases must be evaluated individually by the investigating physician and Neunos technical support team

f) Identification and justification of the number of participants in the study

Based on the experience gained from our previous study (1), we plan to enroll 30 patients with drug-resistant epilepsy, characterized by either generalized spike-wave EEG patterns or focal epileptic seizures. [redacted]

Identification of the assets under investigation

[redacted]

g) Identification of other devices not subject to the test but bearing the CE conformity marking

[redacted]

h) Identification of Other Devices Not Subject to the Test but Not Bearing the CE Conformity Marking, with a Detailed Description of How the Safety of the Test Can Be Ensured

No additional devices that lack CE conformity marking are involved in this study. Therefore, no further safety considerations are required in this context..

i) Risk analysis and risk assessment, detailed assessment of the likely risks and side effects, how to avoid or reduce them

The studies to be presented in this protocol involve the following risk factors:

1) The safety risk associated with MRI is minimal, with very few incidents reported over the past 20 years. Earplugs are provided for noise protection. The primary safety concern with

MRI is the mechanical force exerted by the magnetic field on ferromagnetic materials. Any such materials must be removed from the vicinity of the subject prior to entering the MR environment. If removal is not possible, the subject will be excluded from the study. A detailed screening questionnaire (see Appendix) will be completed before entering the MR zone (console room), and access will be granted only after confirming the absence of ferromagnetic materials.

2) Transcranial magnetic stimulation (TMS) involves passing an electric current through a coil placed on the scalp, generating a variable magnetic field for a brief period. Among repetitive TMS procedures, high-frequency stimulation carries a known risk of inducing seizures. However, in this study, only low-frequency or single-pulse TMS will be applied, which has not been associated with similar risks.

2) Electrophysiological tests involve recording electroencephalographic (EEG) activity in response to spontaneous and stimulus-related brain signals. These recordings do not interfere with brain function and are considered minimally risky.

3) The main risks associated with electrode implantation are local infection and subgaleal bleeding. To minimize these, strict aseptic and antiseptic procedures will be followed throughout the surgical and postoperative periods. Outside the operating theatre, sterile dressings will not be removed unless medically indicated (e.g., for wound checks conducted in hospital or at home as part of the study protocol). Antibiotic prophylaxis will be administered perioperatively. According to current guidelines and clinical trial data, postoperative antibiotic prophylaxis is not recommended (37).

To reduce the risk of subgaleal hemorrhage, electrodes will be implanted by experienced neurosurgeons, with design and placement guided by anatomical and safety considerations. If significant bleeding or infection occurs, the procedure will be halted and electrodes removed. Based on the literature, these complications are rare.

During the maximum 2 × 30-day home-based phases of the study, regular wound inspections will be conducted by hospital nursing staff to ensure wound integrity. Notably, long-term externalized neuromodulation systems, such as spinal cord stimulation (SCS) devices for chronic pain, also involve percutaneous components. In a large randomized controlled trial (PROMISE RCT (38)), the infection rate was 5.2% (9 of 174 patients). Compared to SCS systems, the present study's design is less prone to infection: cables exit through the scalp, which is well vascularized, and electrodes are placed extracranially, under the scalp.

Other long-term external systems, such as bone-conduction hearing aids (39) and brain-machine interfaces (40), also involve chronic connections through the scalp and rarely require non-conservative treatment for infections—even over long periods of use.

4) The risks associated with transcranial electrical stimulation are somewhat higher than those in points 1 and 2. Both animal and human studies confirm that electrical stimulation affects cortical excitability. Anodal stimulation increases neuronal firing rates, while cathodal stimulation decreases it (Bindban et al., 1964; Creutzfeldt et al., 1962; Purpura and McMurty, 1965; Ward and Weiskrantz, 1969). In humans, direct current (DC) stimulation applied to the motor cortex has been shown to alter motor-evoked potentials elicited by TMS (18), as well as modulate early visual processing—such as contrast sensitivity and visual evoked potentials (19).

Additional studies confirm that stimulation effects on cortical excitability can persist beyond the stimulation period, likely due to plastic changes in the brain. These have been successfully leveraged in learning enhancement (20) and in the treatment and rehabilitation of neurological conditions (21)(22).

To date, transcranial stimulation has been regarded as safe, with no serious side effects reported in a significant body of literature. The stimulation is typically painless, as the large electrode surface area produces a low charge density, supported by existing research (23).

Nonetheless, several safety aspects must be considered:

High-frequency stimulation has the potential to induce seizures in epilepsy patients (16). This risk is mitigated by using continuous video-EEG monitoring under clinical supervision. During the initial three sessions—when stimulation is not seizure-triggered—patients will remain on antiepileptic medication. If seizure activity occurs during this phase, the neurologist may terminate the study and administer treatment according to protocol. In the fourth session, seizure provocation (e.g., medication tapering) will follow established video-EEG protocols, as decided by the treating physician team. To prevent false stimulation during non-seizure events, stimulation will only be activated after manual confirmation by the investigator.

During all phases, medical care follows current clinical standards:

Patients are maintained on antiepileptic drugs throughout hospitalization. If seizure risk is elevated (e.g., due to stimulation), a neurologist will remain present at all times.

Emergency treatment protocols include:

First-line: IV benzodiazepines (diazepam, clonazepam, lorazepam)

Second-line: IV antiepileptics (levetiracetam, valproate, lacosamide)

In case of status epilepticus, anesthesia and ICU admission may be required.

Electrode heating is also considered, but is unlikely with the surface area and charge density used in this trial. This has been confirmed in previous studies (18). Given that only ~50% of the current reaches the brain through the skull, the likelihood of heating is even lower.

There is no evidence that long-term stimulation causes structural harm. A 2004 study by Nitsche et al. found no signs of edema, blood-brain barrier disruption, or anatomical changes on MRI. Similarly, EEG readings and serum neuron-specific enolase levels did not indicate neuronal damage (18). Repeated daily stimulation has also been shown to be safe, with no adverse effects reported in the literature (24).

Finally, the study carries inherent risks related to the two surgical procedures and the presence of a foreign body beneath the scalp. All surgical interventions will be performed using minimally invasive techniques. The choice between general anesthesia and local scalp-block will be determined by the anesthesiologist, with preference for local methods to minimize risk.

Potential hypersensitivity reactions to medications administered during surgery will be handled per clinical protocols. If such a reaction occurs, the study will be terminated for that patient.

Subgaleal hematoma may develop due to the foreign body or manipulation of the subgaleal space. Hematoma status will be routinely monitored. If excessive bleeding is detected, electrodes will be removed and the hematoma managed according to clinic protocols.

Infection risk due to surgery or externalized components will be minimized through prophylactic treatment with second-generation oral cephalosporins during the single-phase hospitalization. If infection occurs, the electrodes will be removed, and appropriate treatment administered per clinical guidelines.

j) Analysis and Justification of the Acceptability of the Planned Performance and the Likely Risks and Side-Effects Ratio

The significance of ISP brain stimulation lies in its ability to deliver targeted deep brain stimulation non-invasively or with minimal invasiveness, eliminating the need to open the

skull. The ISP stimulator under investigation is a compact, high-efficiency portable device, capable of reaching and modulating brain regions that traditionally required neurosurgical access. This approach represents a potential paradigm shift in neuromodulation—providing a feasible alternative to invasive surgical procedures and large-scale, stationary magnetic stimulation technologies. The medical utility of this research is clear, and its potential for industrial application follows directly from the study's findings. If successful, the method could broaden therapeutic options for drug-resistant epilepsy and related neurological conditions.

Brain stimulation techniques have long been established as clinical diagnostic tools for epilepsy, especially in identifying evoked pathological responses, after-discharges, and provoked seizures (25). However, conventional transcranial electrical stimulation cannot be performed during standard scalp video-EEG procedures due to technical limitations. The device used in this study overcomes these challenges by allowing for simultaneous EEG recording and spatially precise stimulation. This capability can enhance the diagnostic process by providing additional functional information about the epileptogenic focus. Seizures elicited during the study may also offer valuable diagnostic insights.

Through this investigation, we may demonstrate the therapeutic potential of spatially and temporally targeted neurostimulation, paving the way for a novel, effective treatment option for patients with drug-resistant epilepsy. Should chronic ISP neuromodulation prove viable and the study results support its efficacy for an individual patient, the data collected from this clinical video-EEG study may serve as a personalized screening tool to guide future therapy planning.

[redacted]

Given the low incidence of expected adverse events, and in light of the potential long-term benefits, the risk-to-benefit ratio of this study is considered acceptable and ethically justified.

Copies of certificates of qualification of the staff who carried out the tests

See Annex 4

k) Patient information and informed consent

See Annexes 6, 7, 12, 13, 15, 16

l) Procedure to be followed in the event of an unforeseen event, list of persons to be notified, deadline for notification

Patients enrolled in the study will be closely monitored throughout the brain stimulation procedures at the healthcare facility (SEINK). Participation in the study will not interfere with the patients' standard clinical care. During ISP stimulation, patients will be observed under the standard clinical video-EEG monitoring protocol, which runs concurrently with the investigational procedures. As such, no additional or special monitoring procedures are required beyond those routinely applied in clinical practice. In the event of epileptic seizures occurring as unexpected adverse events, management will follow the established clinical protocol, as detailed in Section 16/n of this document.

m) Criteria for stopping a clinical trial

Participation in the protocol will be immediately suspended upon the subject's request, without the need for justification. Additionally, participation will be discontinued if the subject's cooperation is found to negatively impact their clinical care or the course of their illness. Under no circumstances should participation in the protocol interfere with the patient's current or future medical care.

n) Confirmation of a Health Care Provider Conducting a Clinical Trial to Cover the Indemnity of the Research Before the Start of the Research Activity, in Accordance with the Risks Covered by the Research Liability Insurance Contract

As experimental stimulation cannot be separated from the diagnostic process, the same insurance conditions apply to this intervention as to other patients in clinical practice.

o) research equipment and staff

Both the material and human resources required for the research are fully in place. The facilities at SEINK are well-equipped with the necessary personnel, instrumentation, and infrastructure to conduct the planned investigations. The ISP stimulators to be tested, along with the electrophysiological recording systems, are housed at SEINK. The institute also operates a fully functional video-EEG monitoring unit as part of its routine clinical services, where all study-related recordings can be performed under standard clinical protocols. The neurologists and researchers involved in the project possess significant expertise, and their longstanding experience in working with epilepsy patients ensures the scientific and clinical robustness of the study. Their contributions to the field include decades of clinical practice and a strong track record of high-quality international scientific publications in the area of brain stimulation.

On the scientific and technical side, the instrument development, experimental design, and data analysis are grounded in collaborative research with New York University, further reinforcing the study's credibility. The study will be designed, conducted, documented, and reported in full compliance with Good Clinical Practice (GCP) guidelines, ensuring ethical integrity and scientific validity throughout.

p) Draft text of the call for applications and description of the recruitment method

[redacted]

Epilepsy patients:

Patients included in the study will be drug-resistant individuals with focal epilepsy who have been deemed unsuitable for resective epilepsy surgery. This determination will be made by an interdisciplinary epilepsy team, based on comprehensive evaluations including non-invasive or invasive EEG monitoring, neuropsychological assessments, and imaging studies performed according to epilepsy protocols—such as cranial MRI, FDG-PET/CT, FDG-PET/MRI, and/or ictal SPECT scans. Eligible patients will be selected from the clinical database maintained at the SEINK epilepsy outpatient clinic. Identified candidates will be offered participation in the study. The neurologists involved in the project will be responsible for both selecting potential participants and informing them about the study. Eligibility will be determined based on detailed clinical evaluations, including confirmation of epilepsy type and suitability for the study. Importantly, diagnosis and eligibility assessments are made prior to any offer of participation, and are conducted independently, in the best interests of the patient's health and recovery, and in full accordance with ethical medical standards, including the Hippocratic Oath.

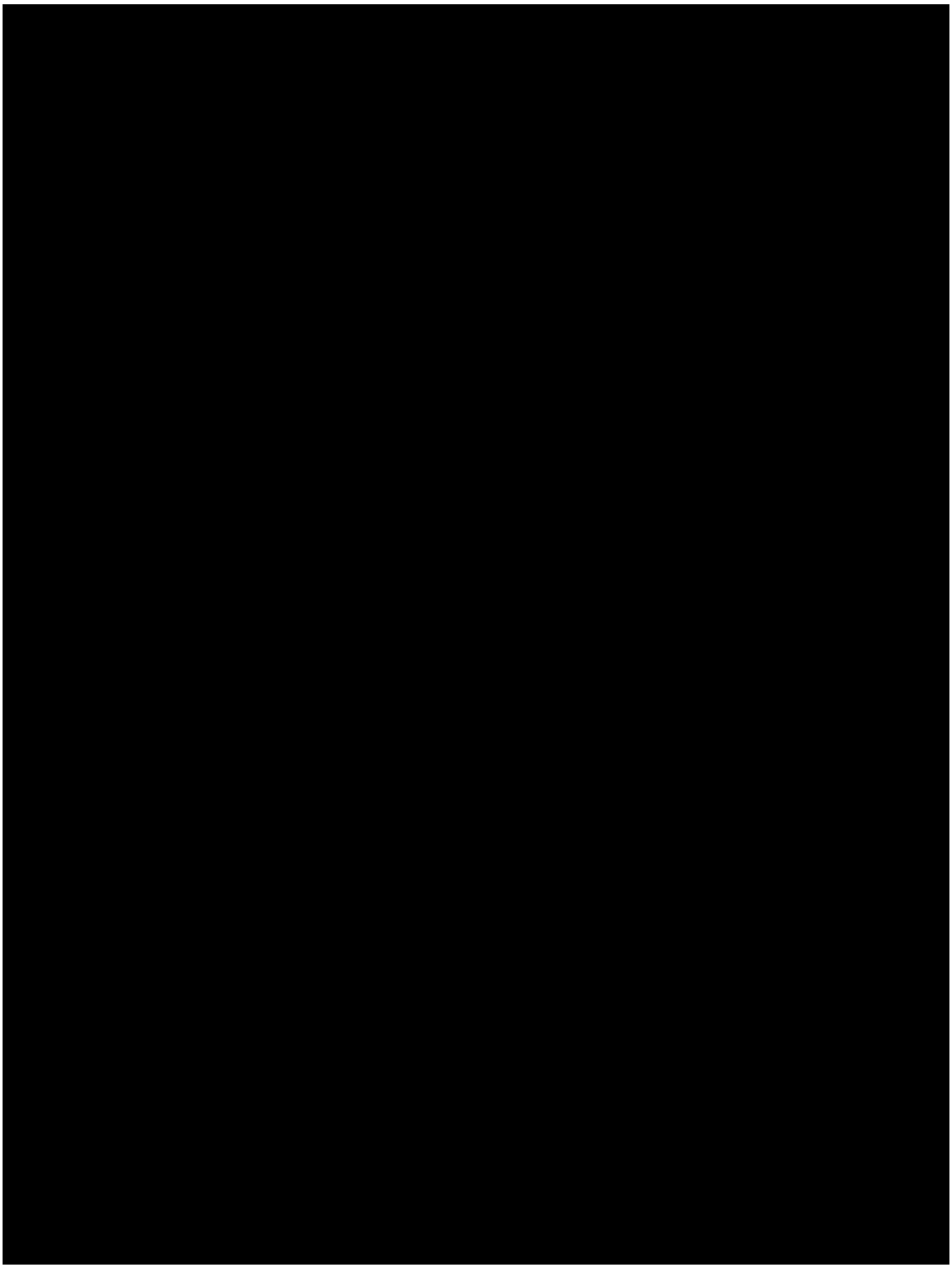
16) Quality assurance certificate for clinical investigations of devices and active implants in risk class III

No active implant is involved in the study.

The electrodes manufactured by [redacted]

SEMMELWEIS UNIVERSITY
Neurosurgery and Neurointerventional Clinic

clinic director
DR. HABIL. LORÁND ERŐSS



Address: 1145 Budapest, Amerikai út 57.
Postal address: 1085 Budapest, Üllői út 26.; 1428 Budapest, Pf. 2.
E-mail: titkarsag.amerikaiut@semmelweis.hu
Tel: (+36-1) 467-9301
semmelweis.hu

[redacted]

E-mail: titkarsag.amerikaiut@semmelweis.hu
Tel: (+36-1) 467-9301
semmelweis.hu

17) In the case of a multicentre study, the opinion already issued by the Ethics Committee of the EEA State Party on the study, if available

The study is not multicentric, so this point is not meaningful.

18) Annexes

Annex	Title
1	Declaration of admission
2	Authorisation from the manufacturer to the investigator-in-charge
3	Manufacturer's declaration of conformity
4	Documents of the investigators
5	CV of the Principal Investigator
6	Factsheet
7	Declaration of consent
8	Liability insurance - SEINK
9	Liability insurance - NEUNOS
10	Declaration of Helsinki
11	Data protection statement
12	Patient information for volunteers
13	Declaration of consent for volunteers
14	Call for volunteers
15	Informed consent - for participation in the three-phase trial
16	Patient information leaflet - for participation in the three-phase trial

References

1. *Direct effects of transcranial electrical stimulation on brain circuits in rats and humans.* **Vöröslakos, et al.** , : Nat Comm, 2018.
2. **Eross, L.** *The role of neuronavigation in the assessment and surgical treatment of drug-resistant epilepsy*. no place : Neurology Review p.333-7, 2011. 64(9-10).
3. **Anthony L. Ritaccio, Peter Brunner, Gerwin Schalk.** *Electrical Stimulation Mapping of the Brain: Basic Principles and Emerging Alternatives.* Journal of Clinical Neurophysiology Volume 35 : unknown author, 2018/03.
4. *Transcranial Electrical Stimulation Motor Threshold Can Estimate Individualized tDCS Dosage from Reverse-Calculation Electric-Field Modeling. Brain Stimul.* **Caulfield KA, Badran BW, DeVries WH, Summers PM, Kofmehl E, Li X, et al.** 2020, p. 13: 961-969 doi:10.1016/j.brs.2020.04.007**.**
5. *Deep brain stimulation: foundations and future trends.* **David J. Aum, Travis S. Tierney.** 2018., Frontiers In Bioscience.
6. *Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).* **Lefaucheur et al.** 2020., Clinical Neurophysiology.
7. *Electricity, Neurology, and Noninvasive Brain Stimulation: Looking Back, Looking Ahead.* **Renga, Vijay.** 2020., Neurol Res Int.
8. *Deep brain stimulation in Parkinson's disease***. by Raja Mehanna, Eugene Lai.** 2013., Transl Neurodegener.
9. *Deep brain stimulation: clinical applications.* **Dougherty, Darin D.** 2018., Psychiatr Clin North Am.
10. *Transcranial direct current stimulation: state of the art 2008.* **Michael A Nitsche et al.** 2008, Brain Stimulation.
11. *Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).* **Jean-Pascal Lefaucheur et al.** 2014., Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology.
12. **Roth Y, Pell GS, Chistyakov AV, Sinai A, Zangen A, Zaaroor M.** *Motor cortex activation by H-coil and figure-8 coil at different depths: Combined motor threshold and electric field distribution study.* Clin Neurophysiol. 2014 Feb;125(2):336-43. doi: 10.1016/j.clinph.2013.07.013. : unknown author, 2013. PMID: 23994191.
13. *Mechanisms of deep brain stimulation***. Todd M. Herrington et al.** 2016., J Neurophysiol.
14. *Mechanism of Deep Brain Stimulation***. Satomi Chiken, Atsushi Nambu.** 2016., Neuroscientist.
15. *Plasticity induced by non-invasive transcranial brain stimulation: A position paper.* **Ying-Zu Huang et al.** 2017, Clin Neurophysiol.
16. *Convulsive Therapy: Theory and Practice***, Fink, M.** 1979, Cambridge University Press.
17. *Immediate neurophysiological effects of transcranial electrical stimulation***. Anli Liu, Mihály Vöröslakos**. 2018., Nature communications.

18. *Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation*. 2000., The Journal of Physiology.
19. *Direct Current Stimulation over V5 Enhances.* **Antal et al.** 2004., Journal of Cognitive Neuroscience.
20. *Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans.* **Kincses et al.** 2004, Eur J Neurosci.
21. *A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients.* 2006., **Felipe Fregni et al.**, Stroke.
22. *Improvement of Motor Function with Noninvasive Cortical Stimulation in a Patient with Chronic Stroke.* **Friedhelm Hummel, Leonardo G Cohen.** 2005., Neurorehabilitation and neural repair.
23. *Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation*. **Prateek C Gandiga, Friedhelm C Hummel, Leonardo G Cohen.** 2006., Clin Neurophysiol.
24. *Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients.* **Poreisz C, Boros K, Antal A, Paulus W.** 2007, Brain Research Bulletin.
25. *Single pulse electrical stimulation for identification of structural abnormalities and prediction of seizure outcome after epilepsy surgery: a prospective study.* **Antonio Valentín et al.** 2005, Lancet Neurol.
26. *Safety of transcranial direct current stimulation: evidence based update.* **Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al.** , : Brain Stimul., 2016.
27. *Basis of electrical stimulation of the cochlea and the cochlear nucleus.* **B, Shepherd R K and McCreery D.** , : Advances in Oto-rhino-laryngology, 2006.
28. *Closed-Loop Control of Epilepsy by Transcranial Electrical Stimulation* **Berenyi A, Belluscio M, Mao D, Buzsaki G.** , : Science (80-), 2012.
29. *Safety limits of cathodal transcranial direct current stimulation in rats.* **D. Liebetanz, R. Koch, S. Mayenfels, F. Konig, W. Paulus, and M. A. Nitsche**, Clin Neurophysiol. 2009.
30. *Regulatory Considerations for the Clinical and Research Use of Transcranial Direct Current Stimulation (tDCS): review and recommendations from an expert panel.* **Fregni et al.** , : unknown author, 2015.
31. *Can transcranial electrical stimulation with multiple electrodes reach deep targets?* **Huang Y, Parra LC.** , : Brain Stimul. Elsevier Ltd, 2019;12: 30-40. doi:10.1016/j.brs.2018.09.010.
32. *Sustained efficacy of closed loop electrical stimulation for long-term treatment of absence epilepsy in rats.* **Kozák G, Berényi A.** , : Sci. Rep., 2017.
33. *Tolerability of repeated application of transcranial electrical stimulation with limited outputs to healthy subjects.* **Paneri B, et al.** , : Brain Stimul, 2016;9(5):740-754.

34. *Behavioral and brain responses to verbal stimuli reveal transient periods of cognitive integration of the external world during sleep*, **Basak T. et al.,**Nature neuroscience; 26, 1981-1993 (2023), https://www.nature.com/articles/s41593-023-01449-7.
35. *Association of Closed-Loop Brain Stimulation Neurophysiological Features With Seizure Control Among Patients With Focal Epilepsy,* **Kokkinos et al**, JAMA Neurol 2019 Jul 1;76(7):800-808. doi: 10.1001/jamaneurol.2019.0658.
36 *Dissection using pulsed radiofrequency energy device (PlasmaBlade) is safe and efficient in experimental revision neuromodulation implant surgery,* **Alistair Paterson et al**, Br J Neurosurg; doi: 10.1080/02688697.2021.1885622
37. *the Neurostimulation Appropriateness Consensus Committee (NACC) Recommendations for Infection Prevention and Management,* **Timothy R. Deer et al.,** The Neurostimulation Appropriateness Consensus Committee (NACC), Volume 20 Issue 1 January 2017 Pages 31-50, doi: 10.1111/ner.12565
38 *Postoperative Infections Associated With Prolonged Spinal Cord Stimulation Trial Duration (PROMISE RCT),* **Richard North et al,** Neuromodulation. 2020 Apr 8;23(5): 620-625, doi: 10.1111/ner.13141
39 *Bone anchored hearing aid: an evidence-based analysis*, **Medical Advisory Secretariat,** Ont Health Technol Assess Ser 2002;2(3):1-47. epub 2002 Sep 1, PMCID: PMC3387772
40 *Interim Safety Profile From the Feasibility Study of the BrainGate Neural Interface System,* **Daniel B. Rubin et al.,** Neurology Journals March 14, 2023 issue 100 (11) e1177-e1192, doi: 10.1212/WNL.0000000000201707