Clinical Neurophysiology Practice 11 (2026) 16–23

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

journal homepage: www.elsevier.com/locate/cnp

Research paper

Ultra long-term EEG monitoring for developmental and epileptic encephalopathies: protocol for a prospective study using subscalp EEG

Leonardo Affronte [a,b,1], Stefania Maffei [a,1], Mara Malerba [a], Giada Giovannini [a], Paolo Manganotti [c], Antonietta Coppola [d], Leonilda Bilo [d], Anna Elisabetta Vaudano [a,b], Marina Trivisano [e], Nicola Specchio [e], Stefano Meletti [a,b,*]

[a] Neurophysiology Unit and Epilepsy Centre, Neuroscience Department, Modena AOU, Italy
[b] Department of Biomedical Metabolic Sciences and Neurosciences, University of Modena and Reggio Emilia, Italy
[c] Clinical Unit of Neurology, Department of Medicine, Surgery and Health Sciences, ASUGI, University of Trieste, Italy
[d] Epilepsy Center, Neurology Unit, University Hospital Federico II, Naples, Italy
[e] Neurology, Epilepsy and Movement Disorders Unit, Bambino Gesù Children's Hospital, Scientific Institute for Research and Health Care, Full Member of European Reference Network on Rare and Complex Epilepsies EpiCARE, Rome, Italy

ARTICLE INFO

Keywords:
EEG
epilepsy
DEE
Mobile technology
Intellectual disability
Seizures
Wearables
subcutaneous EEG

ABSTRACT

Objective: Poor documentation of seizures can be a major challenge in epilepsy. Objective seizure counting with mobile devices might improve this challenge and the patient management. We investigate whether ultra long-term subcutaneous EEG improves seizure documentation and disease monitoring in adults and adolescents with developmental and epileptic encephalopathies (DEEs).
Methods: Ultra long-term subcutaneous EEG Monitoring In Rare Epilepsies and DEE (EMIRE) is a multi-centre prospective interventional study with an expected duration of 6 months. 33 Adolescents and adult participants will be implanted with 24/7 EEG SubQ and collect 2-channel EEG data up to 6 months. Data will be reviewed by experts on a weekly basis and a summary sent to the treating clinician.
Results: (1) safety and tolerability of subcutaneous EEG in this special patient population; (2) seizure detection sensitivity and specificity with respect to patients' seizure-diaries and 'ground truth'; (3) whether and how home monitoring can affect the clinical management of the patients.
Conclusions: This project will investigate home and remote patient monitoring systems, offering an accuracy that is unthinkable today.
Significance: This trial of home monitoring is intended to be of clinical utility to the patient by allowing objective assessment of therapeutic interventions and their effectiveness.
Plain language summary.
We present a clinical trial protocol for a prospective cohort study in people with severe epilepsies across Italy. The study aims to assess whether an EEG implant placed under the skin (1) is more accurate than patient-reported seizure diary, (2) is feasible and acceptable to patients and clinicians, (3) affect the clinical management of the patients, (4) reduces the impact of epilepsy.

1. Introduction

1.1. Background and rationale

Epilepsy is characterized by repetitive epileptic seizures that are unpredictable and often short-lasting (generally less than 2 min) but can, nevertheless, be life-threatening. Epileptic seizures vary widely in clinical phenomenology from abnormal sensations to motor signs, which can either be subtle or obvious, and might be accompanied by impaired consciousness.

Both children and adults with epilepsy, even those with a low seizure frequency, bear a high burden from disease in their daily lives because of

* Corresponding author at: Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Azienda Ospedaliera-Universitaria di Modena, Via Giardini, 1355 – Ospedale Civile Baggiovara, 41126, Modena, Italy.
E-mail address: stefano.meletti@unimore.it (S. Meletti).
[1] Joint first authorship, equal contribution.

https://doi.org/10.1016/j.cnp.2025.12.005
Received 15 September 2025; Received in revised form 27 November 2025; Accepted 15 December 2025
Available online 20 December 2025

lifestyle limitations. For about 70 %, epilepsy can be controlled pharmacologically with anti-seizure medications (ASMs). However, the remaining 30 % are pharmacologically uncontrolled being a substantial therapeutic challenge. This is particularly true for patients affected by Developmental and Epileptic Encephalopathies (DEE). DEEs represent a group of disorders characterized by severe epilepsy, difficult to treat seizures and intellectual disability (Scheffer et al., 2025).

In epilepsy, seizure classification and quantification are among the main parameters that contributes to define the degree of severity of an epileptic condition. Patient-reported seizure counts represent a key outcome measure for individual treatments and randomized clinical trials. However, patient self-evaluation compared with objective evaluation by video-electroencephalography (EEG) monitoring or long-term ambulatory EEG revealed that patients document fewer than 50 % of their seizures on average, and with variable accuracy (Blum et al., 1996; Tatuum et al., 2001; Hoppe et al., 2007) (Blachut et al., 2015, 2017; Elger and Hoppe, 2018) (Baud et al. 2021).

As therapeutic interventions focus on reduction or elimination of seizures, the accurate documentation of seizure occurrence is essential, therefore novel and feasible seizure detection techniques for ambulatory (home) ultra long-term use are needed. Moreover, undiagnosed seizures may increase the burden of the disease and the potential negative effects on cognitive abilities during development in children.

Recently, novel EEG recording devices have been developed, consisting of EEG electrodes designed for subcutaneous implantation (subcutaneous EEG, subscalp EEG). To date, one device has received CE mark for ultra long-term ambulatory EEG recording—the 24/7 EEG SubQ system (UNEEG Medical; Allerød, Denmark). The device has been shown to be able to record EEG of acceptable quality (Duun-Henriksen et al. 2020; Viana et al., 2021a,b) in awake, healthy subjects and in people with focal epilepsy (Weisdorf et al., 2018, Weisdorf et al., 2019; Rubboli et al, 2024) for periods of time up to 15 months (Viana et al., 2021a,b, Viana et al., 2025). Studies are ongoing in adults, mainly with focal epilepsy (McWilliam et al., 2025).

To our knowledge, clinical trials on the use of sqEEG in patients with DEE are lacking. In this group of conditions, epilepsy is uncontrolled by ASMs in a high proportion of cases.

Effective management of DEEs relies heavily on accurate seizure reporting, which is essential for evaluating the efficacy of therapies, adjusting treatment regimens, conducting natural history studies, and administering acute rescue medications. However, seizure reporting in DEEs is often challenging due to the complexity of seizure semiology, the presence of non-epileptic events, and reliance on caregiver observations (van der Lende et al., 2016, van der Lende et al., 2018). These challenges are exacerbated in the presence of intellectual disability. Underreporting of seizures can lead to an underestimation of disease burden, while over-reporting of non-epileptic events can result in unnecessary interventions and adverse effects.

To overcome these limits, an ultra long-term EEG recording at home is expected to improve our clinical management of these patients (Meinert et al., 2025).

The purpose of this project is to evaluate the feasibility, reliability, and clinical value of sqEEG in patients with rare and complex, drug-resistant epilepsy, including subjects with intellectual disabilities.

1.2. Objectives

The primary objectives of this study are to evaluate whether 24/7 EEG SubQ: (1) is more accurate than patient-reported seizure diary, (2) is feasible and acceptable to patients and clinicians, (3) affect the clinical management of the patients, (4) reduces the impact of epilepsy.

2. Methods

2.1. Trial design

EMIRE (Clinical Trials NCT06855901) is a prospective, non-randomized, multicenter, interventional study that is performed across four III level comprehensive epilepsy centers in Italy. Adolescents and adults with DEE, treated as part of their routine clinical care across the recruitment sites, will be enrolled.

2.2. Study settings

The study will take place in the following hospitals with integrated neurology centers, recruiting participants as outpatients: AOU Modena, AOU Federico II Naples, AOU Trieste, Bambino Gesù Children's Hospital.

2.3. Eligibility criteria

Inclusion criteria are: (1) given written informed consent. For subjects not able to give an informed consent, the consent is given by the patient's legal representative/guardian. In all cases, an in-depth discussion will be held with caregivers to explain the potential benefits and risks associated with participation in the study; (2) adolescents and adults (≥12 years of age); (3) routinely keep a seizure diary; (4) uncontrolled epilepsy, either focal or generalized; (5) one or more seizure types as established by previous epilepsy history and EEG seizure recoding, which has allowed to define seizure type and scalp topography of the ictal discharge; (6) seizure frequency at the time of enrollment of more than two seizures per months, assessed in the 3 months preceding the implantation of the device; (7) willing to comply with study procedures.

Exclusion criteria are: (1) cochlear implant(s); (2) participants involved in therapies with medical devices that deliver electrical/radiofrequency energy into the area around the implant; (3) participants at high risk of surgical complications, such as active systemic infection and hemorrhagic disease; (4) allergy to the local anesthetics used during implantation; (5) infection at the site of device implantation; (6) participants who operate MRI scanners or are planned to have an MRI scan during the study period; (7) participants with profession/hobby that includes activity imposing extreme pressure variations (e.g. diving or parachute jumping). NB: diving/snorkeling is allowed to 5 m of depth; (8) participants with profession/hobby that includes activity imposing an unacceptable risk for trauma against the device or the site of implantation; (9) subject unable or does not have the necessary assistance to properly operate the device system; and (10) any other serious medical condition that in the opinion of the Chief Investigator would be incompatible with participation in the study.

Given the type of study population, patients with doubtful psychogenic seizures or possible paroxysmal movement disorders are eligible for the study as subscalp EEG could prove to be of great utility in documenting the absence of electrographic correlates in cases of acute behavioral alterations misinterpreted as seizures by caregivers.

We adopted here the last definition of DEEs proposed by Scheffer et al., (2025) that is deliberately inclusive in order to enroll several forms of DEEs and syndromes with different epilepsy clinical phenotypes.

2.4. Sample size

We powered our study based on the primary outcome measure of diagnostic accuracy. We will assess the improvement in accuracy of seizure documentation using AI-driven algorithm applied to 24/7 EEG SubQ data compared to self-reported participant diary alone.

To inform sample size calculations, we referenced data from a previous intracranial EEG study in people with focal epilepsy (Cook et al., 2013), which reported a correlation of 0.30 (SD 0.41) between the

monthly number of seizures recorded in participant self-reported diaries and the actual number of seizures per month, as captured by the intracranial Neurovista device. Our aim is to show that the AI-detected seizures (EpiSight software) yield a stronger correlation with the ground truth (sqEEG recorded seizures verified by human expert) respect with subjective seizure counts by patients/caregivers. For this study, we selected a target correlation of 0.5—modestly higher than the previously observed value, as proposed in an ongoing study with subscalp EEG (McWilliam et al. 2025). With an alpha of 0.05, a sample size of 33 participants provides 85 % power to detect an increase in within-participant correlation from 0.3 to 0.5 (calculated using G*Power).

2.5. Recruitment

Subjects with uncontrolled seizures and previously investigated in outpatients' epilepsy clinics and in the Epilepsy Monitoring Unit (EMU) will be evaluated by review of the medical records. The aim is to select subjects in whom assessment of seizure frequency is extremely relevant for their clinical management, including adjustment of medicines and need of support measures in their daily life. The indication to recruit also patients with epilepsy and intellectual disabilities is supported by the evidence that in these patients, either when living at home or in institutions, it is particularly difficult to have an objective assessment of their seizure frequency and of the response to treatment or to treatment adjustments.

The subjects will be selected regardless of a diagnosis of focal or generalized epilepsy, and regardless previous surgical treatments. However, it will be necessary that, based on the previous EMU admission/video-EEG studies: (a) for focal epilepsies, the site of the focus is defined at a lobar level; (b) for generalized epilepsies that the ictal discharge is truly diffuse to both hemispheres.

The subjects that might potentially be included in the study according to the inclusion/exclusion criteria will be invited to the investigational site for detailed information on the project.

The written consent form will be presented and discussed with the subject/legal guardians; all questions related to the informed consent will be answered. In all cases patients will receive detailed information regarding the procedure and purposes.

3. Study procedures

The project design includes two sequential parts, 'Part 1′ which is a short-term study evaluating sqEEG compared to standard EEG monitoring in the EMU. 'Part 2′ represent the core of the project and consists of the ultra long-term sqEEG monitoring at home for up to 6 months.

Study Part 1

After subjects selection and recruitment (Visit 1) they will be implanted with the UNEEG SubQ by the local surgical team (Visit 2)(see study flow-chart, Fig. 1). Supplementary Figure shows the device.

The implant is inserted in the pre-auricular region in the subgaleal space on a predetermined side (i.e. right or left) and orientation based on the treating clinician's instruction. The implantation procedure will take care to place subcutaneously the electrode contacts over the site of the seizure focus as defined by previous scalp EEG data of the patient. In DEE patients multifocal and generalized abnormalities can be seen and, in these cases, the implant site will be assessed based on the most active area based on scalp EEG findings.

The surgical procedure is performed according to the instruction for use provided with the sqEEG system and follows the steps described in detail in previous studies (Djurhuus et al., 2023). The implant is inserted under local anesthesia with mild sedation according to clinical needs. In case the patient is noncompliant we plan to perform the procedure under general anesthesia. After the procedure, the patient is kept under observation for 2–3 h and then discharged home with an implant ID card.

Earliest 10–14 days after the surgical procedure, the subjects will be admitted to the EMU at the investigational site with the aim of starting recording seizures, test device tolerability, and to instruct patients' caregivers on device usage. Admission in EMU will last from 2 to 10 days with simultaneous recording of standard video-EEG and sqEEG.

Study Part 2

If the device is well tolerated and no complications are observed in Part I of the study, the subject will be discharged at home with the device and all the necessary information on how to handle it.

Caregivers/Participants will be requested to document all events that they believed to be seizures in a seizure diary. The seizure diary will be available in a paper form. In addition, patients and caregivers are instructed in reporting any seizure event through the external logging device integrated to the subcutaneous electrode (event registration by a double-press of the alarm button). In this way, the paper-based clinical diary is supplemented by electronic logging of events deemed seizures. Patients' caregivers will be instructed also to provide a seizure description as detailed as possible by using a specific form.

At every week after EMU discharge an expert visual review of all sqEEG data will be performed and a report is released for the treating physician to give a feedback of seizures occurrence and devise usage time.

In-person outpatient Visits will be planned at 1, 3, 6 months after starting EEG data collection. A telephone consultation to be updated on the ongoing situation will be planned at months 2–4-5. Additional in-person consultations after discharge will be planned at any time, if necessary, based on clinical needs.

Adjustment of the antiseizure medicines will be allowed whenever the clinical conditions will require it. Any changes in the treatment will be noted in the subjects' seizure diary. Data on the use of ASMs will be collected at every study visit.

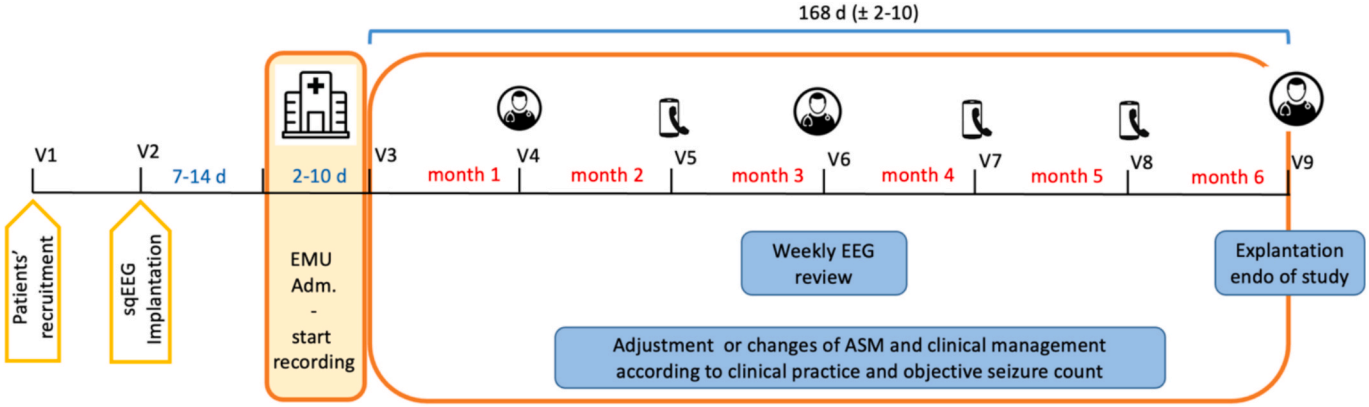

Fig. 1. Study flow-chart. EMU: epilepsy monitoring unit. D: days. V: visit.

At study end (6th month) for patients for whom the device has demonstrated clinical utility and/or for subjects who would like to continue using it, we plan to extend the possibility of continuing home monitoring for up to 36 months (the current limit of the system's usability). This will allow us to collect additional data for many months and thus evaluate the usefulness of the device over a much longer period of time.

Adverse device effects (ADEs) will be defined as any unintended or unfavorable response to the system during the study period possibly related to the use of the device or related procedures. ADEs will be classified according to severity based on their impact on daily life as the following: mild (does not interfere with everyday activities), moderate (interferes with some everyday activities), and severe (prevents some everyday activities) (Weisdorf et al., 2019). Serious ADEs will be defined as ADEs requiring hospitalization, leading to death (or would have done so in the absence of treatment) or lasting disability. These definitions will follow the guidance provided in ISO 14155:2011 Clinical investigation of medical devices for human subjects — Good clinical practice.

3.1. Data collection

At visit 1 and at month 3 and 6 (study end), measures inherent in the patient's quality of life and other patient-reported outcome measures (PROMs) will be collected. Questionnaires will also be administered at the end of the study to the referring clinical physician and caregivers to assess the perceived clinical usefulness of the 24/7 sqEEG system.

PROMs will be collected by study investigators at each site via an electronic web-based case report form (eCRF) specifically developed for the study (Eurosoft srl, Modena, Italy). Data capture system progress surveys and email prompts to review data will be utilized to ensure data completeness with both participants and investigators.

Continuous two-channel EEG data will be recorded from visit 3 to visit 9. Data transfer configuration and EEG data pipeline is shown in Fig. 2.

The participant will connect the external device daily via a USB cable to a tablet with a preinstalled application for data upload and recharging. Each participant is provided with two recorders at home so that brain activity can always be recorded when one of the devices is charging. The recorded EEG data will be automatically downloaded to the tablet, encrypted, and transferred to a dedicated virtual environment running in a third-party cloud hosting service (Microsoft Azure). Data are then stored and made available to the investigators at each study site and treating clinicians in the EEG analytics software (UNEEG EpiSight Analyzer version 2.3), which they can access via a web browser with their respective login credentials.

All treating clinicians and investigators will undergo Good Clinical Practice (GCP) training.

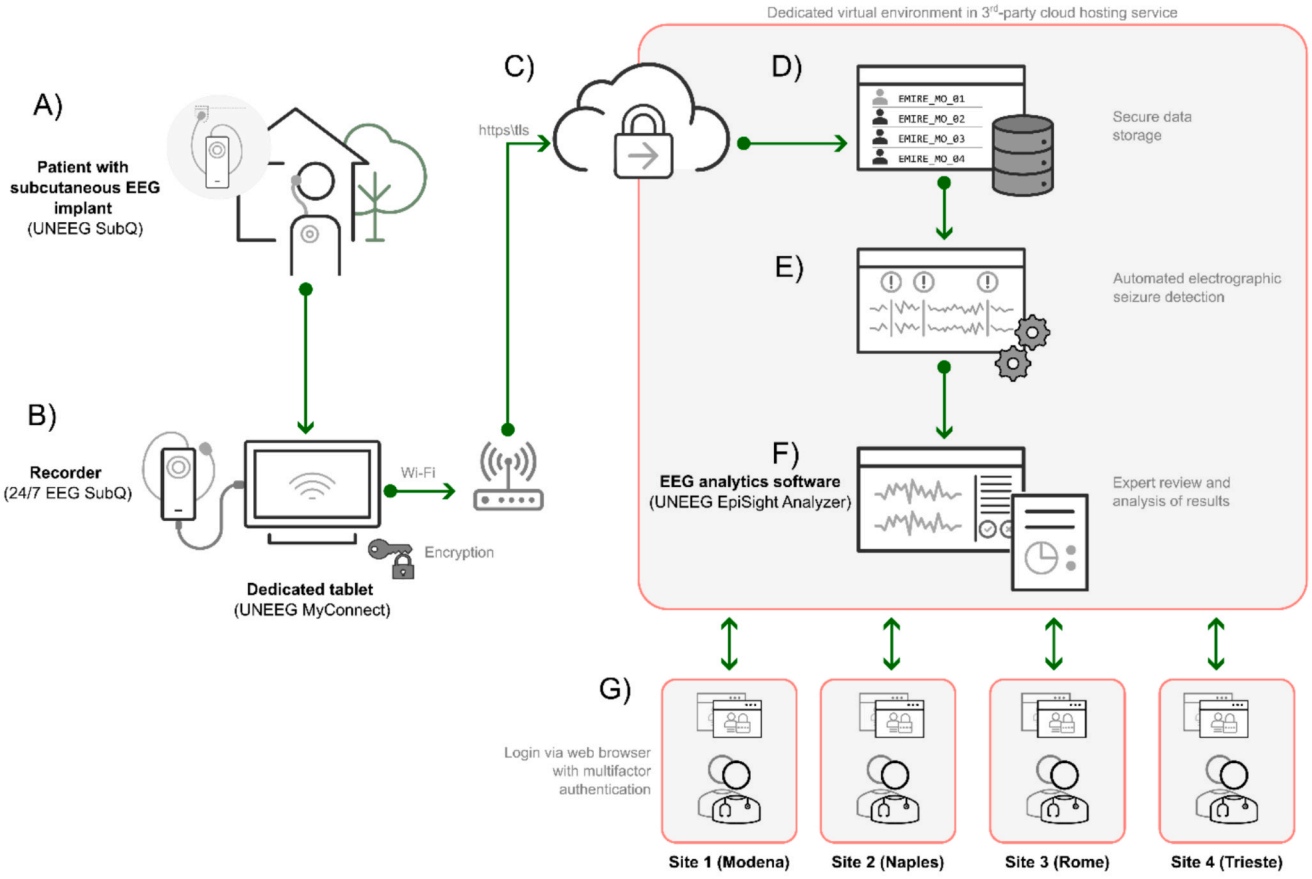

Fig. 2. Data transfer flow of the 24/7 EEG SubQ solution. A) The patients are implanted with a subcutaneous EEG implant, and data are collected in the every-day life by wearing an external recorder. B) The external recorder is connected to a dedicated tablet to charge and download the recorded data. C) Data encrypted in the tablet is transmitted via Wi-Fi to a cloud-based data transfer application. D) Encrypted data are received and stored in a dedicated server running in a 3rd-party cloud hosting service provider. E) Data are automatically analyzed by an AI algorithm that detects potential electrographic seizures. F) The detections and raw EEG can be reviewed by the experts in a dedicated EEG analytics software. G) The healthcare professionals have access to the data via a web browser.

3.2. Seizure detection

Continuous EEG monitoring will generate substantial data; therefore, an automated solution is required. Automated algorithms for seizure detection in multichannel EEG show seizure detection sensitivity 59 %–96 % (median 81.4 %) and false detection rate 0.08–5.38 per hour (median 0.3 per hour) (Baumgartner et al. 2018). The algorithm for electrographic seizure detection that will be utilized (implemented within UNEEG EpiSight Analyzer) was trained using EEGs from 490 people (Temple University) and optimized on 24/7 EEG SubQ data from 32 participants. A deep neural network based on ResNet and a feature pyramid structure was designed to recognize seizures. Using 24/7 EEG SubQ data from nine epilepsy patients a mean sensitivity of 86 % and mean false positive rate 2.4/24 h was achieved (Remvig et al., 2022). Hence, the used algorithm is comparable to other multichannel EEG detection algorithms (Baumgartner et al. 2018).

Importantly, beyond AI-detected events, the entire data recordings will be reviewed by human experts (board certified EEG readers) and all events classified by two experienced neurophysiologists (that here represent the 'ground truth'). Treating clinicians will be provided with annotated EEG data and a report summarizing the previous week's EEG data at weekly intervals and will have access to the continuous EEG recordings at any time.

4. Outcomes

The primary outcome measures of this study include: (*1*) Within participant correlation between seizure counts per month estimated from AI-seizure detection algorithm and 'ground truth' EEG seizure occurrences per month derived from human expert team review of 24/7 EEG SubQ data; (*2*) Within participant correlation between seizure counts per month from participant reported seizure diary and 'ground truth'; (*3*) Average difference between 'correlation 1′ and 'correlation 2′; (*4*) feasibility of 24/7 SubQ in DEEs.

A complete list of primary and secondary objectives with corresponding outcomes can be found in Table 1.

4.1. Analysis of primary outcome measures

The research team will review all raw EEG data from 24/7 EEG SubQ to identify seizures as the 'ground truth'. We will assess the improvement in accuracy of seizure documentation using AI-driven algorithm applied to 24/7 EEG SubQ data ('24/7 EEG SubQ detected seizures'), compared to self-reported participant diary alone. Therefore, we will estimate for each participant (*a*) the Spearman correlation between monthly diary report and the ground-truth, and (*b*) the Spearman correlation between monthly AI-algorithm detected seizures (EpiSight Analyzer) and the ground truth.

We will test the hypothesis that, across the cohort, the correlation between AI-algorithm detected seizures and ground truth is higher than between the patients' diary and ground truth.

We will also calculate for diary reports and AI – detected seizures the sensitivity, specificity, false positive rate, positive predictive value, and negative predictive value, for seizure detection.

A Bland-Altman analysis for bias and comparison of measurement methods will be used to evaluate if there is systematic under-/over-reporting.

Feasibility and acceptability will be assessed by the proportion of participants who continue in the study for > 3 months and for completing 6-months of 24/7 EEG SubQ data collection.

We will report using Standards for the Reporting of Diagnostic accuracy studies (STARD) principles (Cohen et al., 2016).

4.2. Analysis of secondary outcome measures

Clinical relevance, changes in the clinical management plan for the

Table 1
Primary and secondary objectives with corresponding outcome measures.

Primary objectives	**Corresponding endpoint(s)/outcomes variable(s)**
To investigate the diagnostic accuracy of 24/7 EEG™ SubQ Solution	• Within participant correlation between seizure counts per month estimated from AI-seizure detection algorithm and 'ground truth' EEG seizure occurrences per month derived from human expert team review of 24/7 EEG SubQ data • Within participant correlation between seizure counts per month from participant reported seizure diary and 'ground truth' • Average difference between 'correlation 1′ and 'correlation 2′ • diary reports and AI – 24/7 EEG SubQ detected seizures the sensitivity, specificity, false positive rate, positive predictive value, and negative predictive value, for seizure detection
To investigate safety and feasibility of 24/7 SubQ in DEEs.	• Feasibility and acceptability will be assessed by the proportion of participants who continue in the study for > 3 months and for completing 6-months of 24/7 EEG SubQ data collection
Secondary objectives	**Corresponding endpoint(s)/outcomes variable(s)**
To investigate the diagnostic accuracy of 24/7 EEG™ SubQ Solution during part-I of the study	• visual review of 24/7 EEG SubQ detected seizures, IED, sleep transients: the sensitivity, specificity, false positive rate, positive predictive value, and negative predictive value respect to the gold standard (scalp EEG) will be calculated.
To investigate if the EEG data recorded with 24/7 EEG™ SubQ might be used to inform change(s) in clinical management plan for the participant	• Investigators rating of which data provided by 24/7 EEG™ SubQ Solution and/or clinical data led to change(s) of the clinical management plan: (i) Electrographic seizure, (ii) seizure type, (iii) seizure frequency, (iv) seizure severity, (v) cluster patterns, (vi) seizure periodicity, (vii) trigger factors, (viii) side effects of current anti-seizure medication, (ix) lack of effects of current anti-seizure medication, (x) non-adherence to anti-seizure medication, (xi) indication for adjusting or changing anti-seizure medication, (xii) other. • Proportion of investigators (i.e., treating clinicians) with a positive opinion, i.e., answer 'Yes' to the question 'Did you adjust or change the clinical management plan during the past month?' '(Yes/No)'.
To investigate participants'/caregivers perception of the value of receiving feedback about seizure occurrences estimated from EEG data recorded with 24/7 EEG™ SubQ	• Participants overall rating of the value of receiving feedback about seizures occurrences every week, across the full study period, from the EEG data recorded with 24/7 EEG™ SubQ i.e., average score on a 10-point Likert scale.
To investigate the participants' acceptability of real-world implementation with 24/7 EEG™ SubQ Solution	• Subject satisfaction form at 2-months and change over time at 6-months follow-up.
To investigate the participant adherence with 24/7 EEG™ SubQ Solution	• Proportion of participants' percentage wear time with 24/7 EEG™ SubQ, across the study period of 6 months
To report the performance of 24/7 EEG™ SubQ Solution	• Number of Device deficiencies during the study period (6 months)
To assess the quality of life with 24/7 EEG™ SubQ Solution	• A Change over time for average QOLIE-31scores at baseline, 3 months and 6 months.

(*continued on next page*)

Table 1 (*continued*)

	• Change over time for average Impact of epilepsy scores at baseline, 3-months and 6 months. • Change over time for average Perceived Self-Mastery Over Epilepsy scores at baseline, 3-months and 6 months

participant based on the input from the EEG data recorded with 24/7 EEG SubQ Solution, will be assessed by questionnaires.

During part I of the study (co-registration of sqEEG and standard video-EEG) we will also evaluate visual recognition of seizures, interictal epileptiform discharges (IED), and sleep transients (K-complex, spindle) in both modalities and their correlation. We will calculate for visual review of 24/7 EEG SubQ detected seizures, IED, sleep transients, the sensitivity, specificity, false positive rate, positive predictive value, and negative predictive value respect to the gold standard (scalp EEG).

Adherence, acceptability, and performance will be assessed by: (1) proportion of total study time (wear time) during which 24/7 EEG SubQ data are collected; (2) questionnaires; (3) proportion of device deficiencies.

To assess quality of life we will assess change over time for average Participant Weighted Quality of Life In Epilepsy (QOLIE-31) scores at baseline, 3-months and 6 months. In addition to the above, adverse events will be recorded throughout the study.

Finally, the data acquired during the project by sqEEG ultra long-term monitoring may also let the evaluation of the presence of circadian and multidien organization of seizures in DEEs, a factor that has been considered in previous studies in different populations (Karoly et al., 2021).

4.3. Statistical analysis methods

The accuracy of (1) AI-driven algorithm applied to 24/7 EEG SubQ data vs. ground truth and (2) self-reported participant diary vs. ground truth, will be compared by a correlation-based comparison: we will first estimate Spearman correlation coefficients for both groups to evaluate their monotonic relationship with the ground truth. To compare these relations between the two groups, we will use a Wilcoxon signed-rank test. We will also calculate for diary reports and AI – detected seizures the following measures: sensitivity, specificity, false positive rate, positive predictive value, negative predictive value, F1 score.

Questionnaire-based data will be assessed using different methods. For categorical data collected at three different time points (start, 3 months, and 6 months), the Chi-squared test will be used to assess whether there are significant changes in the distribution of responses over time. Likert scale's and the CSRI will be assessed with descriptive statistics (e.g., mean, median, and frequency distributions) to summarize participant responses. For comparing the quality-of-life questionnaires (e.g., QOLIE-31) the Mann–Whitney *U* test will be used. Differences will be considered significant at $p < 0.05$.

5. Oversight and monitoring

Monitoring will be carried out by a clinical study manager at coordinating centre (Modena) during the period of the investigation. The first monitoring visit will be an on-site visit planned after the minimum of three and maximum of five participants have completed their first visit to identify any data entry errors (discrepancy between source data and eCRF), systematic errors caused at the site or by the participant and provide any necessary help and assistance to the site. Most importantly, the aim will be to identify any issues that have or might have impacted the integrity of data and safety of participants early in the study for corrective actions to be implemented. Remote monitoring visits will be held with an appointed investigator at each site, to follow up on recruitment, site progress, safety reporting, and on potential queries in the eCRF system or other outstanding issues. Remote monitoring visits will be planned every 4–8 weeks, or per 5 participants enrolled at the site.

5.1. Harms

All adverse events or device deficiencies will be reported within eCRF. The coordinating investigator at each site must assess all adverse events that occur on their site. All serious adverse events and serious ADE must be reported to the principal investigator (PI) within 3 calendar days of the site becoming aware of the event. It is the responsibility of the PI to ensure that serious adverse events or serious adverse device effects are reported to national regulatory authorities immediately, but no later than 7 calendar days following the date of awareness by the PI.

If a suspicion of an unacceptable risk to participants develops during the clinical investigation, the PI will suspend the study while the risk is assessed. The PI will terminate the study if an unacceptable risk is confirmed. If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at one of the participating investigation sites, the PI will suspend or terminate the investigation site.

6. Discussion

Rare epilepsies and DEEs comprise a collection of rare, often genetically determined diseases that are associated with drug-resistant epilepsy and cognitive impairment (Scheffer et al., 2025; Specchio et al., 2022; Trivisano and Specchio, 2020). The impact of these conditions, both in pediatric and adulthood, is very severe. Not only for the patient but also for the family, society, and the healthcare system. Therefore, it is necessary to develop cross-cutting models of care and evaluation of treatments that allow the assessment of objective measures of disease progression, possibly with precision on the individual patient. A particularly lacking and difficult aspect in this context concerns the actual assessment of the frequency of seizures that the patient presents (Elger and Hoppe, 2018; Nurse et al., 2025).

Treatment decisions are informed by seizure counts, and there have long been calls for more reliable measures than what seizure diaries provide. Although wearables for the detection of tonic-clonic seizures are gaining approval, the ability to automatically detect focal seizures, particularly with impaired awareness or without major motor features, remains unmet. Objective and actual seizure counts may inform clinical decisions to avoid that an effective treatment is abandoned because no discernible effect in self-reported measures was apparent, or that an inefficacious treatment is maintained or initiated on the basis of non-epileptic events, because non-seizure events are incorrectly classified as seizures by the patient/caregivers. All these needs are especially important in fragile patient populations such as those with DEE (Moraes et al., 2025; Nurse et al., 2025).

This study aims to validate a wearable and minimally invasive electroencephalographic (EEG) monitoring system for continuous patient recording over periods of weeks/months in rare epilepsies and DEEs. A majority of patients and caregivers want some form of seizure monitoring, either at night only or 24/7, to feel safer and less stigmatized. This is where subscalp EEG is most likely to improve the everyday life of a person with epilepsy and DEEs in particular. We recently reported a first-in-man use of 24/7 SubQ EEG in a patient with Lennox Gastaut Syndrome with encouraging results (Affronte et al., 2025).

The model of home care and monitoring of the patient is intended to be of clinical utility to the patient (and physician) by allowing objective assessment of therapeutic interventions and their effectiveness in a context that is generally very complex, and where today we rely only on approximate measures. This project is fully in the context of developing home and remote patient monitoring systems, offering accuracy that is unthinkable today and avoiding the need for repeated hospitalizations and evaluations for the patient and family. This represents an

overarching and topical goal of modern healthcare systems. Lastly, this study can become pilot for a more extensive use of the device and the seizure detection algorhythm on a larger scale including different epileptic conditions.

There are also some study limitations. Our sample size is small and may not be representative of the whole epilepsy population. Recruitment may prove challenging given the need for implantation and increased demands for the clinical team. Moreover, for patients in whom the comparison of standard scalp EEG with sqEEG in Study Part 1 demonstrates a discrepancy, or a failure in recording some seizure's types, this could pose a limitation in the definition of the ground truth for the subsequent Study Part 2. Finally, clinicians will need to familiarize themselves with reviewing data, which could prove to be time consuming. If the AI-driven algorithm provided by UNEEG proves to be inadequate from a clinician's perspective, the sheer amount of data analysis may not be feasible for busy clinicians.

We will determine whether 24/7 EEG SubQ is feasible and acceptable to patients with DEEs, caregivers and clinicians alike. EMIRE hopes to establish new avenues to improve quality of life for people with severe epilepsies and intellectual disability.

Author contributions

SM and SM designed the study, coordinated its delivery, and wrote and amended the protocol for ethical approval. SM and LA drafted the protocol for publication. GG, MT, PM, AC, LB, AEV, and NS contributed to reviewing the protocol for publication. All authors have reviewed the manuscript and approved it for publication.

Funding information

The present work was funded by a grant of the MOH (Rafforzamento e potenziamento della ricerca biomedica del SSN – NextGenerationEU). Project Code: PNRR-MR1-2022-12376491. The study is registered on clinical trial.gov: NCT06855901.

9. Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

The study was approved by the local ethical committee (AOU 0029341/23). The study was conducted in accordance with the World Medical Association Declaration of Helsinki.

CRediT authorship contribution statement

Leonardo Affronte: Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Stefania Maffei:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Mara Malerba:** Data curation, Writing – review & editing. **Giada Giovannini:** Writing – review & editing. **Paolo Manganotti:** Writing – review & editing. **Antonietta Coppola:** Writing – review & editing. **Leonilda Bilo:** Writing – review & editing. **Anna Elisabetta Vaudano:** Writing – review & editing. **Marina Trivisano:** Writing – review & editing. **Nicola Specchio:** Writing – review & editing. **Stefano Meletti:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Stefano Meletti received research grant support from the Ministry of Health (MOH); has received personal compensation as scientific advisory board member for UCB, Jazz pharmaceuticals, and EISAI. Antonietta Coppola has received personal compensation as scientific advisory board member for UCB, Jazz pharmaceuticals, Ethypharm, Takeda and Angelini; she has received Speakers honoraria by UCB, Jazz pharmaceuticals and Angelini. Leonardo Affronte, Giada Giovannini, Stefania Maffei, Mara Malerba, Paolo Manganotti, Antonietta Coppola, Leonilda Bilo, Anna Elisabetta Vaudano, Marina Trivisano, Nicola Specchio, report no disclosures relevant to the manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cnp.2025.12.005.

References

Affronte, L., Maffei, S., Malerba, M., Manganotti, P., Coppola, A., Vaudano, A.E., Specchio, N., Rubboli, G., Meletti, S., 2025. Home ultra-long EEG monitoring in Lennox-Gastaut syndrome by subscalp EEG: opportunities and challenges. Clin. Neurophysiol. 5 (177), 2110828. https://doi.org/10.1016/j.clinph.2025.2110828.

Baud, et al., 2021. Under-sampling in epilepsy: Limitations of conventional EEG. Clin. Neurophysiol. Pract. 6, 41–49.

Baumgartner, C., Koren, J.P., Rothmayer, M., 2018. Automatic computer-based detection of epileptic seizures. Front. Neurol. 9, 639.

Blachut, B., Hoppe, C., Surges, R., Stahl, J., Elger, C.E., Helmstaedter, C., 2015. Counting seizures: the primary outcome measure in epileptology from the patients' perspective. Seizure 29, 97–103. https://doi.org/10.1016/j.seizure.2015.03.004.

Blachut, B., Hoppe, C., Surges, R., Elger, C., Helmstaedter, C., 2017. Subjective seizure counts by epilepsy clinical drug trial participants are not reliable. Epilepsy Behav. 67, 122–127. https://doi.org/10.1016/j.yebeh.2016.10.036.

Blum, D.E., Eskola, J., Bortz, J.J., Fisher, R.S., 1996. Patient awareness of seizures. Neurology 47, 260–264. https://doi.org/10.1212/WNL.47.1.260.

Cohen, J.F., Korevaar, D.A., Altman, D.G., Bossuyt, P.M., Johnston, B.C., Salameh, J.P., et al., 2016. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 6 (11), e012799.

Cook, M.J., O'Brien, T.J., Berkovic, S.F., Murphy, M., Morokoff, A., Fabinyi, G., D'Souza, W., Yerra, R., Archer, J., Litewka, L., Hosking, S., Lightfoot, P., Ruedebusch, V., Sheffield, W.D., Snyder, D., Leyde, K., Himes, D., 2013. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 12, 563–571. https://doi.org/10.1016/S1474-4422(13)70075-9.

Djurhuus, B.D., Viana, P.F., Ahrens, E., Nielsen, S.S., Srinivasan, H.L., Richardson, M.P., Homøe, P., Hasegawa, H., Zarei, A.A., Gauger, P.L.K., Duun-Henriksen, J., 2023. Minimally invasive surgery for placement of a subcutaneous EEG implant. Front. Surg. 9 (10), 1304343. https://doi.org/10.3389/fsurg.2023.1304343. PMID: 38026479; PMCID: PMC10665563.

Duun-Henriksen, J., Baud, M., Richardson, M.P., et al., 2020. A new era in electroencephalographic monitoring? Subscalp devices for ultra–long-term recordings. Epilepsia 61, 1805–1817.

Elger, C.E., Hoppe, C., 2018. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. Lancet Neurol. 17 (3), 279–288. https://doi.org/10.1016/S1474-4422(18)30038-3.

Hoppe, C., Poepel, A., Elger, C.E., 2007. Epilepsy: accuracy of patient seizure counts. Arch. Neurol. 64, 1595–1599.

Karoly, P.J., Rao, V.R., Gregg, N.M., Worrell, G.A., Bernard, C., Cook, M.J., Baud, M.O., 2021. Cycles in epilepsy. Nat. Rev. Neurol. 17 (5), 267–284. https://doi.org/10.1038/s41582-021-00464-1. Epub 2021 Mar 15 PMID: 33723459.

McWilliam, M., Viana, P.F., Dursun, E., Davies, J., Winston, J.S., Agren, J., et al., 2025. Real world testing and cost-effectiveness analysis of subcutaneous EEG (REAL-ASE): Protocol for a prospective multicentre interventional trial. Epilepsia Open. 00, 1–12. https://doi.org/10.1002/epi4.70064.

Meinert, E., Milne-Ives, M., Sawyer, J., et al., 2025. Subcutaneous electroencephalography monitoring for people with epilepsy and intellectual disability: co-production workshops. Bjpsych Open. 11 (1), e3.

Moraes, J., Cook, M., Nurse, E., 2025. The silent witness: the unseen gaps in eyewitness recognition of seizures. Epilepsia 00, 1–5. https://doi.org/10.1111/epi.18499.

Nurse, E.S., Cook, M.J., Dalic, L.J., 2025. Seizure reporting in older patients with developmental and epileptic encephalopathies: a retrospective review of ambulatory video-EEG reports. Seizure 8 (131), 50–56. https://doi.org/10.1016/j.seizure.2025.06.003.

Remvig, L.S., Duun-Henriksen, J., Fürbass, F., et al., 2022. Detecting temporal lobe seizures in ultra long-term subcutaneous EEG using algorithm-based data reduction. Clin. Neurophysiol. 142, 86–93. https://doi.org/10.1016/j.clinph.2022.07.504.

Rubboli, G., Bø, M.H., Alfstad, K., et al., 2024. Clinical utility of ultra long-term subcutaneous electroencephalographic monitoring in drug-resistant epilepsies: a "real world" pilot study. Epilepsia 65 (11), 3265–3278. https://doi.org/10.1111/epi.18121.

Specchio, N., et al., 2022. International League against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia 63 (6), 1398–1442.

Scheffer, I.E., French, J., Valente, K.D., Auvin, S., Cross, J.H., Specchio, N., 2025. Operational definition of developmental and epileptic encephalopathies to underpin the design of therapeutic trials. Epilepsia 66 (4), 1014–1023. https://doi.org/10.1111/epi.18265.

Tatum IV, W.O., Winters, L., Gieron, M., Passaro, E.A., Benbadis, S., Ferreira, J., Liporace, J., 2001. Outpatient seizure identification: results of 502 patients using computer-assisted ambulatory EEG. J. Clin. Neurophysiol. 18, 14–19. https://doi.org/10.1097/00004691-200101000-00004.

Trivisano, M., Specchio, N., 2020. What are the epileptic encephalopathies? Curr. Opin. Neurol. 33 (2), 179–184.

van der Lende, M., Cox, F.M.E., Visser, G.H., Sander, J.W., Thijs, R.D., 2016. Value of video monitoring for nocturnal seizure detection in a residential setting. Epilepsia 57 (11), 1748–1753.

van der Lende, M., Hesdorffer, D.C., Sander, J.W., Thijs, R.D., 2018. Nocturnal supervision and SUDEP risk at different epilepsy care settings. Neurology 91 (16), e1508–e1518.

Viana, P.F., Remvig, L.S., Duun-Henriksen, J., Glasstetter, M., Dümpelmann, M., Nurse, E.S., et al., 2021a. Signal quality and power spectrum analysis of remote ultra long-term subcutaneous EEG. Epilepsia 00, 1–9.

Viana, P.F., et al., 2021b. 230 days of ultra long-term subcutaneous EEG: seizure cycle analysis and comparison to patient diary. Ann. Clin. Transl. Neurol. 8 (1), 288–293.

Viana, P.F., Duun-Henriksen, J., Biondi, A., Winston, J.S., Freestone, D.R., Schulze-Bonhage, A., Brinkmann, B.H., Richardson, M.P., 2025. Real-world epilepsy monitoring with ultra long-term subcutaneous EEG: a 15-month prospective study. Epilepsia 1–14. https://doi.org/10.1111/epi.18566.

Weisdorf, S., Gangstad, S.W., Duun-Henriksen, J., Mosholt, K.S.S., Kjær, T.W., 2018. High similarity between EEG from subcutaneous and proximate scalp electrodes in patients with temporal lobe epilepsy. J. Neurophysiol. 120 (3), 1451–1460. https://doi.org/10.1152/jn.00320.2018.

Weisdorf, S., Duun-Henriksen, J., Kjeldsen, M.J., Poulsen, F.R., Gangstad, S.W., Kjaer, T. W., 2019. Ultra-long-term subcutaneous home monitoring of epilepsy-490 days of EEG from nine patients. Epilepsia 60 (11), 2204–2214. https://doi.org/10.1111/epi.16360.