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# EpiSave: A multi-centre, event-driven clinical study to assess the performance of the EpiSave seizure detection ecosystem in people with epilepsy and generalized convulsive seizures in epilepsy monitoring units

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|---|---|
| Research legislation: | Ordinance on human research with the exception of Clinical trials (HRO) [1]. |
| Type of Research Project: | Research project involving human subjects |
| Risk Categorisation: | Risk category A acc. to ordinance HRO Art. 7 - observational study with non-invasive device. The alarm will be available only for the medical team and the patient will be blind to whatever the algorithm detects. |
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# PROTOCOL SIGNATURE FORM

| | |
|---|---|
| Study Title | **EpiSave** - A multi-centre, event-driven clinical study to assess the performance of the EpiSave seizure detection ecosystem in people with epilepsy and generalized convulsive seizures in epilepsy monitoring units (EMU) |

The project leader at the main coordinating centre and the project leader at the local centre/site have approved the protocol version 1.0 (dated XX.XX.2025) and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements [1,2], the current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

The project leader at main centre has received the ICF and consider it appropriate for use.

**Project leader (lead centre/site):**

Site:

Service d'Epileptologie

Département des Neurosciences Cliniques

Centre Hospitalier Universitaire Vaudois (CHUV)

Rue du Bugnon, 46

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Name: Pr. Dr. med. Philippe Ryvlin

Date: _____ Signature: _____

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**Site** : University Children's Hospital, Zurich

**Name of local project leader**: _____

**Date:** _____ **Signature:** _____

**Site** : Swiss Epilepsy Center, Klinik Lengg – Zurich

**Name of local project leader**: _____

**Date:** _____ **Signature:** _____

**Site** : Geneva University Hospitals (HUG), Geneva

**Name of local project leader**: _____

**Date:** _____ **Signature:** _____

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## GLOSSARY OF ABBREVATIONS

| | |
|---|---|
| *BASEC* | *Business Administration System for Ethical Committees* |
| *CE* | *Conformité Européenne* |
| *CRF* | *Case Report Form* |
| *eCRF* | *electronic Case Report Form* |
| *EEG* | *Electroencephalogram* |
| *EMU* | *Epilepsy Monitoring Unit* |
| *FAR* | *False Alarm Rate* |
| *FDA* | *Food and Drug Administration* |
| *FBTCS* | *Focal to Bilateral Tonic-Clonic Seizures* |
| *GCS* | *Generalized Convulsive Seizures* |
| *GDPR* | *General Data Protection Regulation* |
| *GTCS* | *Generalized Tonic-Clonic Seizures* |
| *HRA* | *Human Research Act* |
| *HRO* | *Ordinance on Human Research* |
| *ICF* | *Informed Consent Form* |
| *iOS* | *iPhone Operating System* |
| *PPG* | *Photoplethysmography* |
| *PPI* | *Patient and Public Involvement* |
| *PSSUQ* | *Post-Study System Usability Questionnaire* |
| *PWE* | *People with Epilepsy* |
| *SUDEP* | *Sudden Unexpected Death in Epilepsy* |
| *TWP5* | *TicWatch Pro 5* |
| *VEEG* | *Video Electroencephalogram* |
| *3D-acc* | *3D-accelerometer* |

# 1 BACKGROUND AND PROJECT RATIONALE

Epilepsy is a neurological condition affecting approximately 60 million people worldwide. Among those, 25-30% experience generalized convulsive seizures (GCS), which include focal to bilateral tonic-clonic (FBTCS) and generalized tonic-clonic seizures (GTCS) [4-6].

GCS represent one of the most severe forms of epileptic seizures and are associated with increased risks of physical injury, sudden unexpected death in epilepsy (SUDEP), and significant impact on quality of life [7-9].

Several studies have demonstrated that prompt intervention following GCS detection can reduce seizure duration, prevent secondary complications, and potentially decrease SUDEP risk by up to 40% [10]. Medical devices such as applications that detect GCS and alert caregivers with the patient's location have been developed to enable timely intervention. However, current medically certified seizure detection solutions present significant limitations including high false-alarm rates – FARs – (>1 alarm per week), substantial costs ($250-1,500 USD for device purchase plus monthly subscription fees), limited operational windows (night-only for some systems), and stigmatization concerns related to dedicated medical devices.

**Currently Available Medical Devices:**

1. **EpiMonitor (Empatica Inc.)**: FDA-cleared, multimodal seizure detection device utilizing electrodermal activity, accelerometry, and photoplethysmography (PPG) sensors. Clinical validation studies demonstrate a detection accuracy of 98% compared to hospital-based electroencephalogram (EEG) measurements. Approved for adults and children ages 6 years and older [11, 12].

2. **NightWatch (LivAssured B.V.)**: A nocturnal seizure detection system utilizing heart rate variability and accelerometry for GTCS detection. Clinical validation demonstrates a sensitivity of 86% with a FAR of 0.7 per night. Its use is limited to nocturnal monitoring only [13-15].

3. **Epi-Care Mobile (Danish Care Technology)**: A mobile seizure detection system utilizing accelerometry for convulsive seizure detection. Clinical validation studies show a variable sensitivity ranging from 65% to 90%, depending on seizure type and patient population [16, 17].

4. **EpiWatch**: FDA-cleared iOS (iPhone Operating System) app running on Apple watch detects GCS using 3D-accelerometer (3D-acc) only (note that available publication also mentions using PPG, but the FDA certification only included 3D-accelerometry). Studies showed a sensitivity of 100% with a FAR of 0.05 per day (Ref Shah).

These limitations collectively result in low adoption rates among people with epilepsy (PWE), with only a small minority having access to or choosing to use existing certified seizure detection devices due to cost barriers, usability concerns, and lifestyle restrictions imposed by current solutions.

EpiSave addresses these limitations through an innovative Android-based smartwatch application designed to detect GCS with high sensitivity (preliminary data indicate a 96% detection rate), maintain a low FAR (<1 per week), operate on commercially available low-cost smartwatches that can serve other functions and help reduce stigma, provide immediate alerts to caregivers including patient location, and offer the application free of charge to PWE in low- and middle-income countries.

The development of seizure detecting devices and applications follows a standardized framework. EpiSave has successfully completed phase 2 testing [18], which involved algorithm development and offline validation on data previously collected in EMU where video-EEG (VEEG) serves as a gold-standard. EpiSave algorithm was first trained on data from 37 patients who suffered 54 GCS. It was then tested on an independent dataset from 347 patients, including 33 with 49 GCS, showing a 96% sensitivity (95% CI 90%-100%) and a FAR <1 per week [19].

This study represents a phase 3 validation study in the EMU setting, with VEEG serving as the gold standard reference for seizure detection.

This research project falls under Category A acc. to ordinance HRO Art. 7 as it is an observational study with a non-invasive device. The alarm will be available only for the medical team without interfering with clinical routine and the patient will be blind to whatever the algorithm detects. The intervention itself (wearing a smartwatch) is minimally invasive, and the continuous monitoring does not modify standard clinical care or create additional burden beyond routine EMU monitoring. The patient will therefore not experience any constraints or discomfort related to this study.

## 2 PROJECT OBJECTIVES AND DESIGN

### 2.1 Hypothesis and primary objective

- **Hypothesis**: The EpiSave seizure detection algorithm will demonstrate ≥80% sensitivity (lower 95% confidence interval end) for detecting GCS (including GTCS and FBTCS) when validated against VEEG gold standard in EMU settings.
- **Primary Objective**: To assess EpiSave sensitivity for detecting GCS (including GTCS and FBTCS) in EMU settings validated against VEEG gold standard.
- **Secondary Objectives**:

  1) To evaluate EpiSave FAR in EMU settings
  2) To evaluate the delay between GCS onset and its detection
  3) To test the performance of EpiSave in characterizing seizures such as the precision of the duration of GCS and post-ictal immobility
  4) To assess the reliability and usability of EpiSave in a controlled environment (*Post-Study System Usability Questionnaire - PSSUQ*)
  5) To document any technical issues or limitations encountered with EpiSave (any adverse event)

### 2.2 Primary and secondary endpoints

| | Definition | Measurement | Analysis |
|---|---|---|---|
| **Primary Endpoint** | | | |
| EpiSave sensitivity for detecting GCS validated against VEEG recording in EMU. | Proportion of GCS detected by EpiSave among all GCS confirmed by VEEG | Calculated as (True Positives / (True Positives + False Negatives)) × 100% | 95% confidence intervals |
| **Secondary endpoint** | | | |
| False alarm rate | Proportion of false positive detections per patient per day | Count of false alarms divided by monitoring days and reporting the reason of the false alarm such as teeth brushing etc. | 95% confidence intervals |

| | | | |
|---|---|---|---|
| System Uptime | Proportion of monitoring time with active EpiSave detection | Continuous monitoring logs | Mean uptime percentage |
| Technical Performance | Device performance metrics: battery life, connection reliability statistics | Automated system logs | Descriptive statistics |
| User experience | Staff satisfaction (=caregivers) with the EpiSave App | PSSUQ and custom satisfaction questionnaire | Mean scores with standard deviation |
| Seizure Characterization | Accuracy of seizure characterization | Comparison with VEEG analysis | Descriptive statistics |

Age, gender, epilepsy type, seizure frequency, anti-seizure medication regimen, cognitive status, and prior experience with seizure detection devices are all factors that may influence the primary and secondary endpoints. These variables should therefore be considered in the data analysis.

### 2.3 Independent variables

**Primary Independent Variable**: EpiSave seizure detection algorithm

The primary independent variable is EpiSave, a proprietary machine learning algorithm developed for the detection of GCS. It operates based on continuous analysis of 3D-acc data and is designed to function throughout the entire EMU stay.

**Secondary Independent Variable**: The android smartwatch

The secondary independent variable is a commercially available Android smartwatch running Wear OS 4.0, equipped with a 3D-acc operating at a 27 Hz sampling rate. Data collected by the device is stored locally and securely uploaded to a dedicated server. The seizure alert system is deactivated for participants, who remain unaware of any detections. Alerts are transmitted exclusively to EMU staff, who are responsible for verifying seizure occurrences, documenting false positives (e.g., no seizure despite detection), and reporting false negatives (e.g., seizures not detected by the system).

### 2.4 Project design

The EpiSave study, coordinated by the CHUV, is a multicentre, event-driven, single-arm, open-label, prospective observational validation study conducted in Swiss and European EMUs.

This observational validation study will be conducted across 15 epilepsy centres in Switzerland and Europe, all equipped with EMUs. The observational design is appropriate for validating the performance of the EpiSave seizure detection algorithm against the gold standard of VEEG, without altering standard patient care. The prospective nature of the study allows for real-time data collection from the beginning to the end of each participant's VEEG recording. The multicentre approach ensures generalizability across diverse clinical settings and patient populations.

Participants will be patients with pharmacoresistant epilepsy admitted to the EMU for VEEG monitoring as part of their routine diagnostic evaluation or follow-up. Each participant will wear a TicWatch Pro 5 (TWP5) equipped with the EpiSave system for a period ranging from 2 days to 2 weeks (average: 5 days), corresponding to the duration of their VEEG recording. This duration depends on the occurrence of seizures, which determines when the clinical assessment can be

concluded. The study participation period will not exceed the duration of the clinically indicated VEEG monitoring.

The study includes continuous monitoring throughout the EMU stay, combining real-time seizure detection and post-ictal biosignals recording via TWP5. The detection process remains silent for participants, as no alerts are delivered to them. In parallel, patients undergo standard VEEG monitoring as part of their routine clinical care, entirely independent of the research intervention.

EpiSave is an event-driven study, meaning its completion depends on the occurrence of a predefined number of clinical events. Specifically, the study will conclude once 60 GCS events have been recorded across 40 different PWE. The event-driven design enables efficient recruitment until enough GCS are captured. The total duration of the study, encompassing both recruitment and data analysis phases, will not exceed 3 years.

# 3 PROJECT POPULATION AND STUDY PROCEDURES

## 3.1 Project population, inclusion and exclusion criteria

### Study Population and Design

The study will enrol both adults and children aged 6 years and older with drug-resistant epilepsy, defined as persistent seizures despite trials of at least two appropriate anti-seizure medications. Participants must be at risk of experiencing GCS during their stay in the EMU. The study includes vulnerable individuals who may lack the capacity to provide independent consent. This is an event-driven study, aiming to capture a minimum of 60 GCS events across at least 40 PWE. Based on data from the SEVERITY study (2019-00437 – 398 patients, 84 individuals with 121 GCS), we estimate that approximately 235 patients will be recruited to achieve this target, with 40 participants expected to experience at least one recorded GCS. Recruitment will be conducted to ensure balanced representation across sexes and genders, recognizing that epilepsy affects both males and females and that seizure characteristics may vary accordingly. Recruitment will be competitive between sites, meaning that each centre may enrol participants until the overall target sample size is reached, without predefined quotas per site. This approach allows for flexibility and accelerates enrolment, particularly in centres with higher patient throughput.

*Patients will be recruited according to the following eligibility criteria:*

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Age ≥ 6 years<br>• Confirmed diagnosis of epilepsy (documented by a neurologist)<br>• Drug-resistant epilepsy (persisting seizures despite two adequate anti-seizure drug trials)<br>• Informed consent from patient or legal representative<br>• PWE at risk of suffering a GCS during VEEG monitoring, either due to:<br>- Documented history of GCS (from medical records or patient/caregiver reports), or<br>- Planned tapering of anti-seizure medication during the monitoring | • Age < 6 years<br>• Uncertain epilepsy diagnosis<br>• Inadequate anti-seizure medication trials<br>• No GCS risk during VEEG monitoring<br>• Lack of informed consent<br>• Inability to wear smartwatch device due to physical limitations<br>• Known allergy to smartwatch materials (silicone, metal components) |

### 3.2 Recruitment, screening and informed consent procedure

Participant recruitment will be conducted continuously throughout the study. Only patients admitted to the EMU for a VEEG monitoring will be considered for inclusion. Recruitment will take place at participating clinical centres across Switzerland and Europe.

Screening will be conducted during the EMU admission process. No additional procedures beyond standard EMU care will be required. Eligibility will be assessed based on predefined inclusion and exclusion criteria.

Eligible candidates will be identified during their EMU hospitalization. During an explanatory meeting, the project leader explains to each participant the nature of the research project, its purpose, the procedures involved, the expected duration, the potential risks and any discomfort it may entail. Each participant is informed that the participation in the research project is voluntary and that he/she may withdraw from the research project at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participants are informed that he/she can ask any question. Enough time is given to the participant. To increase the chances to catch any potential GCS that the patient may experience while being at the EMU, we suggest starting the monitoring with the EpiSave system within the 24-hour post admission, knowing that not all patients will stay for the entire week.

All participants are given an information document and a consent form describing the research project. The formal consent of a participant, using the approved consent form, is obtained before the participant is enrolled in the research project. The participant should read, understand, and voluntarily agree before signing and dating the informed consent form (ICF), and is given a copy of the signed document. The consent form is signed and dated by the participant and the project leader (or her/his designee). The signed consent form it is retained as part of the investigation records.

For paediatric participants, age-appropriate information will be provided. Children aged 6 to 13 years will receive both verbal and written information adapted to their developmental level. Adolescents aged 14 and older will receive the same information as their parents or legal representatives and will be asked to sign the consent form themselves.

No monetary compensation will be provided to participants.

### 3.3 Study procedures

The study is event-driven and anticipated to last up to 36 months, including recruitment period of 30 months and data analysis period of 6 months.

The site's physician-investigator and co-investigator are responsible for screening patients upon admission to the EMU by verifying inclusion and exclusion criteria, in order to identify potential candidates for study participation. The duration of each patient's involvement in the study corresponds to that of standard video-EEG monitoring—typically around 5 days, with a minimum of 2 days and a maximum of 2 weeks. No additional procedures beyond routine clinical care are performed as part of the study.

**During the first visit (V1),** upon admission to the EMU, the principal investigator or co-investigator will explain the study's objectives and procedures to the patient. The patient will be given as much time as needed to review the information and sign the ICF. Once the consent is obtained, the investigator will collect demographic and clinical data through a brief interview and review of the patient's electronic medical records. Prior to the enrolment of the first patient, EMU staff will receive training on the TWP5 device and the EpiSave system.

**During the monitoring period** in the EMU, the participant will wear the TWP5 smartwatch on their wrist alongside standard VEEG recording. This setup enables continuous monitoring via the EpiSave application, allowing direct comparison between smartwatch data and the gold-standard

VEEG. EpiSave detects and records seizures in real time; however, no alerts will be sent to the patient, who will remain unaware of any detections. Alerts will be transmitted exclusively to the nursing staff via the paired smartphone running the EpiSave companion app. In addition to seizure detection, the smartwatch will record biosignals—such as photoplethysmography and gyroscope data—for 15 minutes following each detected seizure. Daily checks will be performed to ensure proper device functioning, including battery status and connectivity. Data collected by the smartwatch will be automatically uploaded to the Exoscale server in Switzerland when the device is charging and connected to Wi-Fi or Bluetooth via the provided smartphone.

The EpiSave algorithm was developed, trained, and validated using data from the SEVERITY study (2019-00437), which combines wearable sensor data with VEEG recordings, enabling precise event labelling for model development. The model is an ensemble of sub-models, each trained on a distinct subset of the training data. All sub-models share the same architecture—a convolutional neural network followed by a multi-layer perceptron—and process 30-second segments of motion data. Each sub-model outputs a confidence score between 0 and 1, representing the likelihood of a seizure. The final decision score is the median output from the sub-models, with a median score above 0.5 indicating a detected seizure.

If the algorithm detects a GCS that is not confirmed by VEEG review (false positive), or if a GCS is missed by EpiSave but identified in the VEEG (false negative), EMU staff must document these events in the companion smartphone app (EpiSave e-diary). For false positives, the staff should report the motor activity that triggered the alert. For false negative, a GCS entry must be manually added to the e-diary. The app records the date and time of each alert, whether a true GCS was confirmed by VEEG, and—if no seizure occurred—details about the patient's activity or context that may have led to the false positive. Corresponding video recordings (true GCS, false positives, and false negatives) will be archived for subsequent analysis.

No other action will be taken regarding the participant's medical care unless the physician considers that the patient's safety is at risk.

**At the end of the VEEG recording (Visit 2)**, the smartwatch will be retrieved. The EMU nurse/technician will be asked to complete two short questionnaires: the PSSUQ and a custom EpiSave satisfaction questionnaire.

***The Android TicWatch Pro 5 smartwatch***

The Android smartwatch used in this study is a commercial CE-marked device capable of measuring various biosignals. For the purpose of this study, only the 3D-acc data will be collected continuously throughout the monitoring period. The other signals—PPG (photoplethysmography), and gyroscope data—will be recorded exclusively during the 15 minutes following a detected seizure.

The EpiSave app is pre-installed on the smartwatch to detect GCS and send alerts to EMU nursing staff. The device will be fully configured and ready for use before the first study visit (V1). The patient will begin wearing the TWP5 immediately after it is handed over. At that point, the EpiSave app will already be active and ready to record data—specifically, continuous 3D-acc and post-seizure biosignals such as PPG and gyroscope data.

The smartwatch battery allows for approximately 22 hours of data recording and requires less than 2 hours for a full recharge. Further details on its functionality with EpiSave is described in the appendix 2.

Several biases may arise during the EpiSave study. These include:

- **Selection Bias**: Mitigated through consecutive recruitment and clear inclusion criteria
- **Observer Bias**: Mitigated through standardized training and blinded VEEG review
- **Technical Bias**: Mitigated through standardized device setup and calibration
- **Reporting Bias**: Mitigated through automated data collection and standardized questionnaires

### 3.4 Withdrawal and discontinuation

Patients will be withdrawn from this study for the following reasons:

- Withdrawal of informed consent
- Lack of compliance
- Upon patient request at any time
- Changes in health condition leading to the appearance of an exclusion criterion
- Device intolerance or adverse reactions
- Early discharge from EMU (less than 48 hours)

In case of withdrawal from the study, coded data of withdrawn patient will remain for analysis. The data collected until withdrawal (eCRF, device and app) will be used in a coded manner to avoid compromising the scientific validity of the study. Patient's care and medical follow-up will not be affected in case of withdrawal.

## 4 STATISTICS AND METHODOLOGY

### 4.1. Statistical analysis plan

Sample size calculation was conducted in accordance with established guidelines for the clinical validation of seizure detection devices [18]. Based on our experience from the SEVERITY study (398 patients, 84 with 121 GTCS), we estimate that 60 GCS would require recruiting 235 patients, with 40 expected to have at least one recorded GCS.

**Power Calculation**:

- **Primary Endpoint**: Sensitivity for GCS detection
- **Target Sensitivity**: ≥80%
- **Expected Sensitivity**: 96% (based on preliminary data)
- **Power**: 80%
- **Significance Level**: α = 0.05 (two-sided)
- **Sample Size**: 60 GCS events minimum

**Statistical Methods**:

- **Primary Analysis**: Sensitivity calculation with 95% confidence intervals using Wilson's method
- **Secondary Analyses**:
    - False alarm rate per patient per day
    - System reliability metrics (descriptive statistics)
    - Caregivers experience measures (descriptive statistics)
    - Seizure characterization accuracy (descriptive statistics)
    - Software: Python, or R version 4.2.0 or later

**Level of Significance**: Two-sided α = 0.05 for primary endpoint. No adjustment for multiple testing as secondary endpoints are exploratory.

**Interim Analyses**: Planned for safety monitoring and early stopping rules. The Data Safety Monitoring Board will review safety data every 6 months.

### 4.2. Handling of missing data

**Missing Data Types**:

- Incomplete EMU stays
- Technical failures during monitoring
- Missing questionnaire responses

**Handling Methods**:

- **Multiple Imputation**: For missing questionnaire data using chained equations
- **Sensitivity Analyses**: To assess impact of missing data on primary outcomes
- **Per-Protocol Analysis**: For participants with complete data
- **Intention-to-Treat Analysis**: Including all enrolled participants

**Missing Data Prevention**:

- Robust device testing and backup systems
- Standardized data collection procedures
- Regular quality control checks
- Participant education and support

# 5 REGULATORY ASPECTS AND SAFETY

## 5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The project leader acknowledges his responsibilities as both the project leader and the Sponsor.

## 5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)

If, during the research project, circumstances arise which could jeopardise the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection are to be taken without delay.

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures must be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

## 5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21.

The project leader reports to the ethics committee on the connection between the event and the collection of health-related personal data. At the same time, the project leader submits proposals concerning the next steps to be taken.

Any new relevant information and the outcome to the original Serious Event is reported to the ethics committee via BASEC.

## 5.4 Procedure for investigations involving radiation sources

This study does not involve radiation sources. No additional procedures are required.

## 5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

The following are considered to be substantial changes:

a. changes affecting the participants' safety and health, or their rights and obligations;
b. changes to the protocol which concern the objectives of the research project;
c. a change of research site or conducting the research project at an additional site; or
d. a change of project leader or Sponsor.

### 5.6 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days. The completion of the research project is defined by the last collection of health-related personal data. All data collected are coded, with the exception of consents, which are treated as confidential. Research data will be stored during at least 10 years after research completion.

### 5.7 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable. The liability coverage covers damage occurring up to 10 years after the completion of the research project. In the event of project-related damage or injuries, each participating hospitals will be liable for their own participants recruited in their own hospital, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO).

## 6 FURTHER ASPECTS

### 6.1 Overall ethical considerations

This study addresses a significant unmet need in epilepsy care by evaluating an innovative and affordable seizure detection solution. The findings are expected to generate robust evidence to support FDA and CE medical device certification, with the potential to greatly improve access to reliable seizure detection for millions of individuals living with epilepsy worldwide.

EpiSave is a prospective observational study involving patients hospitalized in the EMU. Data are collected using a non-invasive wearable device, without sending any alerts to the patient in the event of a GCS detection. The study does not expose participants to any additional risk, nor does it require extra time or effort on their part. The EpiSave study presents minimal risks while offering potential benefits to the broader epilepsy community. Its observational design ensures that standard clinical care remains unchanged, and the smartwatch intervention is both discreet and minimally invasive.

The multicentre design of the study ensures that the results are generalizable across various EMU settings and patient populations. The study is expected to provide robust evidence to support regulatory approval and future clinical implementation.

All participants, including vulnerable individuals such as children and those with cognitive impairments, receive an information sheet and a consent form that clearly describe the study and provide sufficient details to support an informed decision regarding participation. For minors, consent is obtained from their legal guardians, and assent is sought from the child when appropriate. For participants with impaired decision-making capacity, consent is obtained from a legal representative.

The consent process includes simplified materials and additional support to ensure participant understanding. Consent or assent must be given voluntarily and is documented by the signature and date of the participant, their legal representative or parent, and the principal investigator or designated study staff. A copy of the signed consent form is provided to the participant or their representative, while the original is retained in the study records.

Participants who do not wish to take part in the study are not enrolled. Additional safeguards are implemented for vulnerable populations, including simplified consent procedures, enhanced monitoring, and regular reassessment of consent or assent throughout the study.

Participants retain the right to withdraw from the study at any time and may request information regarding the progress and results of the study.

### 6.2 Risk-Benefit Assessment

The EpiSave study is observational. To the best of our knowledge, participants are not exposed to any risk throughout the study, as they will be wearing a commercially available CE-marked Android smartwatch. The only potential risk is minor skin irritation from wearing the device. To mitigate this, regular skin checks will be conducted. This research does not involve any additional examinations and does not interfere with the standard care provided in the EMU.

Concerning privacy risks, the watch will record signals non-invasively and will send recorded data automatically to the Exoscale server when placed on its charger and connected to a Wi-Fi network or Bluetooth. To ensure patient data confidentiality, encrypted data transmission, secure storage, and limited access will be implemented.

No direct individual benefits are anticipated for study participants. However, the results may contribute to the development of improved seizure detection technologies. The validation of the EpiSave application could potentially enhance future access to seizure detection for patients with epilepsy.

The minimal risks are justified by the potential societal benefit of improved seizure detection technology. The study does not modify standard clinical care and provides additional monitoring without additional burden.

### 6.3 Rationale for the inclusion of vulnerable participants

The EpiSave study includes minors (ages 6–17) and adults with cognitive impairments who may lack the capacity to provide independent consent. These groups are considered vulnerable populations in clinical research. PWE who present with neurobehavioral comorbidities or cognitive dysfunction requiring a legal representative are at increased risk of GCS and SUDEP compared to the general epilepsy population. Due to these impairments, they may be unable to alert caregivers about an impending or past seizure, or to reposition themselves safely following a GCS. This underscores the importance of seizure detection devices for these populations and justifies their inclusion in the study.

Similarly, young children may be at increased risk, as they often lack the reflex to notify caregivers when a seizure occurs and may be unable to reposition themselves afterward. Moreover, equivalent findings cannot be obtained through other means, as these populations exhibit unique seizure characteristics and needs that must be studied directly.

To protect vulnerable participants, the study includes several safeguards: consent is obtained from legal representatives for individuals lacking capacity; assent is sought from minors in addition to legal consent; simplified consent forms are provided for participants with cognitive limitations; monitoring and support are enhanced throughout the study; and ongoing consent and assent are regularly reassessed.

## 7 QUALITY CONTROL AND DATA PROTECTION

### 7.1 Quality measures

The project personnel will be trained on all important project related aspects, planned quality visits or independent data review. Standardized training will be provided across all participating centres, including investigator training on protocol procedures and technical staff training on EpiSave

system setup and troubleshooting. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions. The project leader has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 4 HRO).

### 7.2 Data recording and source data

The ICFs, which contain identifiable patient information, along with a separate sheet listing contact details, will be stored in a locked filing cabinet at the local study site where the participant was enrolled. Data storage and access are under the responsibility of the local project leaders and designated study personnel.

Demographic and clinical data will be collected during patient interviews and extracted from the electronic medical record. After coding, these data will be entered directly into an electronic Case Report Form (eCRF) created in the REDCap database hosted on secure CHUV servers (see: https://www.project-redcap.org). Each participating centre will be provided with a secure access allowing direct entry of demographic and medical data into REDCap. EMU nurses/technicians will also complete two questionnaires – the PSSUQ and a custom EpiSave satisfaction questionnaire – directly within REDCap.

The REDCap system ensures secure data entry with controlled access, user rights management, and an audit trail for all modifications, thereby guaranteeing data traceability and integrity throughout the study.

Data from the EpiSave smartwatch will be collected during the participant's stay in the EMU. These data are automatically transferred to a secure Swiss server (Exoscale) when the smartwatch is placed on its charger and connected to a Wi-Fi network or Bluetooth. Data will reach the Exoscale server in the form of a unique ID with the time of the session, and will be linked to the subject ID code (see 7.3. for subject ID code generating). Once the upload is confirmed via a "successfully uploaded" notification on the smartwatch, all temporarily stored data on the device are automatically deleted.

The CHUV study personnel will maintain password-protected excel file with the coding key for the study ID and device unique ID on a firewall secured CHUV desktop. The study personnel will regularly check patient compliance and be also aware of any technical device failures by means of verifying that the data were transferred towards the secured Exoscale server.

The Exoscale server complies fully with European GDPR regulations. It allows secure streaming of mobile health data without routing through third-party cloud providers, thereby enhancing data protection and giving investigators full control over data flow.

Upon site's principal investigator request, data from the smartwatches acquired within the participants from their centre can be made available. However, data from other sites will not be shared.

Data acquired from the VEEG (true events, false positive and false negative) will be copied from the locally used devices, coded with the patient study ID, encrypted and stored on an appropriate media. Staff from the coordinating centre (CHUV) will physically retrieve the media containing the VEEG files and personally take the data back to the CHUV NeuroTech IT Server.

### 7.3 Confidentiality and coding

**Project data** will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. Coding is done using a method based on the current state of the art that must be based on the current state of the art (Art. 26 HRO).

Health related personal data captured during this project from participants are strictly confidential and disclosure to third parties is prohibited; coding will safeguard participants' confidentiality.

The complete project raw data from the smartwatches shall be handled with utmost discretion and will only be accessible to the study personnel at the CHUV. However, only CHUV personnel will have access to the coding key, during and after the research project. Access to the protocol is reserved to the project partners, and other individuals who are directly implicated.

A password-protected Excel-based log will be prepared, called "subject information", which contains the patient names, dates of birth and attributes the subject ID code via the formula, study ID + centre acronym + patient number (e.g. EPI-CHV-001 for CHUV, EPI-HUG-001 for HUG, etc.).

Only the investigators at each site will have access to the identities of the patients enrolled at their respective centres. Access to subject ID codes, both during and after the study, will be restricted to locally involved study personnel.

The code may only be broken if it is necessary to avert an immediate risk to health of the person concerned, to guarantee the rights of the person (e.g. in revoking the consent), or if a legal basis exists for breaking the code.

### 7.4 Retention and destruction of project data and biological material

The project leader retains all the research project data for a period of at least ten years after the completion or early termination of the research project. The study source data generated by the watch will be kept in an archive on the CHUV IT servers. Once the study is concluded, the data will immediately be deleted from the Exoscale server (after analysis). Patients will be asked to sign a consent for additional further use of their data.

Study electronic files will be password protected and saved in a secure directory on each site's institutional server.

This study does not involve collection of biological material.

## 8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

**Funding Sources**: [TO BE DETERMINED - Funding sources will be disclosed]

**Publication Policy**: Results will be published regardless of outcome in peer-reviewed journals. Authorship will follow ICMJE guidelines. All investigators will have opportunity to review and comment on manuscripts before submission.

**Data Sharing Policy**: Codified data may be shared with qualified researchers for secondary analysis, subject to appropriate data sharing agreements and ethics approval.

**Declaration of Interest**: All investigators will disclose any conflicts of interest annually. No conflicts of interest are currently identified.

## 9 REFERENCES

[1] Ordinance on Human Research with the Exception of Clinical trials (HRO)

[2] Human Research Act (HRA)

[3] Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

[4] World Health Organization. Epilepsy. Geneva: World Health Organization; 2024

[5] Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020;54(2):185–91

[6] Shan T, Zhu Y, Fan H, Liu Z, Xie J, Li M, et al. Global, regional, and national time trends in the burden of epilepsy, 1990–2019: an age-period-cohort analysis for the global burden of disease 2019 study. Front Neurol. 2024;15:1418926. https://doi.org/10.3389/fneur.2024.1418926

[7] Tan M, D'Souza W. Seizure-related injuries, drowning and vehicular crashes – a critical review of the literature. Curr Neurol Neurosci Rep. 2013;13(7):361

[8] Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. Neurology. 2020;94(4):e419–e429

[9] Salas-Puig X, Iniesta M, Abraira L, Puig J, QUIN-GTC Study Group. Accidental injuries in patients with generalized tonic-clonic seizures. A multicenter, observational, cross-sectional study (QUIN-GTC study). Epilepsy Behav. 2019;92:135–9, https://doi.org/10.1016/j.yebeh.2018.10.043

[10] Ryvlin P, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS). Lancet Neurol. 2013;12(10):966-977

[11] EpiMonitor (Empatica): FDA-cleared seizure detection device. Available at: https://www.empatica.com/en-gb/epimonitor/

[12] Onorati F, et al. Prospective Study of a Multimodal Convulsive Seizure Detection Wearable System on Pediatric and Adult Patients in the Epilepsy Monitoring Unit. Front. Neurol. 2021;12:724904.
https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.724904/full

[13] Nightwatch: Night-time seizure detection system. Available at: https://nightwatchepilepsy.com

[14] van Westrhenen A, et al. The effectiveness of a new non-invasive home monitoring device for detecting nocturnal seizures in children with epilepsy. Epilepsia. 2023;64(8):e176-e182. https://onlinelibrary.wiley.com/doi/10.1111/epi.17654

[15] van Westrhenen A, et al. Automated detection of nocturnal seizures using a wearable device. Neurology. 2023;101(24):e2488-e2499. https://www.neurology.org/doi/10.1212/WNL.0000000000006545

[16] EpiCare: Mobile seizure detection system. Available at: https://danishcare.co.uk/epicare-mobile

[17] Beniczky S, et al. Detection of generalized tonic-clonic seizures by a wireless wrist accelerometer: a prospective, multicenter study. Epilepsia. 2013;54(4):e58-e61. https://onlinelibrary.wiley.com/doi/10.1111/epi.12120

[18] Beniczky S, et al. Recommendations for clinical trials of seizure detection devices. Epilepsia. 2018;59(11):1794-1803 [19] Spahr et al. (2025). Deep learning based detection of generalized convulsive seizures using a wrist-worn device. Epilepsia. https://onlinelibrary.wiley.com/doi/10.1111/epi.18406

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**Appendix 1: Schedule of assessments**

| Time (days) | Day 0 | Day 0 (V1) | Day 0 to EMU discharge | Day 2 to 14 (V2) |
|---|---|---|---|---|
| **Assessment** | **Information** | **Screening** | **Daily Monitoring** | **End of EMU Stay** |
| **Oral and written Information** | X | | | |
| **Written consent** | | X | | |
| **Demographics** | | X | | |
| **Medical History** | | X | | |
| **EpiSave Monitoring** | | | Continuous | |
| **VEEG** | | | Continuous | |
| **Seizure Events** | | | As occurred | |
| **False Alarms** | | | As occurred | |
| **System Usability Scale (SUS) and a custom EpiSave satisfaction questionnaire completed by the nurse** | | | | X |
| **Technical Performance** | | | Daily | |
| **Data retrieval and erased from account** | | | Daily | |
| **Device Return** | | | | X |

***Notes**: - All assessments are conducted during standard EMU care - No additional visits or procedures beyond routine EMU care - Device monitoring is continuous throughout EMU stay - End-of-study assessments are conducted on the last day of EMU admission*

**Appendix 2: EpiSave Smartwatch System:**

Our EpiSave App will be compatible with smartwatches running Wear OS, including the commercially available CE-marked TicWatch Pro 5 by Mobvoi used in this study.

The detection system will be based on 3D-acc measurements, with 32Hz sampling rate (can be upsampled from 25Hz or downsampled from 50Hz).

- **Application**: EpiSave seizure detection algorithm

- **Data Storage**: Data is initially stored locally on the smartwatch and automatically uploaded to a secure Swiss-based server – Exoscale – when the device is placed on its charger and connected to a Wi-Fi network with the Internet access or Bluetooth via the smartphone connection to the Internet.

- **Alert System**: The alert system is disabled for the patient during their stay in the EMU. When the EpiSave app detects a GCS, an alert is transmitted in real time to a dedicated smartphone/tablet held by the EMU nursing staff. Upon receiving the alert, the staff must verify whether a true GCS occurred by reviewing the VEEG data. If no seizure is confirmed—indicating a false positive – the staff should document the reason, such as the patient's activity or movement that may have triggered the alert. Conversely, if a seizure is observed in the VEEG but was not detected by EpiSave (a false negative), the staff must report the missed event and describe the patient's activity and arm position before and during the seizure within the smartphone companion app.

**- Device Management**: The smartwatch used in this study is an off-the-shelf Android device running Wear OS namely TicWatch Pro 5 from Mobvoi. Before use, each device undergoes standardized calibration procedures to ensure consistent performance. Monitoring is continuous throughout the EMU stay. To avoid interruptions when the smartwatch needs to be charged, a second pre-configured device will be provided to the participant, ensuring seamless data collection.

Data recorded by the smartwatch is initially stored locally. Once the device is placed on its charger and connected either to a Wi-Fi network or Bluetooth, the data is automatically uploaded to the secure study server hosted by Exoscale in Switzerland.

At the end of the EMU stay, the smartwatch is retrieved and any remaining data is downloaded to complete the data collection process.