Clinical Investigation Plan (CIP)

Title: EpiSave Step 2: A Multi-Center, Event-Driven Clinical Investigation to Assess the Real-World Performance of the EpiSave Seizure Detection Ecosystem in People with Epilepsy and Generalized Convulsive Seizures in Ambulatory Settings

Short title : EpiSave Step 2: Outpatient Validation Study

Type of investigation:	Clinical investigation concerning medical devices (interventional)
Categorisation:	Category C
Registration:	EpiSave-002 HumRes-Number If applicable: EUDAMED-number
Identifier:	Investigation ID (e.g. institutional or Sponsor CIP identifier) [make sure this corresponds to the Investigation ID in the footer]
Sponsor-Investigator:	Centre Hospitalier Universitaire Vaudois (CHUV) Address : Rue du Bugnon 46, 1011 Lausanne, Switzerland Contact Person : Prof. Dr. med. Philippe Ryvlin Email : philippe.ryvlin@chuv.ch Phone : +41 21 314 39 66
Sponsor representative (if the Sponsor is not located in Switzerland)	NA
Medical Device (MD):	**Name of the MD:** EpiSave EpiSave is a smartwatch application with proprietary Generalized Convulsive Seizures (GCS) detection algorithm developped by the research group NeuroDigital. The application as developed by an Italian company name Uquido. **Hardware Platform**: Smartwatch, TicWatch Pro 5 (Android Wear OS 2.0+) **Softweare version:** EpiSave v2.0 (investigational version)
CIP Version and Date:	**CIP Version:** 1.0 **CIP Version Date:** 01/10/2025

CONFIDENTIAL

Add, if applicable, an institutional confidentiality statement here respecting that it is not in conflict with applicable transparency rules.

e.g. “The information contained in this document is confidential and the property of the xx (or “Sponsor”). The information may not - in full or in part - be transmitted, reproduced, published, or disclosed to others than the applicable Competent Ethics Committee(s) and Regulatory Authority(ies) without prior written authorisation from the Sponsor except to the extent necessary to obtain informed consent from those who will participate in the investigation.

Signature Pages

ID number of the investigation : Investigation ID

Title :	**EpiSave Step 2:** A Multi-Center, Event-Driven Clinical Investigation to Assess the Real-World Performance of the EPISAVE Seizure Detection Ecosystem in People with Epilepsy and Generalized Convulsive Seizures in Ambulatory Settings

The Sponsor, the Principal Investigator and the Statistician have approved the CIP version 1.0 (dated 01.10.2025), and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155:2020, ICH-GCP as far as applicable, and the local legally applicable requirements.

The Investigator has received the ICF and consider it appropriate for use.

Sponsor-Investigator: Prof.Dr.med Philippe Ryvlin

Place/Date	Signature

Statistician

Place/Date	Signature

Principal Investigator at the local investigational site:

I have read and understood this CIP version [1.0 (dated 01.10.2025), and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155:2020, ICH-GCP as far as applicable, and the local legally applicable requirements.

I have received the ICF and consider it appropriate for use.

Site:	**HUG - Geneva University Hospitals**
Principal investigator at the local investigational site:	Pr. S. Vuillemoz

Place/Date	**Signature**

Site:	**USB – Universitätsspital Basel (adult)**
Principal investigator at the local investigational site:	Dr. M. Hardmeier

Place/Date	**Signature**

Site:	**UKBB - Universitäts-Kinderspital beider Basel (pediatric)**
Principal investigator at the local investigational site:	Pr. A. Datta

Place/Date	**Signature**

Site:	**InselSpital – Universitätsspital Bern**
Principal investigator at the local investigational site:	Dr. C. Friedrichs-Maeder

Place/Date	**Signature**

Site:	**USZ – Universitätsspital Zürich (adult)**
Principal investigator at the local investigational site:	Dr. M. Galovic

Place/Date	**Signature**

Site:	**Klinik Lengg AG, Swiss Epilepsy Center – Zurich**
Principal investigator at the local investigational site:	Dr. L. Imbach

Place/Date	**Signature**

Site:	**EOC – Ente Ospedaliero Cantonale, Lugano Regional Hospital**
Principal investigator at the local investigational site:	Dr C. Prosperetti

Place/Date	**Signature**

Table of Contents

SYNOPSIS

Sponsor-Investigator	Centre Hospitalier Universitaire Vaudois (CHUV)
Title:	**EpiSave Step 2** A Multi-Center, Event-Driven Clinical Investigation to Assess the Real-World Performance of the EpiSave Seizure Detection Ecosystem in People with Epilepsy and Generalized Convulsive Seizures (GCS) in Ambulatory Settings
Short title / Investigation ID:	**EpiSave Step 2 :** Outpatient Validation Study
Clinical Investigation Plan, version and date:	**CIP Version**: 3.0 **CIP Version Date**: 29/09/2025
Registration:	**ClinicalTrials.gov**: [Registration number to be assigned] **EU-CTR**: [Registration number to be assigned] **Swiss National Portal**: HumRes
Category and its rationale:	**Category**: Medical Device Category C **Risk Level**: Moderate risk **Justification**:
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	**Name of the MD:** EpiSave EpiSave is a smartwatch application with proprietary GCS detection algorithm developped by the research group NeuroDigital. The application as developed by an Italian company name Uquido. **Smartwatch**: TicWatch Pro 5 (Android Wear OS 2.0+) **Software version:** EpiSave E v2.0 (investigational version)
Stage of development:	Pivotal stage The purpose of this study is to generate robust clinical data on the safety and performance of the device
Background and rationale:	Epilepsy affects approximately 60 million people worldwide, with 25-30% experiencing GCS. 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. Current medically certified seizure detection solutions suffer from critical limitations: - High false-alarm rates (>1/week) - Substantial costs ($250-1,500 USD plus monthly fees) - Limited availability (night-only operation for some devices) - Stigmatizing dedicated wrist devices - Lack of reimbursement in most countries The EpiSave system addresses these limitations through an innovative Android-based smartwatch application designed to detect GCS with high sensitivity and low false alarm rates. The development follows a standardized framework, with EpiSave having successfully completed phase 2 testing, which involved algorithm development and offline validation on data previously collected in EMU where video-EEG serves as a gold standard.
Objectives:	**Primary objective:** To assess EpiSave sensitivity for video-confirmed nocturnal GCS detection in real-world ambulatory settings **Secondary objective:** evaluate the system's performance in detecting GCS during different time periods, evaluate false alarm rate, caregiver response, seizure duration precision, device usability, quality of life impact

Outcomes:	**Primary outcome:** EpiSave sensitivity for video-confirmed nocturnal GCS detection **Secondary outcomes:** false alarm rate, caregiver response time, seizure duration precision, device usability score, quality of life Impact
Design:	Prospective, interventional, multi-centre, event-driven clinical investigation Single-arm, open-label study
Inclusion / exclusion criteria:	Patients eligible for inclusion in the study must meet all of the following criteria: be over 6 years of age at the time of enrolment; have a confirmed diagnosis of drug-resistant epilepsy, documented by a neurologist; have experienced ≥2 GCS in the past 12 months, including ≥2 nocturnal GCS per year; be able to wear and feel comfortable wearing a smartwatch; own a compatible smartphone; have a caregiver living nearby who can intervene quickly if needed; provide informed consent (or have it provided by a legal guardian, if applicable). Participants will be excluded if they meet any of the following criteria: Age < 6 years, uncertain or unconfirmed diagnosis of drug-resistant epilepsy; GCS frequency <2 GCS during the last 12 months or <2 nocturnal GCS per year; not be able or not feel comfortable wearing a smartwatch; haven't a caregiver living nearby who can intervene quickly if needed; unable to provide informed consent or assent and no legal representative available. **Vulnerable Participants:** The EpiSave study include paediatric participants (6-17 years) and those with cognitive limitations, as these vulnerable populations are particularly at risk of SUDEP, especially due to their inability to alert others or reposition themselves after a generalized seizure. Their inclusion is essential to evaluate the effectiveness of seizure detection devices, as their specific needs cannot be studied indirectly.
Measurements and procedures:	The participant must wear the smartwatch continuously during the day, with the application active, preferably on the wrist of the non-dominant arm. The smartwatch provides continuous 24/7 monitoring and records PPG data for 15 minutes following each detected seizure. The EpiSave algorithm detects GCS in real time and automatically sends an SMS alert to the designated caregiver, notifying them of the seizure event and the patient's geographic location. The patient will complete questionnaires on quality of life and device usability. To confirm whether nocturnal seizures are occurring, participants will be asked to install a camera at home and record themselves overnight.
Intervention:	**Device:** EpiSave smartwatch application with proprietary GCS detection algorithm **Hardware Platform**: Smartwatch, TicWatch Pro 5 (Android Wear OS 2.0+) **Specifications:** 3D accelerometer (50Hz), gyroscope (50Hz), PPG sensor, SpO2 sensor, GPS, Bluetooth 4.0+, 22-hour battery life, IP67 water resistance **Core Application**: EpiSave v2.0 (investigational version) **Duration of intervention:** 6 months per participant, up to 24 months total recruitment period. **Mode of Action:** - Continuous monitoring of motion data via smartwatch 3D-accelerometry sensor - Real-time analysis using proprietary GCS detection algorithm - Upon seizure detection: collection of additional biosignals for 15 minutes post-seizure - Automated dual-alert system to patient and caregiver

Control intervention (if applicable):	No Active Comparator (Single-arm study design) **Historical Controls:** Comparison with published performance metrics from current certified devices **Internal Controls:** Comparison with Phase 2 EMU validation results
Number of subjects with rationale:	Recruitment of up to 100 patients.
Duration of the investigation:	21 months
Investigation schedule:	First- subject –In (planned): Month 3 Last- subject –Out (planned): Month 18-20
Investigators:	**Prof. Dr. med. Philippe Ryvlin** **Centre Hospitalier Universitaire Vaudois (CHUV)** **Address: Rue du Bugnon 46, 1011 Lausanne, Switzerland** **Email: philippe.ryvlin@chuv.ch** **Phone: +41 21 314 39 66** Prof. G Ramantani Pr. S. Vuillemoz Dr. M. Hardmeier Dr. O. Henning Pr. A. Datta Dr. C. Friedrichs-Maeder Dr. M. Galovic Dr. L. Imbach Dr C. Prosperetti Pr. C. Baumgartner Pr. E. Trinka Pr. S. Beniczky Pr. S. Rheims Pr. M. Holtkamp Pr. R. Surges Pr. F. Rosenow
Investigational Site:	Multicentric multinational investigation with: - 6 centres in Switzerland (Lausanne, Geneva, Basel, Berne, Zürich, Lugano) - 3 centres in Germany (Frankfurt, Bonn, Berlin) - 2 centres in Austria (Vienna, Salzburg) - 2 centres in Denmark (Copenhagen, Dianalund) - 1 centre in France (Lyon) - 1 centre in Norway (Oslo)
Statistical considerations:	Regulatory Requirement: Aligns with FDA/CE guidelines for medical device validation studies Literature-Based: Based on published recommendations for phase 4 seizure detection studies Power Calculation: Provides 90% power to detect sensitivity ≥90% with 95% confidence Event-Driven Design: Ensures adequate statistical power regardless of recruitment timeline Dropout Consideration: Accounts for 20% anticipated dropout rate Recruitment Timeline: 24 months (≤1 PWE/4 months/centre)

Compliance statement:	This investigation will be conducted in full compliance with the CIP, the current version of the Declaration of Helsinki, ISO 14155:2020 ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements. *If safety reporting in this investigation is not fully compliant to the version of ISO 14155, details must be described in section 10.3.*

ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority (e.g. Swissmedic)
CE	European Conformity marking
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO	Ordinance on Clinical Trials in Human Research *(in German KlinV, in French Oclin, in Italian OSRUm)*
ClinO-MD	Ordinance on Clinical Trials with Medical Devices *(in German: KlinV-Mep, in French: Oclin-Dim, in Italian: OSRUm-Dmed)*
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
DD	Device Deficiency
DMC / DSMC	Data Monitoring Committee, Data Safety Monitoring Committee
FADP	Federal Act Data Protection
FBTCS	Focal to Bilateral Tonic-Clonic Seizures
GCS	Generalized Convulsive Seizures
GDPR	EU General Data Protection Regulation
GTCS	Generalized Tonic-Clonic Seizures
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH-GCP	International Council for Harmonisation – guidelines of Good Clinical Practice
IECs	Independent Ethics Committees
IFU	Instruction For Use
IRBs	Institutional Review Boards
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
MedDO	Medical Devices Ordinance *(in German: MepV, in French: Odim, in Italian: Odmed)*
MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SUDEP	Sudden Unexpected Death in Epilepsy
SOP	Standard Operating Procedure
HumRes	Swiss Human Research Portal
USADE	Unanticipated Serious Adverse Device Effect

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change

INVESTIGATION SCHEDULE

Insert a flow chart (graphic) or tabular listing of schedule of events and assessments and procedures of the investigation (an example is provided below, amend and expand according to the specific investigation). To be repeated in chapter 9.1.

e.g.:

Investigation Periods	Screening	Follow-up visits each month by phone during monitoring with smartwatch and camera					End of study
Visit	1	2	3	4	5	6	7
Time (week)	0	4	8	12	16	20	24
Patient Information	x						
Patient consent (ICF)	x						
Demographics	x						
Medical History	x						
In- /Exclusion Criteria	x						
Smartwatch provided to participant	x						
Participant and caregiver training	x						
System validation and testing	x						
Confirmation of alert system functionality	x						
QOLIE-31 questionnaire	x						x
Compliance assessment		x	x	x	x	x	x
Adverse Events, Adverse device effects		x	x	x	x	x	x
Device performance evaluation		x	x	x	x	x	x
Data collection verification		x	x	x	x	x	x
Device Deficiencies		x	x	x	x	x	x
Smartwatch return							x
Download and deletion of data							x
SUS questionnaire							x
Custom EpiSave questionnaire							x

1. INVESTIGATION ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

The sponsor of this investigation is the CHUV | Centre hospitalier universitaire vaudois. The CHUV is responsible for initiating, designing, and overseeing the clinical investigation, ensuring regulatory, ethical, financial, and legal compliance. They manage data collection, monitoring, and analysis, and ensure the integrity of results. The sponsor also prepares and submits the final clinical report. If acting as Sponsor-Investigator, they additionally conduct the study directly at the investigation site.

Sponsor contact details:

- Address: Rue du Bugnon 46, 1011 Lausanne, Switzerland
- Contact Person: Prof. Dr. med. Philippe Ryvlin
- Email: philippe.ryvlin@chuv.ch
- Phone: +41 21 314 39 66

1.2 Principal Investigators

Swiss Centres:

Investigator of the CHUV | Centre hospitalier universitaire vaudois
Name: Prof. Dr. med. Philippe Ryvlin
Title: Professor of Neurology, Head of Epileptology
Address: Rue du Bugnon 46, 1011 Lausanne, Switzerland
Email : philippe.ryvlin@chuv.ch
Phone : +41 21 314 3966

Investigator of the HUG - Geneva University Hospitals
Name: Pr. S. Vuillemoz
Title:
Address:
Email:
Phone:

Investigator of USB – Universitätsspital Basel (adult)
Name: Dr. M. Hardmeier
Title:
Address:
Email:
Phone:

Investigator of the UKBB - Universitäts-Kinderspital beider Basel (pediatric)
Name: Pr. A. Datta
Title:
Address:
Email:
Phone:

Investigator of the InselSpital – Universitätsspital Bern
Name: Dr. C. Friedrichs-Maeder
Title:
Address:
Email:
Phone:

Investigator of the USZ – Universitätsspital Zürich (adult)
Name: Dr. M. Galovic
Title:
Address:
Email:
Phone:

Investigator of the Klinik Lengg AG, Swiss Epilepsy Center – Zurich
Name: Dr. L. Imbach
Title:
Address:
Email:
Phone:

Investigator of the EOC – Ente Ospedaliero Cantonale, Lugano Regional Hospital
Name: Dr. C. Prosperetti
Title:
Address:
Email:
Phone:

Austria Centres:

Investigator of the KL - Karl Landsteiner Institute – Vienna
Name: Pr. C. Baumgartner
Title:
Address:
Email:
Phone:

Investigator of the SALK - Landeskrankenhaus Salzburg – Salzburg
Name: Pr. E. Trinka
Title:
Address:
Email:
Phone:

Denmark Centres:

Investigator of Rigshospitalet – Copenhagen
Name: Pr. S. Beniczky
Title:
Address:
Email:
Phone:

Investigator of the Filadelfia, The danish Epilepsy Hospital – Dianalund
Name: Pr. S. Beniczky
Title:
Address:
Email:
Phone:

France Centre:

Investigator of HCL - Hospices Civils of Lyon
Name: Pr. S. Rheims
Title:
Address:
Email:
Phone:

Germany Centres:

Investigator of Charité, Universitätsmedizin Berlin
Name: Pr. M. Holtkamp
Title:
Address:
Email:
Phone:

Investigator of UKB – Universitätsklinikum Bonn
Name: Pr. R. Surges
Title:
Address:
Email:
Phone:

Investigator of University Hospital Frankfurt
Name: Pr. F. Rosenow
Title:
Address:
Email:
Phone:

Norway Centre:

Investigator of Oslo University Hospital
Name: Pr. M. Lossius
Title:
Address:
Email:
Phone:

1.3 Statistician ("Biostatistician")

Name: Mireille Moser
Tittle: Master in Statistics
Adress: Centre Hospitalier Universitaire Vaudois (CHUV)
Email: mireille.moser@chuv.ch
Tel: +41 79 556 28 75
Role: Statistical analysis and study design consultation

1.4 Laboratory

Not applicable for this study.

1.5 Monitoring institution

The investigation will be internally monitored by the Clinical Research Unit of the CHUV.

1.6 Data Safety Monitoring Committee

The Independent Data Safety Monitoring Board (DSMC) is composed of neurologist, statistician and ethicist in order to safe oversight and interim analysis review.

1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

2 ETHICAL AND REGULATORY ASPECTS

The final positive decision of the CEC and of the CA on the conduct of the investigation will be made and given in writing to the Sponsor before the investigation can start (Category C investigations: In Switzerland the national approval is issued by Swissmedic and includes the approval of the CEC). Additional requirements set by the authorities must be implemented.

2.1 Registration of the investigation

Registry	Registration number	Date
ClinicalTrials.gov	NCT	Not obtained yet
EU Clinical Trials Register (EU-CTR)	EudraCT	Not obtained yet
Swiss National Portal	HumRes	Not obtained yet

2.2 Categorisation of the investigation

In this investigation, the medical device being tested is EpiSave, an application designed to detect GCS and alert the patient's relatives. The application itself doesn't have CE marking (European Conformity marking); however, it is used on a connected smartwatch (TicWatch Pro 5) that is CE-marked. This investigation is an interventional study involving a medical device classified as Category C (according to Art. 6 ClinO-MD).

The device under investigation is considered to present a moderate risk level.

According to the regulatory pathway, approval from Swissmedic is required under the ClinO-MD ordinance.

3 Clinical trials correspond to category C if:

b. the product does not bear a conformity mark according to Article 13 MedDO (subcategory C2); or

c. the making available on the market, the putting into service or the use of the product in Switzerland is prohibited (subcategory C3).

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator will submit the investigation to the CEC and obtain ethical committee approval before the start of the investigation. Each PI at each participating investigational site ensures that approval from the CEC is obtained and filed in the Investigator site file before the investigation starts.

2.3.1 Reporting duties to the Competent Ethics Committee

Amendments are reported according to Art. 15 ClinO-MD (see also 2.10).

The regular or premature end of the investigation as well as the interruption of the investigation is reported to the CEC within 15 days (within 24 hours if it is due to security reasons) (Art. 36 ClinO-MD). The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation. A summary in easily understandable terms must be included with the final report (Art. 37 ClinO-MD).

2.4 Competent Authorities (CA)

The Sponsor-Investigator will submit the investigation to the CA and obtain regulatory approval before the start of the investigation. Each PI at each participating investigational site ensures that approval from the CA is obtained and filed in the Investigator site file before the investigation starts.

2.4.1 Reporting duties to the competent authorities

Mention the reporting duties and allowed time frame for the reporting to the CA including the reporting duties in case of planned or premature end of the investigation and the final report. Reporting duties and timelines are the same as for CEC, except of non-substantial amendments that shall be reported as soon as possible (Art. 20 ClinO-MD). Refer to chapter 10 for safety reporting. Amendments are reported according to Art. 20 ClinO-MD (see also 2.10). A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation. A summary in easily understandable terms must be included with the final report (Art. 38, resp. 37 ClinO-MD).

Amendments to the CIP are reported according to Art. 20 ClinO-MD (see also chapter 2.10).

For safety reporting including reporting of safety and protective measures, as well as the safety and general progress report (jointly “annual report”) refer to chapter 10.

The regular or premature termination of the investigation as well as the interruption of the investigation is reported to the CA within 15 days and within 24 hours if it is due to safety reasons (Art. 36 ClinO-MD). The reasons for a premature termination or an interruption shall be explained.

A final report is submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation. A summary in easily understandable terms will be included with the final report (Art. 37 ClinO-MD).

2.5 Ethical Conduct of the Investigation

The investigation will be carried out according to the CIP and with principles enunciated in the current version of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 (MDR), the Norms ISO14155 and ISO14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, the Swiss Human Research Act (HRA) and its Ordinances and Swiss regulatory authority’s requirements.

2.6 Declaration of interests

All investigators and study personnel will declare any potential conflicts of interest (independence, intellectual, financial, proprietary etc.). No financial interests in the EpiSave device or competing products are permitted.

2.7 Patient Information and Informed Consent

The PI explains to each subject the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the investigation is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the investigation. Enough time is given to the subjects.

The subjects are informed that authorised individuals other than their treating physician may examine his/her medical records. All subjects a given a subject information sheet and a consent form describing the investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation. The formal consent of a subject, using the consent form approved by the CEC, is obtained before the subject is submitted to any study procedure. The subject should read, understand, and voluntarily agree before signing and dating the informed consent form and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee, when applicable). The subjects are informed, with their approval, that their personal physicians are informed about the subjects’ participation in the clinical investigation, when applicable. The signed consent form it is retained as part of the clinical investigation documents. The subject’s medical records are clearly marked to indicate that the subject is enrolled in the clinical investigation. The subject is provided with well-defined procedures for possible emergency situations related to the performance study. The PI makes the necessary arrangements for emergency treatment.

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.

2.8 Subject privacy and confidentiality

The Sponsor and the PI affirm and uphold the principle of the subjects' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the subjects shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

The investigator 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. 5, ClinO-MD).

Individual subject medical information obtained as a result of this investigation is considered confidential and disclosure to third parties is prohibited.

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.

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.

The Principal Investigator and participating institutions shall permit investigation-related monitoring, audits, review by Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and regulatory inspections. To support these activities, direct access to all relevant source data and documents (including medical records and informed consent forms) will be granted to authorized personnel. This access will be provided in compliance with applicable data protection regulations, including the Swiss Federal Act on Data Protection (FADP) and the EU General Data Protection Regulation (GDPR).

For data verification purposes, authorised representatives of the Sponsor, the CA or a CEC may require direct access to parts of the medical records relevant to the investigation, including subjects' medical history.

2.9 Early termination of the investigation

The Sponsor may terminate the investigation prematurely according to certain circumstances, for example:

- Safety concerns,
- Regulatory authority decision,

- Sponsor decision,
- Insufficient subject recruitment,
- Alterations in accepted clinical practice that make the continuation of the investigation unwise,
- Early evidence of benefit or harm of the experimental intervention

2.10 Clinical investigation plan amendments

Amendments to the Clinical Investigation Plan may only be initiated and approved by the Sponsor. Suggestions may be submitted by investigators, clinical experts, or regulatory authorities, but require Sponsor approval before implementation.

Substantial amendments (e.g., changes to eligibility criteria, outcomes, analyses, or safety procedures) will be promptly communicated to all relevant parties, including: investigators, Competent Authorities,ethics Committees (CEC/IRB/IEC), study participants (if applicable), Clinical trial registries, Scientific journals (if previously published), other stakeholders directly involved.

All amendments will be documented, dated, and version-controlled, and the latest CIP version will be made available to study personnel. Updated consent forms will be provided and re-consent obtained if required by regulations.

Substantial amendments are only implemented after approval by the CEC (Art. 15 ClinO-MD) and, for category C investigations, after approval by the CA also (Art. 20 ClinO-MD). The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of the subjects may proceed without prior approval by the Sponsor and the CEC (and for category C investigations without prior approval by the CA). Such deviations shall be documented and reported to the Sponsor and the CEC (and to the CA for category C investigations) within 2 days (Art. 34 ClinO-MD).

All non-substantial amendments are communicated to the CEC annually together with the safety report / general progress report of the clinical investigation (Art. 15 ClinO-MD), and for category C clinical investigations to the CA as soon as possible (Art. 20 ClinO-MD). The report will include any deviations from the CIP that may have affected the rights, safety or well-being of the subject or the scientific integrity of the investigation (ISO14155).

2.11 Deviation from the Clinical Investigation Plan

The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Write a statement that the investigator is not allowed to deviate from the CIP, except as specified in 2.10. Describe the procedure for recording, reporting and analysing CIP deviations. Describe corrective and preventive actions and investigator disqualification criteria.

3 BACKGROUND AND RATIONALE

3.1 Background and Rationale for the clinical investigation

3.1.1 Clinical Need and Medical Problem

Describe the relevance of the clinical investigation in the context of the state of the art of clinical practice and the proposed benefits of the new device (Annex XV, chapter 2, Art. 3.2 MDR).

Describe the research question, including summary of relevant investigations (published and unpublished) examining benefits and harms for each intervention; including disease background, e.g. epidemiology and current standard of care (if relevant). Refer to literature where is the current lack of information, why the investigation will be done and establish its context by giving a clear statement on its purpose.

Are “sex and gender” dimensions relevant to the topic of the study (specifying genetic/biological or social mechanisms at play)? To address this question, refer to the recommendations “sex and gender in research involving humans according to the HRA” (swissethics.ch / topics / sex and gender equitable research). If it is considered that “sex and gender” dimensions are not relevant, provide a justification.

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures, affecting approximately 50 million people worldwide, making it one of the most common neurological diseases globally (1). The International League Against Epilepsy (ILAE) defines epilepsy as a disease of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (1).

Among the various seizure types, generalized convulsive seizures (GCS), including generalized tonic-clonic seizures (GTCS) and focal to bilateral tonic-clonic seizures (FBTCS), represent one of the most severe manifestations of epilepsy. These seizures are associated with a 15-20 times higher risk of sudden unexpected death in epilepsy (SUDEP) compared to other seizure types (2), with physical injury occurring in 30-50% of GCS episodes including falls, fractures, and head trauma. The significant impact on quality of life encompasses fear of seizures, social stigma, and activity restrictions, while the economic burden is substantial with direct and indirect costs estimated at $15.5 billion annually in the United States alone (9).

Drug-resistant epilepsy affects approximately 30% of individuals with epilepsy, defined as failure to achieve sustained seizure freedom despite adequate trials of at least two appropriately chosen and tolerated anti-seizure medications (ASMs). This population faces particularly high risks, with SUDEP rates of 1.1-5.9 per 1,000 person-years, compared to 0.1-0.3 per 1,000 person-years in the general epilepsy population (2,3). The devastating nature of SUDEP is underscored by the fact that it affects approximately 60,000 people with epilepsy worldwide each year, with an incidence of 1.2/1,000 patient-years (3,4), often affecting young adults as well as children and adolescents (5,6), particularly those with developmental and epileptic encephalopathies (DEE) where the incidence can reach 6/1,000 patient-years in conditions such as Dravet syndrome (7,8).

3.1.2 Nocturnal Seizures and SUDEP Risk

Nocturnal GCS represent a critical clinical challenge due to their association with SUDEP, which accounts for 8-17% of all deaths in people with epilepsy (2). The term "unexpected" reflects the fact that most patients and their families are unaware of SUDEP risk, as they are rarely informed by their physicians (10). SUDEP victims are typically found deceased in bed by family members or caregivers (11,12), who often report profound and lasting grief, guilt, and trauma. Many families believe that a reliable GCS detection device could have saved their loved ones.

Most SUDEP cases are precipitated by a GCS followed by a fatal post-ictal respiratory arrest, frequently exacerbated by the prone position (12). These events usually occur at night, while the individual is sleeping alone, limiting the chance for timely intervention (12,13). Established risk factors include the presence, frequency and nocturnal occurrence of GCS, living or sleeping alone, and non-adherence to antiseizure medication (13-17). Recently, additional risk factors have been identified, such as peri-ictal apnea (16,17), extratemporal epileptogenic zones (particularly perisylvian) (19), high body mass index (18-21), and lower polygenic risk scores for longevity and intelligence (21).

Clinical evidence demonstrates that nocturnal GCS are associated with more severe hypoxemia (oxygen saturation <70% in 50% of cases), increased postictal generalized EEG suppression (PGES), prolonged postictal immobility periods, and higher risk of cardiac arrhythmias and respiratory depression (12). The MORTEMUS study, the most cited original SUDEP study, provided the original description of

the sequence of events leading to SUDEP following a GCS, establishing the critical importance of timely intervention during the post-ictal period (12).

3.1.3 Current Limitations in Seizure Detection

Traditional monitoring approaches face significant limitations that compromise effective seizure detection and SUDEP prevention. Patient self-reporting is unreliable, with studies showing that 85% of nocturnal seizures go unreported (36), while caregiver observation is limited by sleep patterns and physical proximity. Inpatient video-EEG monitoring, while providing gold standard data, is expensive, short-term, and not representative of the home environment where most SUDEP events occur (12). Seizure diaries are subject to recall bias and underreporting, further limiting their clinical utility.

The 2020 practice guideline of the International League Against Epilepsy (ILAE) and the International Federation of Clinical Neurophysiology concluded that there is high-level evidence supporting the accuracy of automated GCS detection and recommends the use of clinically validated wearable devices in selected patients (34). However, currently available medically certified GCS detection devices face several critical limitations that limit their widespread adoption and effectiveness.

Currently, four medically certified GCS detection devices are available: EpiMonitor (Empatica, wrist-worn, 3D-Acc and EDA), Epi-Care Mobile/Free (Danish Care Technology, wrist-worn, 3D-Acc only), NightWatch (LivAssured, upper arm at night, 3D-Acc and PPG), and EpiWatch (App on the Apple Watch, 3D-Acc and PPG) (35,42-47). While these devices demonstrate varying levels of sensitivity (65-100%) and false alarm rates (0.05-0.7 per day) (42-47), they suffer from several critical limitations including high false alarm rates contributing to "alarm fatigue" and device abandonment, stigmatization and usability issues from wearing dedicated devices, limited functionality including the inability to cancel false alarms, restricted operation windows with some devices designed for nighttime use only, and limited access and affordability especially outside Europe and the United States.

Cost represents a particularly critical barrier to adoption, as most health systems do not reimburse GCS detectors, and many people with drug-resistant epilepsy have limited income to afford their cost. A recent US survey identified cost as the primary reason for non-use of GCS detectors in the United States. Current pricing ranges from $250-1,500 USD plus monthly fees for most devices, with only EpiWatch available at device cost only but limited to the Apple ecosystem. These limitations result in poor adoption rates, with only 5-10% of eligible patients using seizure detection devices.

3.1.4 Scientific Background and EpiSave Development

The EpiSave system was developed following a standardized framework for seizure detection device validation (41), building upon two SNSF-funded grants (#320030_179240 and #CRSII5_193813) that enabled the creation of the world's largest dataset combining video-EEG and wrist-worn sensor recordings in people with epilepsy, including data from 398 patients and over 600 seizures—104 of which were GCS (55). This unique dataset enabled the development of EpiSave, an innovative deep learning algorithm designed to detect GCS using only 3D accelerometry (55).

The development process involved algorithm development based on the above SNSF-funded projects database containing data from 400+ patients with 100+ GCS events, technical innovation through ensemble-based convolutional neural network architecture with tunable sensitivity, and Phase 2 validation through a multi-center study across eight European epilepsy monitoring units. The algorithm was successfully embedded into a low-cost off-the-shelf Android-based smartwatch (TicWatch Pro) with the help of the Embedded System Laboratory at EPFL, and a professional-grade companion app was developed to implement key functionalities including user account management, caregiver notifications, false alarm cancellation, and secure data streaming.

Phase 2 Clinical Validation Results (55) demonstrated that the EpiSave algorithm was developed and validated through a prospective multi-center study collecting data from 384 patients undergoing video-electroencephalography (vEEG) monitoring with wrist-worn three-dimensional (3D) accelerometer sensors. The training set comprised 37 patients with 54 GCS across 4,922 hours (~206 days) of recording, while the independent test set included 347 patients across 31,479 hours (~1,312 days) of recording, including 33 patients with 49 GCS (55).

Performance metrics demonstrated 96% sensitivity (95% CI: 90%-100%) on the independent test set, with a false alarm rate of <1/8 days (95% CI: 1/9-1/7 days) and 1 false alarm per 61 nights (55). Detection latency was a median of 26 seconds after GCS onset, while the algorithm's tunable sensitivity allows achievement of up to 100% sensitivity or reduction of false alarms to 1/100 days through quantile adjustment (55). The ensemble-based CNN architecture represents a significant advancement in single-sensor CS detection, introducing two key innovations: an ensemble approach providing inherent robustness against individual model variations, and quantile-based aggregation enabling adaptive

sensitivity tuning without requiring model retraining, offering clinicians and patients flexibility in balancing detection sensitivity against false alarms (55).

3.2 Identification and description of the Investigational Medical Device

In case of systems that consist of several devices, list all the devices.

Medical Device(s) (MD): brand name(s), manufacturer(s), name or number of the model(s)/type(s), incl. software version(s), software algorithms, and accessories if any, to permit full identification (e.g. add a picture of the MD). Whether the device is CE marked for a medical use or for other uses (electrical equipment, pressure vessels, other), give the intended purpose of the MD. See Art. 120 Abs 2 MDR (link) for the period of validity of certificates there were issued in accordance with the European directives directive 93/42/EEC or 90/385/EEC. Describe the populations for which the MD is intended. For CE marked devices, give all deviations from the original CE-marked instructions for use (off-label use) or statement that there are no such deviations. If the MD has a modular design, indicate to which module modifications have been made, and which module/modification is the focus of the investigation. Include description of device materials in contact with body tissues and/or fluids; this shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biological active substances and reference to compliance with applicable national regulations.

Indicate the necessary training and experience required for the use of the MD and the medical and/or surgical procedures involved in the use of the MD.

Give reference to the IB and IFU.

3.2.1 Device Overview

The investigational medical device under evaluation is the EpiSave Seizure Detection System, a Class IIa medical device (proposed) manufactured by NeuroDigital@NeuroTech Group. The device is currently in investigational status for clinical investigation, representing a non-profit academic initiative with no intention to commercialize, ensuring the widest possible access to GCS detection while serving the ultimate goals of reducing SUDEP risk and promoting SUDEP biomarker discovery through large-scale data sharing.

3.2.2 Hardware Platform

The EpiSave system utilizes the TicWatch Pro 5 smartwatch platform running Android Wear OS 2.0+, representing pre-certified hardware in the form of CE-marked off-the-shelf smartwatches. The hardware platform meets comprehensive safety standards including IEC 60601-1 and IEC 60601-1-2 for electromagnetic compatibility, ISO 10993 standards for skin contact biocompatibility, and IEC 62133 battery safety standards.

The technical specifications include a 3D accelerometer with minimum 50Hz sampling rate, gyroscope with minimum 50Hz sampling rate, photoplethysmography (PPG) for heart rate monitoring, blood oxygen saturation (SpO2) monitoring, GPS capability for location services and caregiver alerts, Bluetooth 4.0+ connectivity for data transmission, 24-hour continuous operation battery life, IP67 or higher water resistance, and compatibility with Android 8.0+ and iOS 12.0+ smartphones. These specifications ensure robust performance in real-world ambulatory settings while maintaining user comfort and device reliability.

3.2.3 Software Components

The EpiSave software architecture comprises a core application (EpiSave v2.0 investigational version) designed as an Android Wear OS application with optimized resource requirements including less than 50MB installed size, less than 100MB RAM usage, and less than 200MB storage requirements for data logging. The seizure detection algorithm represents a proprietary machine learning system that processes 3D accelerometry and gyroscope data through real-time signal analysis with less than 2 second latency, utilizing a frozen version 2.0 algorithm (no updates during study) trained on the previous projects database containing data from 400+ patients and 100+ GCS events.

The data collection module provides continuous 24/7 accelerometry and gyroscope recording with 15-minute enhanced monitoring post-detection, ensuring comprehensive seizure documentation. All data is protected through AES-256 encryption for stored data, with local storage utilizing a 7-day rolling buffer system combined with cloud synchronization for data integrity and accessibility.

3.2.4 Communication and Alert System

The EpiSave communication and alert system encompasses a smartphone application compatible with Android (8.0+) and iOS (12.0+) platforms, providing seizure alerts, caregiver notifications, and data synchronization capabilities. The alert system utilizes multiple communication methods including SMS, push notifications, and in-app alerts, with GPS coordinates integrated into seizure alerts for precise location information. The system maintains offline capability through local data storage with synchronization when connectivity is restored, ensuring continuous monitoring even during network interruptions.

The caregiver alert system implements a dual-alert approach with primary alerts delivered via SMS containing patient location and seizure detection time, supplemented by secondary push notifications to the caregiver smartphone app. Alert content includes patient identification, location, timestamp, and seizure type information, while the system incorporates response confirmation mechanisms with caregiver acknowledgment and response time logging to enable assessment of intervention effectiveness and system performance.

3.3 Preclinical Evidence

Summarise, if applicable, the available non-clinical data (published or available unpublished data) that could have clinical relevance and justify its use in humans. Preclinical evidence can be omitted in the CIP if the MD is CE marked as medical device and if there is no off-label use.

NA

3.4 Clinical Evidence to Date

Summarise the available clinical experience with relevance to the investigation (published or available unpublished data that should be based on or referred to a systematic review). This shall include an analysis of adverse device effects, benefits, and any history of modification or recall. If none is available, include a statement that there is no available clinical experience to date on the MD. Also include postmarked experience if applicable.

3.4.1 Phase 2 Clinical Validation Study

The Phase 2 clinical validation study employed a prospective, multi-center, observational design across eight European epilepsy monitoring units, representing the most comprehensive validation of a seizure detection algorithm to date (55). The study population comprised 384 patients with an age range of 6-80 years, encompassing focal, generalized, and combined epilepsies, with all seizure types included but particular focus on GCS (55). Data collection spanned 4,922 hours of training data and 31,479 hours of test data, utilizing 3D accelerometer at 32Hz sampling rate, with video-EEG monitoring serving as the gold standard for expert annotation (55).

The study documented 54 GCS in the training set and 49 GCS in the test set, providing robust statistical power for performance evaluation (55). Primary results demonstrated 96% sensitivity (95% CI: 90%-100%) on the independent test set, with a false alarm rate of less than 1/8 days (95% CI: 1/9-1/7 days) and detection latency of median 26 seconds (IQR: 15-45 seconds) (55).

3.4.2 Comparison with Existing Devices

Performance comparison with existing medically certified seizure detection devices demonstrates EpiSave's superior performance across multiple metrics (55). EpiSave achieved 96% sensitivity with less than 1/8 days false alarm rate in a study population of 384 patients over 1,312 days, compared to EpiMonitor (95-98% sensitivity, variable false alarm rate, 135 patients, 6 months), Nightwatch (80-100% sensitivity, 0.7/night false alarm rate, 28 patients, 3 months), and EpiCare Mobile (65-90% sensitivity, variable false alarm rate, 15 patients, 1 month) (42-47). EpiSave's key advantages include higher sensitivity (96% vs. 80-98% for other devices), lower false alarm rate (less than 1/8 days vs. 0.7-1.0 per day), larger validation dataset (384 patients vs. 15-135 patients), longer study duration (1,312 days vs. 1-180 days), and tunable sensitivity adjustable based on patient needs (55).

3.4.3 Real-World Performance Considerations

The transition from EMU to home environment presents both advantages and challenges that necessitate comprehensive ambulatory validation. EMU settings provide controlled environments with continuous video monitoring and expert staff, but represent artificial settings with limited movement and

potential stress factors that may not reflect real-world usage patterns. Home environments offer natural settings with typical daily activities and comfort, but present challenges including environmental noise, device wear compliance issues, and variable caregiver availability.

The Phase 2 EMU validation provides proof-of-concept evidence, but real-world ambulatory validation is essential for clinical utility assessment of device performance in actual use conditions, user acceptance evaluation of device usability and patient satisfaction, and safety assessment monitoring of device-related adverse events in home settings. This comprehensive validation approach ensures that EpiSave's performance translates effectively from controlled clinical environments to real-world ambulatory settings where the device will be used by patients and caregivers.

3.5 Justification for the design of the clinical investigation

Provide the justification for the use of the MD (use, method of application, regimen, period of intended use, …), which shall be based on the conclusions of the evaluation, as specified in the above chapters 3, 3.1-3.4).

3.5.1 Study Design Rationale

The study employs an event-driven design targeting ≥75 nocturnal GCS events in ≥50 participants, which is justified by statistical power providing 90% power to detect sensitivity ≥90% with 95% confidence, clinical relevance focusing on the most clinically significant seizure type (nocturnal GCS), and SUDEP prevention addressing the highest-risk period for SUDEP occurrence. These figures correspond to the standards proposed for phase 4 studies of seizure detection devices in ambulatory patients (72), with anticipated recruitment of 65-80% of patients who will eventually suffer a nocturnal GCS for which both video recordings and EpiSave data will be available for analysis, translating into the recruitment of 77 to 100 people with epilepsy over 24 months.

The single-arm, open-label design is appropriate because medical device validation represents the standard approach for device performance studies, historical controls provide sufficient comparison data available from published literature, and clinical equipoise exists as there is no established standard of care for seizure detection devices. This design approach ensures comprehensive evaluation of EpiSave's performance while maintaining scientific rigor and clinical relevance.

3.5.2 Ambulatory Setting Rationale

The ambulatory validation study is essential because environmental differences between home environments and EMU settings may significantly affect device performance, natural daily activities and movement patterns may impact detection accuracy, 24-hour daily wear requirements need validation in real-world conditions, and caregiver integration and alert system effectiveness require real-world testing to ensure optimal clinical utility. This represents a significant methodological advancement for evaluating GCS detector performance at home, which has not been used in previous studies, with all video recordings stored locally on a memory stick within the camera exclusively, with no data transfer or streaming involved to protect patient privacy.

Clinical investigation requirements mandate this approach, as real-world performance data is essential for understanding device effectiveness in clinical practice, user acceptance evaluation requires assessment in natural environments, and safety monitoring needs to capture device-related events in home settings. The study design incorporates autonomous camera systems for nocturnal monitoring to generate ground truth for nocturnal GCS detection in real-world environments, with patients and caregivers invited to show recordings of detected and missed GCS events, as well as false alarms, to their physician during follow-up visits.

3.5.3 Nocturnal Focus Rationale

The focus on nocturnal GCS detection is justified by the critical role of nocturnal seizures in SUDEP prevention, as 70-80% of SUDEP cases occur during sleep, nocturnal GCS are associated with more severe hypoxemia, postictal immobility periods are longer during sleep, and caregiver response is typically delayed for nocturnal seizures. This nocturnal focus addresses the highest-risk period for SUDEP occurrence and represents the most clinically significant application of seizure detection technology.

The clinical impact encompasses immediate benefits through reliable nocturnal GCS detection for high-risk patients, short-term benefits through timely caregiver intervention potentially reducing SUDEP risk, and long-term benefits through improved quality of life and reduced seizure-related anxiety. The study design specifically targets nocturnal GCS as the primary endpoint, with secondary endpoints including EpiSave sensitivity for daytime and nighttime GCS, false alarm rate, delays between GCS onset and detection, and caregiver intervention times, ensuring comprehensive evaluation of the device's performance across all seizure timing scenarios.

3.6 Explanation for choice of comparator

Explain the rationale for the comparator (other MD, other therapy (e.g. active control), sham MD/intervention or no treatment, or historical data) used in the control group. In addition to the scientific rational, give the ethical justification for the choice of the comparator.

NA

3.7 Risk evaluation (Risk-to-Benefits rationale)

Note: The risk management process, which includes risk analysis, risk-to-benefit assessment and risk control is described in ISO14971.

Describe in this chapter the anticipated adverse device effects, residual risks associated with the MD and the procedures involved in its use. Indicate the risks due to interaction with concomitant treatments. Risks associated with participation in the investigation shall be described and possible interactions with concurrent medical interventions shall be listed. A statement of the anticipated clinical benefit shall be given, as well as the risk-benefit rationale. This shall include an analysis of adverse device effects and any history of modification or recall in relation to safety and clinical performance in relation to both the device under investigation and the comparator(s).

For investigations without immediate benefit to the subjects, a rationale should be provided stating how the results of the investigation could be beneficial for future subjects due to e.g. improved treatment options a better understanding of the disease, etc.

Describe and discuss measures to control or mitigate the risks (give the reference to the risk analysis report) and how post-investigation care is organised.

Include harm caused directly by the MD, invasive procedures carried out for using the devices (for implantable devices indicate risks for implantation and removal), medical consequences of device deficiencies and side effects (risks due to rescue surgery, etc.), insufficient efficacy, withholding proven therapies from subjects, wrong diagnostic output (false positive or false negative results obtained with diagnostic MD), delaying correct screening/ diagnosis/ treatment in subjects.

3.8 Justification of the choice of the investigation population

Describe the choice of the investigation population and the rationale for it. Provide information on the representativeness of the investigation population in relation to the target population (Annex XV, chapter 2, art 3.6.3 MDR).

Ensure that the criteria for selecting the persons intended to participate and the trial design allow an appropriate representation of the groups of persons who are relevant for answering the scientific question; in particular, they must take into account the distribution of genders and age groups. The exclusion or intended underrepresentation of relevant groups of persons must be stated and justified (Art. 4a ClinO).

Describe how recruitment of the subjects is conducted to ensure “sex and gender” balance is achieved, or give an explanation why this would not be possible and how this imbalance would impact the scientific validity of the investigation result. Refer to the recommendations “sex and gender in research involving humans according to the HRA” (swissethics.ch / topics / sex and gender equitable research) to address “sex and gender” issues in this chapter. *If it is considered that “sex and gender” dimensions are not relevant, provide a justification.*

For vulnerable subjects (e.g. minors, subjects incapable of judgment or subjects under tutelage), the following aspects need to be addressed in the CIP: Rationale for the inclusion of vulnerable subjects (i.e. reasons why comparable results / findings cannot be obtained from adults capable of judgment, Art. 11 HRA).

If both vulnerable and non-vulnerable subjects are foreseen for recruitment: Describe the aspects of the

research question that are specific to the vulnerable subjects. Describe in chapter 11, the numbers needed to evaluate those aspects (for pilot investigations) and the sample size calculation (for pivotal investigations), the stratification process for recruitment of the correct number of vulnerable and non-vulnerable subjects.

3.9 Patient and public involvement

Report if and how patients or members of the public (PPI-contributors) have been involved in the design of the protocol and study-related procedures. For example: "Patients have been involved in preliminary discussion regarding the relevance of the research question, for the choice of outcomes or visit planning. If available, provide a patient and public (PPI) strategy including the role of PPI-contributor(s) as well as objective and influence on the study.

CLINICAL INVESTIGATION OBJECTIVES

Describe the overall, primary and secondary objective(s) of the investigation in a clear and simple form. The primary objective should be clearly marked as such.

Overall Objective

Provide a clear, simple statement describing the overall purpose(s) of the investigation, explaining why the investigation is performed.

To assess the real-world performance of the EPISAVE seizure detection system in detecting generalized convulsive seizures (GCS) in ambulatory patients with epilepsy, with particular focus on nocturnal GCS detection for SUDEP prevention.

Primary Objective

Provide one clear, simple statement describing the primary objective of the investigation (e.g., The investigation seeks primarily to determine the performance of an implanted subcutaneous insulin pump on glucose levels in blood compared to Insulin Pen A).

To assess EpiSave sensitivity for video-confirmed nocturnal GCS detection in real-world ambulatory settings.

Secondary Objectives

Provide a clear, simple statement describing the secondary objectives of the investigation (e.g., Secondary objectives are to assess usability of an implanted subcutaneous insulin pump on glucose levels in blood compared to Insulin Pen B).

1. **Daytime and Nighttime GCS Detection**: To evaluate the system's performance in detecting GCS during different time periods
2. **False Alarm Rate**: To assess the system's false alarm rate in ambulatory settings
3. **Caregiver Response**: To evaluate delays between GCS onset, detection, and caregiver intervention
4. **Seizure Duration Precision**: To assess the precision of GCS and post-ictal immobility duration calculations
5. **Device Usability**: To evaluate device usability scores and adverse events
6. **Quality of Life Impact**: To assess changes in QOLIE-31 scores
7. **Technical Performance**: To evaluate system reliability and technical performance

Safety Objectives

In investigations with efficacy as primary and secondary endpoints safety is always an additional objective.

Provide a clear, simple statement describing the safety objectives of the investigation. (e.g. the investigation aims to assess long-term safety of Device A and its tolerability in terms of allergic reactions against the component B of the device and use of rescue medication).

To assess the tolerability and safety of the EpiSave system in real-world ambulatory settings, including device-related adverse events, psychological impact, and system reliability.

CLINICAL INVESTIGATION OUTCOMES

Describe the primary, secondary, and other outcomes, in the corresponding chapters below, including the specific measurements and variables (e.g., blood sugar levels), analysis metric (e.g., change from baseline, final value, time to event, any evaluation criteria), time point for each outcome etc. Explanation of the clinical relevance of chosen efficacy and safety outcomes is strongly recommended.

Primary Outcome

The primary outcome (or endpoint) is the main result that is measured at a precise time-point or at the end of treatment/intervention to verify whether a given treatment was successful or not.

Provide a short description of the primary outcome variable (usually only one and with regard to efficacy) and the rationale for the choice of outcome. (Safety can also be a primary endpoint in a safety investigation.)

There is only one primary safety and one primary performance endpoint.

Note: a pivotal investigation is carried out for risk/benefit assessment. Both risks and benefits generally need to be primary endpoints and sufficiently powered. Separate sample size calculations are carried out for both parameters (efficacy and safety), the higher n needs to be taken. Note: the statistical analysis needs to be carried out on each specific population separately. A detailed description of the statistical analysis must be given in chapter 11. Statistical Methods.

Other endpoints will be listed as secondary endpoints.

EpiSave sensitivity for video-confirmed nocturnal GCS detection

- **Definition**: Proportion of true nocturnal GCS detected by **EpiSave** out of total verified nocturnal GCS
- **Validation Method**: Home video recordings with autonomous camera system
- **Statistical Analysis**: Sensitivity calculation with 95% confidence intervals
- **Target**: ≥90% sensitivity

Secondary Outcomes

Provide a short description of the secondary outcome variables and the rationale for the choice of outcomes.

1. **False Alarm Rate**
   - **Definition**: Number of false alarms per patient per day
   - **Validation Method**: Patient/caregiver feedback through app interface
   - **Target**: <1 false alarm per week
2. **Caregiver Response Time**
   - **Definition**: Time from GCS onset to caregiver intervention
   - **Measurement**: Automatically logged response times
   - **Target**: ≤5 minutes for 90% of alerts
3. **Seizure Duration Precision**
   - **Definition**: Accuracy of GCS and post-ictal immobility duration calculations
   - **Validation Method**: Comparison with video recordings
   - **Target**: ±10% accuracy
4. **Device Usability Score**
   - **Definition**: Standardized usability assessment
   - **Measurement**: SUS questionnaire and custom EpiSave questionnaire
   - **Target**: ≥4.0/5.0 satisfaction score
5. **Quality of Life Impact**
   - **Definition**: Change in QOLIE-31 scores
   - **Measurement**: Baseline and 6-month follow-up
   - **Target**: Clinically meaningful improvement

Other Outcomes of Interest

Provide a short description of other outcome variables of interest. If applicable, describe how 'other outcomes of interest' are assessed in chapter 9.2.3. If statistical analysis is done, describe it in chapter 11.

- **System Uptime**: ≥95% over study duration
- **Battery Performance**: Daily charging requirements
- **Environmental Robustness**: Performance across different activities
- **Age Group Performance**: Adult vs. pediatric population differences

Safety Outcomes

Provide a short description of the safety outcome variables referring to e.g. specific adverse events, rate of adverse events in general, laboratory parameters and/or vital signs.

- **Adverse Events**: Device-related and procedure-related events
- **Serious Adverse Events**: Life-threatening or hospitalization events
- **Device Deficiencies**: Technical malfunctions affecting safety
- **Biocompatibility Issues**: Skin reactions or allergic responses

CLINICAL INVESTIGATION DESIGN

General clinical investigation design and justification of design

Note: The scientific integrity of the investigation and the credibility of the data from the investigation depend substantially on the design of this investigation.

Describe the design of the investigation and its rationale, the type (e.g., blind – who is blinded, with comparator, parallel design), allocation ratio and framework (e.g., superiority, equivalence, non-inferiority, exploratory). Provide a description of intended procedures and stages, the expected duration of subject's participation, description of sequence and duration of all investigation periods, incl. follow-up. Provide a discussion of the known or potential problems and limitations of the design.

The following information should be included in this chapter:

Intervention to be studied (MD and procedures),

Population to be studied and the number of subjects to be included (if known or applicable),

Level and method of blinding/masking (e.g. double-blind, open, blinded evaluators and unblinded subjects and/or PI(s)),

Kind of comparator(s), (e.g. sham, no treatment, active drug, dose-response, historical and investigation configuration (parallel, cross-over)). Describe the control group(s)

Method of assignment to intervention (randomisation, stratification),

Expected duration of subject participation and a description of the sequence and duration of all investigation periods, including follow-up, if any.

Study Type: Prospective, interventional, multi-center, event-driven clinical investigation
Study Design: Single-arm, open-label study

Study Setting: Outpatient/ambulatory settings with patient homes as primary location
Study Duration: 6 months per participant, up to 24 months total recruitment period

Justification: Event-driven design ensures adequate statistical power while allowing for real-world variability in seizure frequency. Single-arm design is appropriate for medical device validation studies where historical controls provide sufficient comparison data.

Methods for minimising bias

Describe measures to be taken in order to minimise or avoid bias; if applicable describe randomisation, blinding and other measures in the chapters below.

Randomisation

Describe the exact randomisation method (unit, what, allocation ratio, number generation mechanisms, block randomisation, stratification, how it is done and concealment of list). You can refer to chapter 7.3 as appropriate.

Not Applicable: Single-arm study design

Blinding procedures

Describe how blinding is ensured, and who will be blinded after subjects' assignment to the intervention(s) (e.g., investigation subjects, care providers, outcome assessors, data analysts).

Open-label Design: Participants and investigators are aware of device assignment
Video Analysis: Blinded analysis of video recordings for seizure validation

Other methods for minimising bias

Describe other methods if applicable (e.g., the use of validated questionnaires).

- **Standardized Training**: All participants receive identical device training
- **Objective Measurements**: Automated data collection reduces subjective bias
- **Video Validation**: Independent video analysis for seizure confirmation
- **Statistical Analysis**: Pre-specified analysis plan

Unblinding Procedures (Code break)

If the investigation is blinded, describe under which circumstances unblinding is permissible and the unblinding procedures. Describe the unblinding procedure in case of suspension or premature termination of the investigation.

Not Applicable: Open-label study design

CLINICAL INVESTIGATION POPULATION

Describe in the subchapters below the population to be studied; this should include a description of the investigation settings if relevant (e.g., out-patients, community clinic, academic hospital) and list of centres/countries where data will be collected (or reference to where list of investigational sites can be obtained). Provide plan of actions to be taken if the enrolment goals are not met.

Eligibility criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

1. **Age Requirement**:
   - Age ≥ 6 years at the time of enrolment
2. **Epilepsy Diagnosis**:
   - Confirmed diagnosis of epilepsy documented by a board-certified neurologist
   - Diagnosis established through clinical evaluation, EEG findings, and/or neuroimaging as per ILAE diagnostic criteria
3. **Drug-Resistant Epilepsy**:
   - Persisting seizures despite adequate trials of at least two anti-seizure medications (ASMs)
   - Adequate ASM trial defined as: appropriate dose for the specific medication, adequate duration (minimum 3 months), and good compliance
4. **GCS History and Frequency**:
   - Documented history of generalized convulsive seizures (GCS), including:
     - Generalized tonic-clonic seizures (GTCS)
     - Focal to bilateral tonic-clonic seizures (FBTCS)
   - **Minimum seizure frequency**: ≥2 GCS during the last 12 months
   - **Nocturnal GCS requirement**: ≥2 nocturnal GCS per year
5. **Device Compatibility and Comfort**:
   - Patient must be comfortable wearing wrist-worn devices
   - No known hypersensitivity or skin conditions that would prevent smartwatch wear
   - No physical disabilities that would prevent wearing a wrist-worn device
   - Willingness to wear the device for 22 hours per day (with 2 hours for charging)
6. **Technical Requirements**:
   - Access to a compatible smartphone (Android or iOS devices from 2020 and later)
   - Normal smartphone cellular connectivity for SMS transmission
   - Ability to charge the smartwatch daily
7. **Caregiver Requirements**:
   - Must have a designated caregiver available for monitoring
   - Caregiver must be living with the patient or in close proximity (maximum 10 minutes travel time)
   - Caregiver must be able to respond to alerts within 10 minutes at night
   - Caregiver must be willing and able to operate the EpiSave system
8. **Informed Consent**:
   - Written informed consent from patient or legal representative
   - For participants aged 6-17 years: assent from the participant and consent from legal guardian

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject

1. **Age and Legal Status**:
    - Age < 6 years at the time of enrolment
    - Unable to provide informed consent or assent and no legal representative available
2. **Epilepsy-Related Exclusions**:
    - Uncertain or unconfirmed epilepsy diagnosis
    - Inadequate anti-seizure medication trials (<2 adequate ASM trials)
    - <2 GCS during the last 12 months
    - <2 nocturnal GCS per year
    - No GCS risk during the study period
    - History of non-epileptic psychogenic seizures only
    - Active status epilepticus within the last 3 months
3. **Device and Technical Exclusions**:
    - Inability or unwillingness to wear wrist-worn devices
    - Known hypersensitivity to smartwatch materials
    - Skin conditions that would prevent smartwatch wear
    - Physical disabilities that would prevent wearing a wrist-worn device
    - No access to compatible smartphone
    - No cellular connectivity for SMS transmission
    - Inability to charge the smartwatch daily
4. **Caregiver-Related Exclusions**:
    - No designated caregiver available for monitoring
    - Caregiver not living with patient or not in close proximity
    - Caregiver unable to respond to alerts within 10 minutes at night
    - Caregiver unwilling or unable to operate the EpiSave system
5. **Medical and Safety Exclusions**:
    - Unstable medical condition that would interfere with study participation
    - Active psychiatric illness that would impair study compliance
    - Substance abuse that would interfere with study participation

Recruitment and screening

Describe how, where and by whom subjects are recruited / preselected for the investigation. Subjects must be given enough time to consider and to council with relatives and experts (see the guidance document “Guideline of swissethics for the time for consideration between information and consent” published on swissethics.ch/topics/position papers, available in German and French). Indicate the expected duration of the recruitment period. Mention details in case of advertisement; describe any screening requirements (e.g. laboratory or diagnostic tests), if the investigation foresees a screening visit. Describe any payment or compensation given to subjects (ISO14155). Refer to section 9.3. for description of screening procedures.

Recruitment Strategy:

- EMU patients during monitoring periods
- Outpatient clinic visits
- Referrals from treating neurologists
- Epilepsy support group outreach

Screening Process:

1. **Initial Screening** (Week 0):
    - Review of medical records for epilepsy diagnosis and GCS history
    - Assessment of ASM trial history for drug resistance confirmation
    - Evaluation of seizure frequency over the last 12 months
    - Assessment of device compatibility and caregiver availability

2. **Informed Consent Process** (Week 0):
    - Detailed explanation of study procedures and requirements
    - Review of inclusion/exclusion criteria
    - Discussion of risks and benefits
    - Obtainment of written informed consent
3. **Baseline Assessment** (Week 0):
    - Complete demographic information and medical history
    - Documentation of current ASM regimen
    - Assessment of seizure frequency and characteristics
    - Evaluation of caregiver availability and technical capabilities

Assignment to investigation groups

Describe how subjects are randomised (tools, by whom, when) and how associated treatment assignment will be made. Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned. Refer to chapter 6.2.1, if appropriate).

Single-arm Study: All eligible participants receive the EpiSave device

Criteria for withdrawal / discontinuation of subjects

Describe the criteria and procedures when and how subjects are withdrawn from the investigation and if and under which circumstances subjects will be replaced. Describe reasons that would lead to investigation discontinuation (voluntary withdrawal, non-compliance, …) and the reasons that would lead to intervention discontinuation.

Refer to chapter 9.2.5 for description of follow-up procedures (e.g., withdrawal of informed consent, non-compliance, disease progression, safety, etc. or investigation or routine procedure must be stopped, e.g. due to safety concerns).

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

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.

CLINICAL INVESTIGATION INTERVENTION

Identity of the medical device under investigation

Describe all treatments for each arm of this investigation. Methods, equipment and timing for assessing, recording and analysing variables.

Experimental Intervention (medical device)

Describe the experimental intervention, the specific medical or surgical procedures involved in the use of the MD, route and place of implantation, and any deviation from the commercial product, if applicable. Do not repeat here the information provided in the chapter 3.2.

Include a description (especially for pre-market investigations) of how the MD is used or implanted, the necessary training and experience needed for its use (e.g. may also be supported by pictures or sketches of the handling, application, implantation), proctoring during the intervention.

Device: EpiSave smartwatch application with proprietary GCS detection algorithm

Hardware Platform:

- **Smartwatch**: TicWatch Pro 5 (Android Wear OS 2.0+)
- **Specifications**: 3D accelerometer (50Hz), gyroscope (50Hz), PPG sensor, SpO2 sensor, GPS, Bluetooth 4.0+, 24-hour battery life, IP67 water resistance

Software Components:

- **Core Application**: EpiSave v2.0 (investigational version)
- **Algorithm**: Proprietary machine learning algorithm for GCS detection
- **Data Collection**: Continuous 24/7 monitoring with 15-minute post-seizure recording
- **Alert System**: Dual-alert to patient and caregiver via SMS with location

Mode of Action:

- Continuous monitoring of motion data via smartwatch 3D-accelerometry sensor
- Real-time analysis using proprietary GCS detection algorithm
- Upon seizure detection: collection of additional biosignals for 15 minutes post-seizure
- Automated dual-alert system to patient and caregiver

Control Intervention (standard/routine/comparator)

If applicable: Describe the intervention with the comparator(s): routine (standard) MD, or medicinal product, or any other intervention used as comparator, as applicable. Give and describe the name, material, model/type, including software version and accessories, if any, etc. of the routine (standard) MD (e.g. add a picture of the MD), route and place of implantation, and any deviation from the commercial product, if applicable. Describe any other comparators (medicinal products, interventions, …).

Describe the procedure in case of sham-interventions.

Include a description of the necessary training and experience needed for its use (e.g. may also be supported by pictures or sketches of the handling, application, implantation).

No Active Control: Single-arm study design

Historical Controls: Comparison with published performance metrics from current certified devices

Labelling and Supply (re-supply)

Describe how the MD under investigation and the comparator, if applicable, are labelled and are provided to the investigational site. If applicable describe logistics of re-supply. For post-market device investigations labelling is not mandatory. Describe deviation from the commercial products if applicable. The label of the MD must be done according to Art. 6.10 ISO14155, and indicate that the investigational device is exclusively for use in an investigation, unless this is not required (for example depending on the clinical development stage and of the design of the investigation).

Device Labeling: Investigational device labeling compliant with regulatory requirements
Supply Management: Centralized device distribution and tracking system

Re-supply: Devices replaced as needed for technical issues

Storage Conditions

Describe how the MD under investigation and the MD/medicinal products for the standard/routine/comparator therapy are stored (e.g., temperature range, exposure to light, sterile environment, etc.). MD supplies must be kept in a secure, limited access storage area under the recommended storage conditions.

(For devices already in use: "supply, "storage", "return or destruction" are according to standard procedures and may be simply mentioned in the CIP without specific details.)

Storage: Room temperature (15-25°C), dry conditions

Transport: Secure, temperature-controlled transport

Handling: Standard medical device handling procedures

Discontinuation or modifications of the intervention

Describe criteria for discontinuing or modifying allocated interventions for a given subject (e.g., removal of the implanted MD in response to harms, subject request, or improving/worsening disease).

Discontinuation Criteria:

- 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
- Device malfunction
- Study termination

Modification Procedures: Any device modifications require protocol amendment

Compliance with clinical investigation intervention

Describe the procedures for monitoring subject compliance and the strategies to improve adherence to the intervention, and any procedures for monitoring adherence (e.g., return of unused MD, laboratory tests). Define non-compliance and how such subjects should be handled.

Compliance Monitoring:

- Device wear time tracking (target: 22 hours/day)
- Data transmission monitoring
- Caregiver response tracking
- Monthly compliance assessments

Data Collection and Follow-up for withdrawn subjects

Describe the type and timing of data to be collected for withdrawn subjects. Note: If a subject withdraws from the investigation and gives the reason(s), this/these shall be recorded. If such withdrawal is due to problems related to the MD safety or performance, the PI shall ask for the subjects' permission to follow his/her status/condition outside the investigation.

Data and material already collected will be evaluated as far possible according to Art. 3 Abs. b ClinO-MD. In case of withdrawal, after the evaluation the data will be a) anonymised (if possible) or b) not anonymised (i.e. the data remains coded). Please specify which one. The biological material will be anonymised (if possible) or destroyed after evaluation.

The medical follow-up of withdrawn subjects, or of subjects that drop out from the investigation prematurely is described in chapter 9.2.5 and chapter 9.2.6.

If a participant withdraws from the study, the reason(s) for withdrawal will be documented when provided. In accordance with Art. 3 Abs. b ClinO-MD, any data and material already collected prior to withdrawal will be evaluated as far as possible.

If the smartwatch contains data at the time of withdrawal and is returned to the study team, these data will be downloaded and included in the analysis. After evaluation, the data will be retained in coded form.

In cases where withdrawal is due to issues related to the safety or performance of the medical device (i.e., the smartwatch), such as skin irritation or discomfort, the principal investigator will request permission from the participant to follow their condition outside the scope of the study. However, given the nature of the device (a wrist-worn smartwatch), the risk is minimal and limited primarily to potential skin reactions.

Clinical investigation specific preventive measures

Describe any specific preventive measures, including rescue medication for the subjects or treatments that are prohibited (restrictions). Their use should be recorded in the CRF. Describe their potential impact on the objectives of the investigation.

Safety Measures:

- Comprehensive caregiver training
- Emergency response protocols
- Backup alert systems
- Regular system monitoring

Concomitant Interventions (treatments)

Describe any specific or relevant concomitant care and interventions that are permitted (additional treatments) during the investigation. Their use should be recorded in the CRF. Describe their potential impact on the objectives of the investigation.

Allowed: Standard anti-seizure medications and routine medical care

Restricted: Other seizure detection devices during study participation

Medical Device Accountability

Provide plans of accurate and adequate records maintenance from shipment to the sites until return or disposal including the quantities, the dates of receipt, use, and return, identification of each MD (batch number/serial number or unique code), the expiring date if applicable, the subject identification, the physical storage location, the date on which the MD was returned by the patient/explanted, if applicable, the date of return of unused, expired or malfunctioning MDs, if applicable.

The accountability includes the accountability of the comparator(s).

Device Tracking: Centralized tracking system for all devices

Accountability: Regular inventory checks and device status monitoring

Return, Analysis or Destruction of the Medical Device

Provide a statement if the MD under investigation is shipped back to the Sponsor disposed/destructed at the hospital at the end of the investigation. Add procedures for preparation and shipment of used MD at the end of the investigation.

For MD already in use at the hospital "return or disposed/destructed" are according to standard procedures and mentioning this in the CIP is enough (no details needed).

In case of device deficiencies, including malfunction, usability issues, or inadequacy in the information supplied by the manufacturer including labelling, the devices will be returned to the sponsor for analysis.

At the end of participation, the smartwatch worn by the subject will be returned to the investigational site. Any remaining data stored on the device will be downloaded and automatically deleted from the smartwatch during the data transfer process. The device will then be prepared according to the site's standard operating procedures and reassigned to a new participant.

If the smartwatch is no longer functional or suitable for reuse (e.g., due to technical failure or physical damage), it will be returned to the coordinating centre for secure disposal.

Add procedures for documentation by the centre (e.g. pictures that need to be taken in situ and of the explant), and for preparation and shipment of used devices and explants.

9. CLINICAL INVESTIGATION ASSESSMENTS

Describe the clinical procedures, diagnostic methods, collection, storage of samples taken, etc. relating to the clinical investigation and in particular highlighting any deviation from normal clinical practice (Annex XV, chapter 2, Art. 3.6.5 MDR)

Clinical investigation flow chart(s) / table of clinical investigation procedures and assessments

Provide a detailed graph, chart or table of flow of the investigation and for the subject ("assessment schedule") with what is measured and how, grouped according to primary and/or secondary endpoints. Include the allowed time frames for each visit. The flow chart should comprise all investigation procedures during the whole course of the investigation, not only the assessed endpoints. It may be referred to the chapters “clinical investigation procedures” in case all these details are provided there. It is recommended that the flow chart is repeated here.

Please see Table 1, Schedule of Assessment, (page X).

9.2 Assessments of outcomes

In not already described under chapter 5: Describe for each endpoint (if applicable) what variables will be assessed/observed and how it will be done (e.g., questionnaires, laboratory tests), including any related processes to promote data quality (e.g., duplicate measurements, training of assessors; equipment to be used and arrangements for maintenance and calibration). Provide the rationale or justification to use certain methods and not others etc. Define the time windows allowed.

9.2.1 Assessment of primary outcome

If not already described under chapter 5.1: What will be assessed, when and how (e.g., The primary outcome, change of diastolic blood pressure at Day 21, will be measured as first item of the visit. The equipment xy will be used. The subject should be in supine position and 5 minutes at rest. In case the measurement needs to be repeated, it should be waited for at least 10 minutes. A repeated measurement needs to be recorded in the CRF.).

Primary Outcome: EpiSave sensitivity for video-confirmed nocturnal GCS detection

- **Method**: Home video recordings with autonomous camera system
- **Analysis**: Blinded video analysis for seizure confirmation
- **Timeline**: Continuous throughout 6-month study period

9.2.2 Assessment of secondary outcomes

If not already described under chapter 5.2: What will be assessed, when and how (e.g., The secondary outcome, change of diastolic and systolic blood pressure at the various time-points, will be measured as described for the primary endpoint.).

1. **False Alarm Rate**: Patient/caregiver feedback through app interface
2. **Caregiver Response Time**: Automatically logged response times
3. **Seizure Duration Precision**: Comparison with video recordings
4. **Device Usability**: SUS questionnaire and custom EpiSave questionnaire
5. **Quality of Life**: QOLIE-31 at baseline and 6 months

9.2.3 Assessment of other outcomes of interest

If not already described under chapter 5.3: What will be assessed, when and how (e.g., demographic characteristics, physical examination, quality of life, biomarkers: describe sample kind, preparation, storage (in biobanks and the appropriate procedure with separate PIC) or destruction, shipment to other labs/ countries if applicable. In case of pharmacokinetic parameters: describe condition of subject (e.g., fasting, x hours after treatment with MD), time-points of sampling, size of sample taken, sample processing, storage, shipping, substances to be analysed, how their concentration is measured, validation of analytical system).

- **System Uptime**: Continuous monitoring
- **Battery Performance**: Daily charging logs
- **Environmental Robustness**: Activity-based performance analysis

9.2.4 Assessment of safety outcomes

If not already described under Chapter 5.4: What will be assessed, when and how.

- **Adverse Events**: Continuous monitoring and monthly assessment
- **Serious Adverse Events**: Immediate reporting and follow-up
- **Device Deficiencies**: Technical issue documentation

9.2.4.1 Adverse events

Recording of adverse event information, what information needs to be collected: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with the MD and with the procedures of the investigation, expectedness, seriousness. Define specific process to ask the subject at the visits about adverse events, collection of spontaneous reports.

Refer to chapter 10.1 for AE definition and reporting procedures to CA and CEC.

All adverse events (AEs) occurring during the investigation will be documented and assessed according to standard clinical research procedures. The following information will be collected for each AE:

- **Time of onset**
- **Duration**
- **Resolution status**
- **Actions taken**
- **Assessment of intensity (mild, moderate, severe)**
- **Relationship to the medical device (smartwatch)**
- **Relationship to study procedures**
- **Expectedness**
- **Seriousness**

Given the nature of the medical device (a wrist-worn smartwatch), the risk of adverse events is minimal. Potential AEs may include, but are not limited to, skin irritation, discomfort due to prolonged wear, or technical issues with the device.

At each scheduled study visit, the investigator will actively ask the participant (and/or caregiver) about any adverse events since the last contact. In addition, participants and caregivers will be encouraged to report any spontaneous adverse events at any time during the study period.

In case of device-related adverse events or deficiencies (e.g., malfunction, usability issues, or inadequate labelling), the device will be returned to the sponsor for analysis, as per section 8.8.

9.2.4.2 Laboratory parameters

Specify laboratory parameters to be assessed; define time-points of assessment; describe sampling if deviating from hospital routine; specify tests to be used (e.g., for pregnancy: blood, urine; urinalysis); describe analysis of samples: local or abroad, if abroad, describe procedure for shipment, storage until shipment; if not yet known, refer to instruction to be written for the investigation team and to be part of the investigation manual.

Define when abnormal laboratory parameters are considered as adverse events in chapter 10.3.1 for category C investigations and in chapter 10.4.1 for category A investigations. Refer to chapter 10 for reporting procedures to CA and CEC.

NA

9.2.4.3 Vital signs

Describe how and when they will be assessed (e.g., heartbeat, blood pressure, body temperature, ECG) (e.g., in supine position after 5 minutes resting).

NA

Assessments in subjects who prematurely stop the clinical investigation

Describe follow-up procedures and assessments in subjects who withdrew/drop out from the

investigation prematurely (e.g., recording of adverse events, physical examination, laboratory parameters, vital signs). The information provided here should not contradict the information provided under chapter 7.4. clinical investigation discontinuation criteria. Define follow-up period.

Indicate if and how the collected data of subjects withdrawing their consent during the course of the investigation is used and analysed. Indicate what happens to the data after the analysis. The details given here must match the information given in the patient information and consent form and in chapter 8.4 and 12.6.

If a participant withdraws from the investigation prematurely, a final follow-up will be conducted either in person at the investigational site (when returning the smartwatch) or remotely via telephone if the device is returned by mail. During this final contact, the investigator will:

Ask about any adverse events (including skin reactions or discomfort related to the smartwatch)
Document the time of onset, duration, resolution, and seriousness of any reported events
Assess the relationship of the event to the medical device and study procedures
Record any actions taken and the expectedness of the event

In cases where withdrawal is due to issues potentially related to the safety or performance of the smartwatch (e.g., skin irritation), the investigator will request permission from the participant to follow their condition outside the scope of the investigation. The follow-up period in such cases will be up to 30 days post-withdrawal, unless medically indicated otherwise.

All data collected prior to withdrawal will be included in the analysis and retained in coded form after evaluation. No further data will be collected after withdrawal unless the participant consents to follow-up for safety-related reasons.

9.2.6 Follow-up of the subjects after the regular termination of the clinical investigation

Describe the arrangements for taking care of the subjects after their participation in the clinical investigation has ended, where such additional care is necessary because of the subjects' participation in the clinical investigation and where it differs from that normally expected for the medical condition in question.

Study Completion: Final assessment at 6 months

Optional Continuation: Participants may continue using device post-study

9.3 Procedures at each visit

Describe the procedures at each visit according to investigation phase: e.g., screening, baseline, visits during intervention, close-out visit, follow-up visits. Include additional tasks as scheduling of next visit, time windows permitted, etc.

9.3.1 *Screening and Baseline Visit (Week 0)*

- Medical history review
- Eligibility assessment
- Informed consent process
- Baseline data collection
- Smartwatch and smartphone setup
- Patient and caregiver training
- System validation and testing
- Confirmation of alert system functionality
-

E.g. Screening visit, Day (e.g., -10 to 0): List all exams/tests and other actions to be performed.

E.g. Visit 1, Baseline (Day e.g., 1): List all exams/tests, actions to be performed according to flow chart (chapter 9.1) including also e.g., application of the MD, Scheduling of next visit.

9.3.2 Monthly Follow-up Visits (Weeks 4, 8, 12, 16, 20)

- Compliance assessment
- Adverse event review
- Device performance evaluation
- Data collection verification

E.g. Visit 2-5 (± indicate the window), if they are identical, otherwise describe each visit separately. Final visit, safety follow-up visit 7-9 (± indicate the window). Mention the hand-over of the implant card in case of implantable MD.

9.3.3 End-of-study Visit (Week 24)

Return of the smartwatch

- Either in person at the hospital or by postal mail.

Download and deletion of data

- Remaining data on the smartwatch are downloaded.
- Data are automatically deleted from the device after transfer.

Assessment of adverse events

Completion of study questionnaires

- SUS (System Usability Scale) questionnaire
- Custom EpiSave questionnaire
- QOLIE-31 (Quality of Life in Epilepsy)

10. SAFETY

Describe plans for collecting, documenting, assessing, reporting, and managing solicited and spontaneously reported adverse events, adverse device effects and other unintended effects of the interventions or conduct of the investigation.

10.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

Adverse Event (AE) (Art. 2 Abs 57 MDR)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the MD.

This includes events related to the MD under investigation or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the MD.

Serious Adverse Event (SAE) (Art. 2 Abs 58 MDR)

Any adverse event that led to any of the following:

(a) death,
(b) serious deterioration in the health of the subject that resulted in any of the following:
  (i) life-threatening illness or injury,
  (ii) permanent impairment of a body structure or a body function,
  (iii) hospitalisation or prolongation of patient hospitalisation,
  (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  (v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration of the health status of the subject, is not considered an SAE

Device deficiency (Art. 2 Abs 59 MDR)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer.

The definition includes deficiencies related to the investigational MD or the comparator MD.

Malfunction (ISO14155)

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency with Serious Adverse Event (SAE) potential (Art. 80 Abs 1 letter c MDR; ISO14155)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155)

Adverse event possibly, probably or causally related to the use of an investigational device or procedures.

This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the MD under investigation. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (SADE) (ISO14155)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated SADE (ASADE) is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Causal Relationship of SAE (MDCG 2020-10/1)

A causal relationship towards the medical device or the procedure of the investigation should be rated by the PI and the Sponsor as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible. Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

10.2 Adverse events categorization

The adverse events are categorized by the PI and the Sponsor using the following algorithm:

Does the AE meet the seriousness criteria?

- No, it is not serious
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related AE
    - Yes: ADE
- Yes, it is serious: SAE
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related SAE
    - Yes: SADE
- Is it anticipated (within expected type, severity and frequency of the complications)?
    - No: unanticipated SADE (USADE)
    - Yes: anticipated SADE (ASADE)

10.3 Documentation and reporting in Medical Device Category C clinical investigations

Important note concerning all following sections of this chapter: add, respectively adapt to other local requirements in case of international investigations.

10.3.1 Foreseeable adverse events and anticipated adverse device effects

List here foreseeable AE and anticipated adverse device effects, together with their likely incidence, mitigation or treatment. The SAEs and adverse device effects, together with their likely incidence, can be presented in a tabular form.

10.3.2 Documentation of device deficiencies and adverse events by the investigator

All **device deficiencies (DD),** all **serious adverse events (SAE)** and *choose the applicable* all non-serious **adverse events (AE)** *or* non-serious adverse events (AE) identified in this CIP as being critical to the evaluation of the results of the investigation *(please phrase the compliance statement in the Synopsis accordingly)* are collected, fully investigated and documented in the source document and appropriate CRF during the entire investigation period, i.e. from patient's informed consent until the last CIP-specific procedure, including a safety follow-up period.

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (ISO14155 *[please indicate version/year]*).
- Documentation of DDs by the PI includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE (ISO14155 *[please indicate version/year]*).

Specify here how the information on AEs is systematically collected (e.g., by clinical safety assessment and/or safety lab at the regular visits, as applicable and clinically justified in the context of the specific CIP). Also specify here the follow-up period, if applicable (also in case of premature withdrawal of the subject from the investigation). If no such safety follow-up is needed, please specify and justify.

*In case that AEs identified as being critical to this evaluation and not **all** AEs shall be recorded as defined above, please include a list of the AEs evaluated as being critical and that shall be recorded. Please note that in this case full compliance with ISO 14155:2020 **cannot** be claimed.*

10.3.3 Reporting of (Serious) Adverse Events, device deficiencies, and other safety related events

Describe how, by whom and in what time frame the serious and other reportable AE (health hazards, laboratory abnormalities, pregnancies if applicable, etc.) are reported. Note: The Sponsor is responsible for the notifications to CA and to the CECs. The sponsor may delegate the task, but not the responsibility. Describe the reporting responsibilities of the PI to the Sponsor in case of a multicentre investigation, when the Sponsor and the PI are not the same person. Similarly, define the reporting roles and responsibilities to the manufacturer when the Sponsor and the PI are the same person. Describe if there are exceptions for the reporting.

Reporting to the Sponsor:

The following events are to be reported to the Sponsor by the PI (or authorized designee) *within 24 hours and 3 days (give reporting deadlines as applicable. These depend of stage of development and severity of possible consequences. Refer to the European guidance document MDCG 2020-10/1 for details)* after becoming aware of the event:

- All SAEs
- Health hazards that require measures
- DDs with SAE potential
- Other AEs and DDs identified in this CIP as being critical to the evaluation of the results of the investigation

The Sponsor shall define the timelines for reporting of non-serious AEs and DDs to the Sponsor.

The sponsor shall review the investigator's assessment of adverse events and determine and document in writing the seriousness and relationship to the investigational device and procedures required by the CIP (ISO 14155). The Sponsor shall evaluate AEs and SAEs with regard to causality and seriousness. Device deficiencies are also assessed regarding their potential to lead to an SAE (DD with SAE potential) (Art 32. ClinO-MD, ISO 14155).

Pregnancies

Note: Depending of the investigation, reporting of pregnancies may not be necessary.

If reporting is needed, include in the CIP how pregnancies will be reported (usually within 24 hours to the Sponsor), and how occurrence of pregnancy will be handled in the investigation (patient is withdrawn, outcome of the pregnancy should be followed-up, etc). If it is suspected that the MD may have interfered with the effectiveness of a contraceptive medication/device, specify how this should be reported. Details can depend on the type of investigation and intervention.

Reporting to the Competent Ethics Committee and to Swissmedic:

The following events are to be reported to the CEC and to the CA promptly (Art. 33 ClinO-MD):

a. any serious adverse event that has a causal relationship with the MD to be investigated, the comparator or the investigation procedure, or where such causal relationship is reasonably possible;
b. any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; (DD with SADE potential);
c. any new findings in relation to any event referred to in points (a) and (b).

In order to ensure prompt notification, the Sponsor may initially submit an incomplete notification.

In line with European guidance document MDCG 2020-10/1 Rev. 1, reportable SAE and DD must be sent to Swissmedic within 7 days, or 2 days for SAE requiring prompt action for the safety of other study subjects.

If applicable: For conformity-related clinical trials in sub-categories C1 and C2 that are also being conducted abroad: The sponsor notifies the CEC and CA without delay of all events, device deficiencies and findings as specified above which arise from the conduct of the clinical trial abroad.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC and CA within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

If applicable: For clinical trials that are also being conducted or are also due to be conducted in EU or EEA states, The Sponsor notifies the CEC and CA within 2 days of all imposed or voluntary safety and protective measures that are being implemented in EU or EEA states and the circumstances that necessitated them (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

Once a year, the sponsor submits to the CEC and CA a list of all SAEs and DDs and provides it with a report on their severity, causal relationship with the device and/or the intervention and on the safety of the participants (outcome, event status). The sponsor informs the CEC and CA annually about the general progress and status of recruitment of the clinical investigation *(also abroad)*. Any safety-relevant measures taken by the sponsor or imposed by ethics committees *or authorities anywhere in the world as well as results from other clinical investigations with the investigational device (if applicable)* shall be described. Based on the data presented in the report, the sponsor will draw his/her conclusions regarding the safety of the subjects and the continuation of the investigation. *The safety report and the general progress report can be merged in one single report.*

The cumulative list of reportable serious adverse events and device deficiencies (MDCG 2020-10/2 Rev. 1) per cut-off dateis submitted in parallel.

10.3.4 Follow-up of (Serious) Adverse Events

Describe the follow-up of subjects terminating the investigation (either regularly or prematurely) with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs. Describe how and what is done to follow-up on ongoing SAE and AES, and what is documented. Describe efforts taken in case of loss to follow-up.

10.4 Documentation and reporting in Medical Device Category A clinical investigations

Important note concerning all following sections of this chapter: add, respectively adapt to other local requirements in case of international investigations.

Device deficiencies (DD) and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire investigation period, i.e. from patient's informed consent until the last CIP-specific procedure, including a safety follow-up period.

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (Art. 32 ClinO-MD, ISO14155).

- Documentation of DDs by the PI includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE. The Sponsor shall review all DDs and determine and document in writing whether they could have led to a SAE (DD with SADE potential) (Art 32. ClinO-MD, ISO14155).

Specify here how the information on AEs is systematically collected (e.g., by clinical safety assessment at the regular visits, as applicable and clinically justified in the context of the specific CIP). Also specify here the follow-up period, if applicable (also in case of premature withdrawal of the subject). If no such safety follow-up is needed, please specify and justify.

10.4.1 Foreseeable adverse events and anticipated adverse device effects

List here foreseeable serious adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment. The serious adverse events and adverse device effects, together with their likely incidence, can be presented in a tabular form.

10.4.2 Reporting of Safety related events

Reporting to the Sponsor:

All SAEs, DDs with SAE potential and health hazards that require measures are reported to the Sponsor by the PI (or authorized designee) without delay after becoming aware of the event. DD are assessed regarding their potential to lead to an SAE.

Pregnancies

Depending of the investigation, reporting of pregnancies may not be necessary. If reporting is needed, include in the CIP how pregnancies will be reported (usually within a maximum of 24 hours to the Sponsor), and how occurrence of pregnancy will be handled in the investigation (patient is withdrawn, outcome of the pregnancy should be followed-up, etc.). Details can depend on the type of investigation and intervention.

Reporting to the Competent Ethics Committee:

The Sponsor reports to the CEC without delay any SAE for which a causal relationship between the event and the test procedure used in the clinical trial has been ascertained (Art. 33 ClinO-MD).

In order to ensure prompt notification, the Sponsor may initially submit an incomplete notification.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

If applicable: For clinical trials that are also being conducted or are also due to be conducted in EU or EEA states, the sponsor notifies the CEC within two days of all imposed or voluntary safety and protective measures that are being implemented in EU or EEA states and the circumstances that necessitated them (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

Once a year, the sponsor submits to the CEC a list of the SAEs and DDs and provides it with a report on their severity, causal relationship with the device and the intervention, as well as on the safety of the participants. The sponsor informs the CEC about the general progress of the clinical investigation, annually. *The safety report and the general progress report can be merged in one single report.*

Materiovigilance reporting to Swissmedic:

The Sponsor is responsible for ensuring that Swissmedic is informed of serious incidents in accordance with Art. 66 MedDO.

Materiovigilance reports are not sent to the CEC.

If the Sponsor is the manufacturer of the investigational device or Swiss representative of the manufacturer:

- *the Sponsor has to send reportable incidents to Swissmedic (materiovigilance@swissmedic.ch) with the form available at www.swissmedic.ch/md-materiovigilance-manufacturers (Art. 66 para. 1 to 2bis MedDO).*

If the Sponsor is not the manufacturer of the investigational device or Swiss representative of the manufacturer:

- *In case of incidents, check whether the event is subject to materiovigilance reporting duties for users acc. to Art. 66, para. 4 MedDO (using guidance MU680_20_008e_WL). If the clinical investigation/performance study is conducted in a hospital, the materiovigilance contact person of the hospital may also be contacted (Art. 67 para. 2 MedDO)*
- *The Sponsor has to ensure that reportable incidents are sent to Swissmedic with the form MU680_20_015d_FO (materiovigilance@swissmedic.ch). Guidance and forms are available at www.swissmedic.ch/md-materiovigilance-users.*
- *Users are legally obliged to inform the suppliers of the devices about serious incidents (Art. 66, para 4 MedDO).*

10.5 Assessment, notification and reporting on the use of radiation sources

In investigations involving therapeutic or diagnostic products capable of emitting ionising radiation and/or medical exams that use ionizing radiation (X-rays, CT scans, PET scans, fluoroscopy, …), the Sponsor shall assess compliance with the dose guidance value in accordance with Art. 45 of the Radiological Protection Ordinance of 26 April 2017. The dose guidance values for investigations without expected direct benefit for the subjects is 5 mSv effective dose per year.

If the permitted dose guidance value is exceeded at any time, the Sponsor or the PI notifies the CEC within 7 working days after becoming aware of the event [Art. 39 ClinO-MD].

When applicable, in the case of Category C clinical investigation with MDs that emit ionising radiation:
If in the case of Category C clinical investigations with MDs that emit ionising radiation, if the permitted dose guidance value is exceeded at any time, the Sponsor or the PI notifies the CA within 7 working days after becoming aware of the event [Art. 39 ClinO-MD].

Within one year of the completion or discontinuation of the investigation involving examinations with radioactive sources, the Sponsor sends to the CEC and to the CA a final report containing all information relevant to radiation protection, in particular an estimate of the doses to which the subjects were exposed [Art. 39 ClinO-MD].

11 STATISTICAL METHODS

Describe the statistical considerations done for the investigation, with justification, including a power calculation for the sample size, the statistical methods to be employed, the level of significance that will be used, including timing of any planned interim analysis(ses).

Special reasoning and sample sizes may apply for early clinical investigations (e.g. feasibility studies [ISO14155]).

11.1 Hypothesis

If a Null Hypothesis is tested, state explicitly both Null and Alternative Hypotheses in terms of the primary endpoint(s) and justify them in regard of the subject population and dose. The stated safety and benefit hypotheses have to be used in the determination of Sample Size. Relate these hypotheses to the investigation objectives.

If hypothesis testing is not used, then discuss how the approach used (e.g. Bayesian methods) will address the objectives.

Primary Hypothesis: EpiSave will demonstrate ≥90% sensitivity for video-confirmed nocturnal GCS detection in real-world ambulatory settings.

Secondary Hypotheses:

- EpiSave will maintain a false alarm rate of <1/week in ambulatory settings
- Caregiver response times will be ≤5 minutes for 90% of seizure alerts
- System uptime will be ≥95% over the study period
- Patient and caregiver satisfaction scores will be ≥4.0/5.0 on standardized scales

Determination of Sample Size

Provide the number of subjects planned to be enrolled. Reason for choice of sample size with justification, including a power calculation for the sample size. Provide the estimated number of subjects for each investigation site and investigation arm (if applicable) needed to achieve the safety and benefit objective, how it was determined, including clinical and statistical assumptions supporting any sample size calculations, the power of the investigation, the type I error (one- or two-sided) and the related risk, the clinical justification.

If “sex and gender” dimension is of primary interest, does the sample size estimation integrate this aspect? Are the statistical analyses appropriate?

Target: Minimum of 75 verified nocturnal GCS in at least 50 PWE

Statistical Rationale:

- **Regulatory Requirement**: Aligns with FDA/CE guidelines for medical device validation studies
- **Literature-Based**: Based on published recommendations for phase 4 seizure detection studies
- **Power Calculation**: Provides 90% power to detect sensitivity ≥90% with 95% confidence
- **Event-Driven Design**: Ensures adequate statistical power regardless of recruitment timeline
- **Dropout Consideration**: Accounts for 20% anticipated dropout rate

Recruitment Timeline: 24 months (≤1 PWE/4 months/center)

11.3 Statistical criteria of termination of the investigation

Describe the statistical criteria for the termination of the investigation (“discontinuation criteria”) or the stopping rules, for example in case of evidence of early benefits or harm for parts of investigation and for the entire investigation). If applicable, describe the ‘stop/go’ rules for temporarily discontinuing the investigation.

Early Termination Criteria:

- Safety concerns identified by DSMC
- Regulatory authority decision
- Insufficient recruitment (after 24 months)
- Study objectives achieved

11.4 Planned Analyses

Make brief statements of the analyses that are planned, the methods and types and which variables and with what data sets and when (a detailed statistical analysis plan may be written as a separate document after finalisation of the CIP and may be referred to this document, e.g. statistical analysis plan), including timing of any planned interim analysis(ses).

Include a statement that analyses of “sex and gende”r differences are planned. If such an analysis is not possible, please state the reasons.

11.4.1 Datasets to be analysed, analysis populations

Describe the analysis populations, evaluation groups (i.e. the selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects) and data sets to be used for analysis and methods for any additional analyses (e.g., subgroup and adjusted analyses). This applies to all endpoints / outcomes to be analysed.

Analysis Populations:

- **Per-Protocol (PP)**: Participants completing study with protocol compliance
- **Intention-to-Treat (ITT)**: All enrolled participants regardless of completion
- **Safety Population**: All participants receiving the device

11.4.2 Primary Analysis

Describe the intended primary analysis that will be done, when and how and by whom it will be done. Indicate the pass and fail criteria to be applied to the results of the investigation.

Primary Endpoint Analysis:

- **Sensitivity Calculation**: Proportion of true nocturnal GCS detected by EpiSave
- **Confidence Intervals**: 95% Wilson confidence intervals
- **Statistical Test**: One-sample proportion test against 90% target
- **Analysis Population**: Per-protocol population (all participants with ≥1 nocturnal GCS)

11.4.3 Secondary Analyses

Describe the intended secondary analysis that will be done, when and how and by whom it will be done. Indicate the pass and fail criteria to be applied to the results of the investigation.

Describe the intended subgroup analyses, if applicable, that will be done, when and how and by whom they will be done, add hypothesis related to each subgroup.

False Alarm Rate Analysis:

- **Definition**: False alarms per patient per day
- **Statistical Method**: Negative binomial regression for count data
- **Covariates**: Age, seizure frequency, device wear time
- **Target**: <1 false alarm per week per patient

Caregiver Response Time Analysis:

- **Definition**: Time from alert to caregiver response
- **Statistical Method**: Kaplan-Meier survival analysis
- **Censoring**: Right-censored at 30 minutes
- **Target**: ≤5 minutes for 90% of alerts

System Reliability Analysis:

- **Definition**: System uptime percentage
- **Statistical Method**: Mixed-effects model for repeated measures
- **Random Effects**: Participant and time
- **Target**: ≥95% uptime over study duration

11.4.4 Interim analyses

Describe the intended interim analysis that will be done, why, when and how and by whom it will be done, taking into consideration their purpose, frequency, timing, scope, statistical procedures, Data Monitoring Committee involvement, and stopping guidelines (refer to chapter 11.3). Explain the methods that will be used to adjust for interim analyses, or give a rationale for why adjustment is not necessary.

Interim Analysis Plan:

- **Timing**: After 25%, 50%, and 75% of target events
- **Primary Focus**: Safety and futility assessment
- **Statistical Method**: O'Brien-Fleming stopping boundaries
- **DSMC Review**: Independent review of interim results

11.4.5 Deviation(s) from the original statistical plan

Describe the procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the CIP and/or in the final report, as appropriate).

Protocol Deviations: Any deviations from the statistical plan will be documented and justified

11.5 Handling of missing data and drop-outs

Describe how missing data will be handled (e.g. multiple imputation, last observation carried forward, complete case analysis, consider primary and secondary outcomes…).

Describe efforts taken in case of lost to follow-up. European Considerations are available for ISO 14155. Reference MEDDEV 2.7/2 rev.2, chapter 7.2 Annex A.7, link.

Describe if dropouts are replaced. If sensitivity analyses are planned, specify them. All subjects shall be accounted for and documented, including those withdrawn from the investigation or lost to follow-up).

Missing Data Strategy:

- **Primary Analysis**: Complete case analysis
- **Sensitivity Analysis**: Multiple imputation for missing data
- **Drop-out Analysis**: Comparison of completers vs. drop-outs

Drop-out Management:

- **Prevention**: Regular follow-up and support
- **Documentation**: Reason for drop-out and data completeness
- **Analysis**: Intent-to-treat analysis including all randomized participants

12 QUALITY ASSURANCE AND CONTROL

Describe how quality is assured and controlled. The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions, at all sites in case of multicentric investigations. Indicate the software used. The PI is responsible for proper training of all involved investigation personnel.

12.1 Data handling and record keeping / archiving

Describe how data are handled and that all investigation related documents are archived. A list of the essential clinical investigation documents which should be maintained in the investigation site and sponsor file is given in ISO14155 Annex E.

12.1.1 Case Report Forms

Describe how the investigation data is recorded, e.g. with paper or electronic Case Report Forms (p-/e-CRF). A CRF is maintained for each enrolled subject. CRFs must be kept current to reflect subject status at each phase during the course of the investigation. Subjects must not be identified in the CRF by name or initials and birth date. Describe the coding used for the investigation, e.g. subject number in combination with year of birth (see the guidance document published on swissethics.ch "coding of trial subject accepted by swissethics and secure storage of subject identification list" https://swissethics.ch/assets/Themen/akzeptierte_verschluesselung_e.pdf)

If paper-CRFs are used, describe how data is entered into an electronic database for analysis (e.g., double data entry).

Note: The person(s) authorized by the PI to enter the data in the CRF must be listed on the delegation log.

CRF Design: Electronic case report forms (eCRFs)

Data Elements: All study variables and endpoints

Validation: Built-in validation rules and range checks

Completion: Real-time data entry with immediate validation

12.1.2 Specification of source data and source documents

Source data should be available at the site to document the existence of the investigation subjects. Source data must include the original documents relating to the investigation, as well as the medical treatment and medical history of the subject. In case of electronic source data (e.g. from Apps or from automatic recording devices), describe how the data is handled, transferred, stored and accessed by the PI and authorised staff.

Describe what is considered the source documents in the investigation (specify what is the source document for each data collected in the CRF, e.g., demographic data, visit dates, participation in investigation and ICFs, randomisation codes, SAEs, SADEs, USADEs, and concomitant medication, results of relevant examinations. Identify data that are directly recorded in the CRF, which should also be considered being source data. Also describe where original source data are kept at the site. You can also refer to a separate document in the Appendices ('source data description and source data location').

- Medical records
- Device data logs
- Video recordings
- Patient diaries
- Laboratory reports

Source Data Verification: 100% verification of critical data elements

12.1.3 Archiving of essential clinical investigation documents

All the documents of the investigation must be archived for a minimum of (*time according to local legislation*) years after regular or premature termination of the investigation.

Describe Sponsor (Art. 40 Abs 1 ClinO-MD) and PI (Art. 40 Abs 2 ClinO-MD) responsibilities. Specify location and length of storage. Archiving for 10 years, in the case of an implantable device 15 years in

Switzerland (Art. 40 ClinO-MD).

12.2 Data management

Describe plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). In case electronic data capture systems are used, this chapter shall include a description of procedures for verification, validation and securing the database.

If data will not be anonymised after the statistical analysis, describe in which form they will be stored (e.g. coded). If the data is anonymised, describe how this is done

Reference to where details of data management procedures can be found, if not in the CIP.

12.2.1 Data Management System

Describe what system (including cloud services and software) is being used and who is responsible and how it is tested before the investigation begins (may include a description of where the system is hosted).

System: Electronic data capture (EDC) system

Features: Real-time data entry, validation, and monitoring

Security: Encrypted data transmission and storage

Backup: Daily automated backups

12.2.2 Data security, access and back-up

Describe who has access to data, how, where and when – and which backup systems are in place (if applicable).

- User authentication and authorization
- Encrypted data transmission (AES-256)
- Secure data storage
- Regular security audits

Access Control:

- Role-based access permissions
- Audit trail for all data access
- Regular access reviews

12.2.3 Analysis and archiving

Describe how data are extracted and where they are stored, database status recording, duration and place of storage.

Analysis: Statistical analysis using validated software

Archiving: Long-term storage of all study data and documents

Retention: 15-year retention period as per regulatory requirements

12.2.4 Electronic and central data validation

Describe how data are validated.

- Range checks for all numeric variables
- Consistency checks across related variables
- Completeness checks for required fields
- Cross-validation with source documents

12.3 Monitoring

Describe the regular monitoring visits at the PI's site prior to the start and during the course of the investigation organised by the Sponsor. Give a detailed description of what, which data and documents will be monitored and to which extent (these points are given here as examples only: subject enrolment logs, informed consents and informed consent process, source data verification, inclusion and exclusion criteria, subjects' visit schedule, safety, processing of subjects' data, preservation of subjects confidentiality, reporting to CEC and RA and approvals, provisions of records and data retention, etc…). Indicate which organisation or person does the monitoring; specify monitor qualification and training.

Describe procedure to review the monitoring visit reports, follow-up on monitoring findings and corrective actions.

Alternatively the extent and nature of monitoring activities and all the details described in the above paragraph, based on the objective and design of the investigation, can be written in a Monitoring Plan. The Monitoring Plan must be annexed to the CIP (Annex XV, Chapter 2, Art. 3.6.6. MDR).

Provide a statement that the source data/documents are accessible to monitors and questions are answered during monitoring by the PI and the site staff.

12.4 Audits and Inspections

Describe the frequency and procedures for auditing the investigation, if any, and whether the process will be independent from the PI and the Sponsor. Provide a statement that the documentation of the investigation and the source data/documents are accessible to auditors/inspectors (also CEC and CA) and questions are answered during inspections. All involved parties must keep the subject data strictly confidential.

12.5 Confidentiality, Data Protection

Data protection; should include the statement that direct access to source documents will be permitted for purposes of monitoring (chapter 12.3), audits and inspections (chapter 12.4) and should declare who will have access to the documents of the investiation, dataset, randomization code, etc. during and after the investigation (refer to chapter 13 for publication and dissemination of the results of the investigation).

12.6 Storage of biological material and related health data

In the event the data of the investigation is stored in a data-registry: add here that the coded data of the subjects who consented for the further use of their data (independently of the investigation specific consent) will be stored in a registry for an undetermined length of time, and the data could be re-used for other research projects (provided previous approval by the CEC).

If applicable, describe for how long and where the samples and personal data are stored, or state that samples are destroyed and data anonymised after the end of the storage period. The information provided here must match the information given in chapters 8.4 and 9.2.5.

In the event of Biobank or registry storage, confirm that coded samples and/or data are only stored if the subjects consent for further use has been obtained. This consent is given (or withheld) independently of the participation in the investigation (Art. 17. ClinO).

13. PUBLICATION AND DISSEMINATION POLICY

Give the publication policy of the results of the investigation, if not addressed in a separate agreement, according to Art. 42 ClinO-MD.

Describe plans to communicate the results of the investigation to the subjects, healthcare professionals, the public, and other relevant groups (e.g., via a summary in lay language, publication, reporting in results databases, or other data sharing arrangements); anticipate for authorship eligibility guidelines and any intended use of professional writers and, if any plans for granting public access to the full CIP, subject-level dataset, and statistical code, including who will have ultimate authority over any of the activities. Mention the protection of trade secrets, if applicable.

Confirm that if “sex and gender” effects are observed, they will be published in the final study report. If an analysis is performed but no “sex and gender” effects are observed, this should also be published in the final study report.

The Sponsor will enter and publish a summary of the results of the clinical investigation in a public recognized register (as specified in Art. 64 Abs. 1 lit a or b ClinO) *(complete the paragraph as appropriate)*:

a) immediately after submitting the final report *(for completed clinical trials with devices that already bear a conformity marking and were used in accordance with the instructions, or in the event of an early termination or interruption of a clinical trial: in accordance with Article 37)*

or b) at the latest before the device is placed on the market or one year after submitting the final report if the device has not been placed on the market by this point in time. *(for all other completed clinical trials, in accordance with Article 37).*

The Sponsor also ensures that a lay summary of the results is entered in BASEC within the period specified in the paragraph above. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.

If publication of the results is not possible within the specified period for scientific reasons, the sponsor will explain this in the application documents and indicate when publication will take place. Adapt this paragraph accordingly.

The investigator will provide each participant with the lay summary of the results of the clinical investigation at the end of the study, directly. *The investigator should ensure that participants are adequately informed about this in the patient information document and also that they are informed where the lay summary of the results of the clinical investigation will be published online.*

FUNDING AND SUPPORT

Funding

Provide brief statement of sources and types of financial support for the investigation. If applicable, reference to other places or contracts/documents where this information is captured.

Other Support

Provide brief statement of any other type of support received to conduct the investigation (MD, comparator, investigation material, software's, …). If applicable, reference to other places or contracts/documents where this information is captured.

INSURANCE

Give proof of insurance cover or indemnification of subjects in case of injury, pursuant to Art. 3 ClinO-MD. E.g., "Insurance is provided by the Sponsor and fulfils the legal provision of art. 3 ClinO-MD. A copy of the insurance certificate is filed in Investigator's file and in the Sponsor's file."

Note: Category A1 performance studies are exempt from liability coverage requirements (ClinO Art. 12). Categories A2 and C performance studies need to document the guarantee of liability (insurance certificate or equivalent guarantee) (ClinO Art. 13).

The insurance must cover damage occurring up to 20 years after the end of the clinical investigation.

The policy value shall be set in accordance with ClinO Annex 2.

It can be referred here to another place where the document is found, e.g., chapter 17 or elsewhere.

REFERENCES

Provide a list of the references pertaining and cited in the CIP.

1. Declaration of Helsinki, Version October 2013 (http://www.wma.net)
2. Humanforschungsgesetz, HFG Bundesgesetz über die Forschung am Menschen (Bundesgesetz über die Forschung am Menschen, HFG) vom 30. September 2011/ Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011 / Legge federale concernente la ricerca sull'essere umano (Legge sulla ricerca umana, LRUm) del 30 settembre 2011
3. Verordnung über klinische Versuche mit Medizinprodukten (KlinV-Mep) vom 1. Juli 2020 / Ordonnance sur les essais cliniques de dispositifs médicaux (OClin-Dim) du 1er juillet 2020 /. Ordinanza sulle sperimentazioni cliniche con dispositivi medici (OSRUm-Dmed) del 1 luglio 2020
4. Verordnung über klinische Versuche mit Ausnahme klinischer Versuche mit Medizinprodukten (Verordnung über klinische Versuche, KlinV) vom 20. September 2013 / Ordonnance sur les essais cliniques hors essais cliniques de dispositifs médicaux (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. Ordinanza sulle sperimentazioni cliniche ad eccezione delle sperimentazioni cliniche con dispositivi medici (Ordinanza sulle sperimentazioni cliniche, OSRUm) del 20 settembre 2013
5. Medizinprodukteverordnung (MepV) vom 17. Oktober 2001 / Ordonnance sur les dispositifs médicaux (ODim) du 17 octobre 2001 / Ordinanza relativa ai dispositivi medici (ODmed) del 17 ottobre 2001
6. Medical Device Regulation (EU) 2017/745 of 5 April 2017 (MDR)
7. MDCG 2024-3 Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices
8. MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-1_guidance_safety_reporting_en.pdf)
9. EN ISO 14155: Clinical investigation of medical devices for human subjects - Good clinical practice (www.iso.org)
10. EN ISO 10993: Biological evaluation of medical devices (www.iso.org)
11. EN ISO 14971: Application of risk management to medical devices (www.iso.org)
12. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
13. Strahlenschutzverordnung (StSV) vom 26. April 2017 / Ordonnance sur la radioprotection (ORaP) du 26 avril 2017 / Ordinanza sulla radioprotezione (ORaP) del 26 aprile 2017.
14. International Conference on Harmonization (ICH) Guideline for Good Clinical Practice E6(R2), (www.ich.org).
15. Zz
16. Yy

APPENDICES

NOTE: Further relevant information can be found in the ISO14155, Annex A Clinical Investigation Plan (CIP)

Documents that do frequently change during the course of the investigation can be mentioned as ‘documents provided separately’ and listed here.

The section headings can be renamed accordingly.

1. Investigator’s Brochure
2. General Insurance Conditions, insurance certificate
3. List of norms
4. List of investigational sites / PIs (List of countries or centres where data will be collected)
5. Specific protocols (e.g. MRI)
6. Case Report Form (ISO14155 Annex C)
7. Monitoring Plan
8. Other material handed over to the patients