Clinical Investigation Plan (CIP)

Title: Prospective evaluation of a portable surface EMG device for detection of convulsive seizures and their differentiation from non-epileptic convulsive events

Trial code: DK009

Version: CIP1002-1B

Date: 10/1/2014

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Protocol Approval

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By signing this form (DK009 version 1.0) I engage to complete the trial in accordance with the ethical principles contained in the Declaration of Helsinki, the requirements of the Danish Health and Medicines Authority, DS/EN ISO 14155-1, DS/EN ISO 14155-2 and the protocol.

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1. Abbreviations

AE	Adverse Events
ADE	Adverse Device Events
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Clinical Record Form/Case Report Form
CRO	Clinical Research Organisation
DHMA	Danish Health and Medicines Authority
ECG	ElectroCardioGraphy
EDDI	Epileptic seizure Detector Designed by IctalCare
EEG	ElectroEnchephaloGraphy
EMG	ElectroMyoGraphy
EMU	Epilepsy Monitoring Unit
FDR	False Detection Rate
GTC	Generalized Tonic-Clonic
IFU	Instruction For Use
IRIS	IctalCare Research Investigation System
MD	Medical Doctor
REC	Research Ethics Committee
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effects
sEMG	surface EMG
SNR	Signal-to-Noise Ratio
SW	SoftWare
USADE	Unanticipated Serious Adverse Device Effects

2. General

2.1 Introduction

Epilepsy is the second most common acute neurological disorder, with a world-wide prevalence of 0.8-1.0% [1]. A third of the patients are medically refractory [2-4], and where no other treatment (surgery, ketogenic diet) has an effect, an automatic detection alarm would be of great help to the patients and their relatives.

In a quantitative study we found biomarkers for the differences of epileptic and physiologic tonic activity [5]. Based on the findings a generalized tonic-clonic (GTC) seizure detection algorithm was designed based on conventional surface ElectroMyoGraphy (surface EMG / sEMG), which proved to work with a sensitivity of 100% and a false detection rate (FDR) of 0.04/h in a second study [6]. In a third study this algorithm was implemented into a wireless sEMG device (IctalCare Research Investigation System (IRIS)) and tested on patients. It proved to show equally well results for the sensitivity, and the FDR was decreased to 0/h [7].

A second generation of the wireless sEMG device (EDDI) is designed and this clinical study will serve as a confirmative study, to prove the reliability (based on sensitivity and FDR) of the product.

2.2 Principal investigator, and investigation site(s)

Principal investigator:
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2.3 Other organizations involved in the clinical investigation

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3. Overall synopsis of the clinical investigation

3.1 Background

Epilepsy is a common serious neurological condition with a prevalence of 0.8-1.0%. People with epilepsy find it helpful to consider safety aids or equipment that might help them with day-to-day life. For example, an alarm that can alert family or friends when someone has a seizure, or a safety pillow if they have seizures when asleep. IctalCare developed EDDI (Epileptic seizure Detector Designed by IctalCare), a wireless alarm (in the form of a plaster) that is able to detect GTC seizures in epileptic patients.

In a clinical investigation (DK007-ME) an algorithm, which made it possible to detect GTC seizures, was developed. It was first tested in IRIS a predecessor for EDDI in a second clinical investigation (DK006-ME). IRIS was used on 13 epileptic patients to measure sEMG. GTC seizures were confirmed by the gold standard (video monitoring and ElectroEncephaloGraphy (EEG) recordings) for four patients, and the algorithm proved efficient. No SADE, nor SAEs, nor device deficiencies that might have led to a SAE were reported.

3.1.1 Hypothesis

From our previous results on the same type of data (sEMG) we expect that the sensitivity and FDR of this study will be comparable. The differences lie within the newer version of the device (EDDI) measuring the sEMG signal. The software is the same as used in IRIS, and most of the hardware is aswell the same. The electrode is different, but clinical tests have shown that the newer electrode provides a signal-to-noise ratio (SNR) which is equally good or better compared to the older version of the electrode (used with IRIS in DK006-ME).

3.2 Purpose

The purpose of this clinical investigation is to test the reliability of the epileptic GTC seizure detection device EDDI. Furthermore the study should also evaluate whether the device is able to differentiate the convulsive epileptic (GTC) seizures from non-epileptic convulsive seizures.

EDDI will be tested on patients with epilepsy, who are expected to experience GTC seizures (or non-epileptic psychogenic seizures) during their admission to one of the epilepsy monitoring units (EMUs) participating in the study. These (patients with epileptic GTC seizures) constitute the patient group for which EDDI is intended.

In the investigation the only change from a normal admission in the EMU is the addition of the EDDI, which is placed on the outer side on one of the upper arms of the patient, as shown in the Instruction For Use (IFU) of the device.

It is validated, that this addition will not add any risks to the participating patients.

3.3 Test design

The current clinical investigation will use the algorithm developed in the DK007-ME investigation. It will be conducted as a double-blinded clinical investigation assessing the sensitivity and specificity of EDDI, an epilepsy alarm, for detection of GTC seizures in patients with epilepsy. The double-blinded part will be between the physicians annotating when GTC seizures exists based on EEG and video, the gold standard, and the epilepsy alarm, which annotates when GTC seizures exist based on the EMG signal.

Patients will be hospitalized at a specialized epilepsy center either to investigate suspected epilepsy or to improve their epilepsy diagnosis and treatment. During their hospitalization patients will at least be monitored by the gold standard: video monitoring and EEG.

In this investigation, approximately 20 patients with GTC seizures will be needed, along with approximately 10 patients with PNES. This means that probably 70-80 patients in total will be included and equipped with an EDDI, after providing their informed consent. The Epilepsy Alarm should be placed on one of the upper arms (the outer side of biceps) as shown in the IFU for the device. It will need to be replaced with a new electrode every 24 hours. After a maximum of 4 days, the patient will be discharged from the hospital, thus the investigation is finalized. During the investigation sEMG signals will be recorded through the EDDI, the seizure detections by the algorithm will be electronically annotated to compare against the times annotated by the staff based alone on the gold standard. The detections of the EDDI will be hidden for the clinical personnel until the end of the admission of the patient. When the admission of the patient has ended, the clinical personnel will remove an SD-card from the A-Unit, and ship it off to the device manufacturer, who will extract the seizure times, and sent them to the principal investigator.

The investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155 (2011) and the requirements of the local competent authorities.

3.4 Objectives

3.4.1 Primary objective

- To investigate the sensitivity of EDDI's ability to detect GTC seizures.

3.4.2 Secondary objectives

- To investigate the specificity of EDDI's ability to detect GTC seizures.
- To investigate reasons for possible registered false alarms.
- To investigate the latency of the seizure detection by the EDDI compared to the actual start of the GTC seizure.
- To investigate the EDDI's ability NOT to detect PNES which visually look like GTC seizures.

3.5 Endpoint definitions

3.5.1 Primary endpoint

The sensitivity of the alarms will be defined from comparing the annotated time slots for GTC seizures (by the clinical personnel) with the investigator assessment of whether a GTC seizure occurred or not within the annotated time period (GTC seizures annotated by the EDDI). For the calculation of the sensitivity, the GTC seizure onset annotated by the EDDI should lie within the onset and offset defined by the clinical personnel, when compared. The clinical personnel are blinded to the alarm (EDDI) annotations, and the EDDI is blinded to the annotations set by the physicians (based on the gold standard, EEG and video).

The period to be studied for the primary alarm effect is the entire measurements on a patient. The sensitivity is then calculated as the number of the GTC seizures (defined by the gold standard), that were detected by the EDDI (a detection is counted, when a silent alarm is annotated within the seizure

period), relative to the total amount of GTC seizures (counted based on the gold standard). When a seizure annotated by the clinical personnel is not registered by the EDDI, it should be checked whether the EDDI have been turned on, before it is reported as a false negative.

3.5.2 Secondary endpoints

- **The specificity** is calculated and evaluated indirectly as the false detection rate (the number of false detections per hour). A detection is categorized as a false detection, if it falls outside a seizure period (between start and end of a seizure, defined by the gold standard). Possible alarms during placement or removal of the device are discarded (this will only happen if the device is used wrong). All data (incl. video and EEG) are saved for each patient, which makes it possible to find the reasons for possible false alarms.
- Effect of the GTC seizure alarm in a nocturnal situation (23:00 - 07:00). The sensitivity will be calculated based on the data within this period of time (23:000 – 07:00) for each day.
- The nocturnal specificity will be calculated as the amount of false positives within the nocturnal period (23:00 – 07:00) for all days, with respect to the amount of hours.
- For each possible false alarm, the reason for it is checked to see if there is a reasonable explanation.
- The measure for whether the EDDI captures the PNES is calculated as the total number of PNES minus the number of captured PNES and divided by the total number of PNES. This means that a measure close to 100% ensures that the device will not alarm on PNES, and the closer the measure is to 0%, the more false alarms may come from PNES.

3.5.3 Investigation population

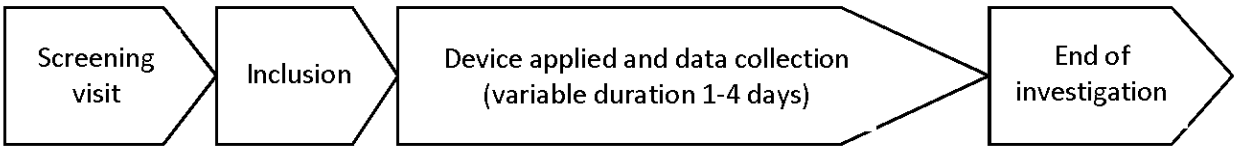
3.5.3.1 Inclusion criteria:

1) Patients referred to video-EEG monitoring (for more than 24 hours).
2) Data in patient history suggesting a convulsive epileptic or non-epileptic (PNES) event.
3) Males and females aged 3-80 years.
4) Patients who can linguistically and mentally participate in the opinion of the investigation.
5) Following receipt of verbal and written information about the investigation, the patient must provide signed informed consent before any investigation related activity is carried out. Considerations regarding patients who are mentally retarded are described in section 17.

3.5.3.2 Exclusion criteria:

1) Suspicion that a patient does not have convulsive epileptic or non-epileptic (PNES) events
2) Pregnancy
3) Patients known or suspected of not being able to comply with a study protocol (e.g. due to alcoholism, drug dependency or psychological disorder)
4) Patients with allergy to the adhesive plaster used to fix the device to the body
5) Patients that are involved in other studies.

3.5.4 Investigation design



First Patient planned to be included: 1st of February 2014

Last Patient planned to complete investigation: 31st of October 2014.

3.5.5 Investigational device

The investigational device is a wireless device (EDDI) that is placed on the upper arm, and measures sEMG. IctalCare have designed an algorithm, which is part of the EDDI. This algorithm will detect GTC epileptic seizures. For more information see section 4. The device is CE marked for detecting GTC epileptic seizures on patients aged 3-80.

3.5.6 Flow chart

Table 1 Flow chart

Assessment	Screening	Inclusion	Data collection	End of investigation
Day	**<21 days prior to inclusion**	**1**	**1-5**	**1-5**
Information to patients and caretakers	X			
Informed consent	X	X		
Eligibility criteria		X		
Demographics		X		
Type and frequency of seizures		X		
AEs (each day)			X	X
Gold standard monitoring (video + EEG)			X	X
EDDI (every 24 hours, changed at the same time each day)			X	X
Details on convulsive seizures (time – abnormalities?)			X	X

Figure 1 Schematic diagram of investigation

4. Identification and description of the investigational device

4.1 Summary description of the investigational device

The wireless medical device class I holds a CE mark. It is named EDDI (Epileptic seizure Detector Designed by IctalCare) and is designed to alarm of GTC epileptic seizures. IctalCare has designed an algorithm, which is implemented in EDDI. This algorithm will make it possible to detect the GTC epileptic seizures.

4.2 Details on EDDI

sEMG Patient Unit (2 pieces) 	The active part, which is placed on the patient during the clinical investigation, is called a patient unit. It consists of two units: an electrode (the plaster) and Senses (the case with the electronics). During the clinical investigations each patient will be wearing one patient unit placed on one of the upper arms. Every 24 hours the electrode and the battery in Senses must be exchanged with new ones.
W 	The electrode consists of gel with three sensors for measurements of bio-signals. It may be used up to 24, and be relocated three times within the 24 hours. (Single patient use only). Afterwards it is disposable.
Senses 	Senses contains electronics for measuring and processing the sEMG signal. The Senses device includes a microprocessor, a frontend, and memory and data storage capability. Furthermore it includes an 868MHz radio, to communicate with the A-Unit. The Senses includes software (SW) that calculates on all the sEMG data, using the seizure algorithm. All seizure events are stored locally and sent via radio to the A-Unit.
A-Unit 	The A-Unit contains a 868MHz radio and communicates with the Senses. All information on the seizure events is stored in the A-Unit. The A-Unit contains software which makes sure that the seizure events are time stamped.

Battery 	Batteries: The Senses needs one CR2450 type battery. The battery will be exchanged every day.

4.2.1 Design properties

EDDI consists of a soft and flexible plaster, electrode, and an active device, Senses. The electrode is designed, to be easily placed on the patient's upper arm, and so that the patient notices the device as little as possible, while it is mounted on the arm. Senses is connected to the electrode with three buttons in a way, which aims at making it unnoticeable to the patient. All material used in the electrode are known to be biocompatible. The high tack multi-purpose hydrogel makes the electrode easy to remove without discomfort for the patient.

The casing of Senses is designed to fit to the new electrode. The Senses contains no SD-card, the data is time stamped and transferred wirelessly via a radio link to the A-Unit, where it is stored on an SD-card.

4.2.2 Materials

Only the electrode is in direct contact with the skin of the patient. This electrode has been tested and validated by the manufacturer, and holds a CE mark.

4.2.3 Biological components or biologic active materials

No biologic materials are used.

4.2.4 Installation, use, control and removal

The EDDI is delivered in a box. The use of the system is described in the "Instruction For Use". The Senses is placed on the patient as described in the IFU, and the two devices are turned on to start the surveillance of the patient. The mounting of the Senses is done by the investigator or a study nurse after instructions by the investigator.

At the end of a trial the Senses is removed from the patient, the electrode is trashed, and the EDDI system is packed away in the allocated box, when the SD-card has been removed from the A-Unit and sent to IctalCare, and a new SD-card has been placed in the A-Unit.

4.2.5 Training and experience

Before the investigation is initiated the staff members in the EMU are instructed by personnel from IctalCare in the preparation, use, control and removal of the system. Furthermore they are shown how to remove the SD-card and replace it by a new one.

4.2.6 Medical procedure

In the investigation all surveillance monitoring of the patients in the EMU is performed as usual, when a patient is admitted for 24 hours surveillance or more in relation to a diagnosis or improvement of the treatment.

4.2.7 Known and potential risks

As the patients are under surveillance according to the normal clinical setting, the only risks are the ones related to the use of EDDI, which are addressed in section 4.2.8.

4.2.8 Results of the risk analysis

A risk management analysis was conducted as part of the design and development process with respect to the guidelines in *ISO14971*: "A risk management plan was included as part of the design and development plan. Product characterization and hazard analysis were performed. Two separate risk analyses were performed for use, and design and manufacturing risks. Finally a risk management report was concluded".

5. Justification for the design of the clinical investigation

Epilepsy is a common serious neurological condition with a prevalence of 0.8-1.0%. People with epilepsy find it helpful to consider safety aids or equipment that might help them with day-to-day life. For example, an alarm that can alert family or friends when someone has a seizure, or a safety pillow if they have seizures while asleep. IctalCare developed EDDI, a wireless alarm (in the form of a plaster) that is able to detect GTC seizures in epileptic patients.

In a clinical investigation (DK007-ME) an algorithm, which made it possible to detect GTC seizures, was developed. It was first tested in IRIS, a predecessor for EDDI, in a second clinical investigation (DK006-ME). IRIS was used on 13 patients with epilepsy to measure sEMG. GTC seizures were confirmed by the gold-standard (video monitoring and EEG recordings) for four patients, and the algorithm proved efficient. No SADE, nor SAEs, nor device deficiencies that might have led to a SAE were reported.

6. Risks and benefits of the investigational device and clinical investigation

Based on the risk management analysis (see section 4.2.8), no known risks are expected during the trial. Only exception: as some patients are allergic to standard plasters, some patients may as well be allergic to the gel used on the electrodes.

There are no known benefits.

7. Objectives and hypotheses of the clinical investigation

7.1.1 Primary objective

- To investigate the sensitivity of EDDI's ability to detect GTC seizures.

7.1.2 Secondary objectives

- To investigate the specificity of EDDI's ability to avoid false alarms.
- To investigate reasons for possible registered false alarms.
- To investigate the latency of the seizure detection by the EDDI compared to the actual start of the GTC seizure.
- To investigate the EDDI's ability NOT to detect PNES which visually look like GTC seizures.

7.1.3 Hypothesis

From previous results on the same type of data (sEMG) it is expected that the sensitivity and FDR of this study will be comparable those previous ones. The differences lie within the newer version of the device (EDDI) measuring the sEMG signal. The software is the same as used in IRIS, and most of the hardware as well. The electrode is different, but clinical tests have shown that the newer electrode provides a signal-to-noise ratio (SNR) which is equally good or better compared to the older version of the electrode (used with IRIS in DK006-ME).

8. Design of the clinical investigation

8.1 General

The investigation is designed as an assessor controlled double-blinded clinical investigation assessing the sensitivity and specificity of EDDI, in detection of GTC seizures in epileptic patients. As a secondary outcome the study furthermore tests EDDI's ability NOT to alarm on PNES.

The assessor is a physician at the site(s) and will provide details on seizure type and time, based upon the gold standard: video monitoring and EEG. The EDDI will not provide a visual or audible indication whether an alarm has occurred. In this way, the assessor will remain blinded to the alarms set by EDDI. The EDDI works in real time and will thereby be blinded from the annotations by the clinical personnel.

The seizure times obtained by the EDDI will be transferred to a computer. This data has an audit trail and cannot be changed.

8.2 Investigational device and comparators

8.2.1 EDDI

EDDI is used to measure sEMG, and detect GTC seizures based on this signal. For this purpose an EDDI is used on biceps of one of the upper arms. The electrode is placed on the outer side of the biceps as shown in the IFU.

8.2.2 Comparators

The alarms of the EDDI are compared to the physician's interpretation of when GTC seizures have occurred. This interpretation is based on both EEG measurements and video surveillance.

8.3 Subjects

Subjects will be selected among patients who are signed up for hospitalized at specialized epilepsy centers for another reason than participation in this study (e.g. to investigate suspected epilepsy or to improve

their epilepsy diagnosis and treatment). Subjects are to fulfill the in- and not the exclusion criteria listed in section 3.5.3.1 and 3.5.3.2 respectively.

Subjects will be asked whether they would be interested in participating in the study at the preliminary consultation before the video-EEG monitoring. Patients will receive written information about the project. Those patients who will be interested in participating in the study will be called to an information meeting, where they can also take an accompanying person with them.

Subjects will participate in the investigation for the duration of their hospitalization (maximum 4 days). Prior to the hospitalization and enrollment into the investigation, subjects are to give their consent to participate as described in section 15.

Total number of subjects to be included is expected to be approximately 80. From these included patients only those with either epileptic GTC seizures or non-epileptic convulsive seizures (PNES) are included in the final evaluation of the EDDI.

The first patient is expected to be included in February 2014 and the last patient is expected to end participation in October 2014 or when the planned number of patients has been included.

8.4 Procedures

The following sections describe the methods of assessments and list the type of data to be recorded in the Clinical Record Form (CRF). A detailed schedule for the different assessments is given in the flowchart in Section 3.5.6.

8.4.1 EEG

EEG is measured on all patients. For this purpose the installed conventional equipment at the different sites are used. The electrodes are placed according to the standard 10-10 or 10-20 system. All standard routines in the EMUs are followed.

Data is recorded continuously throughout the entire period, where the patients are under observation (1-4 days).

8.4.2 Video surveillance

All patients are under continuous video surveillance in the entire time they are under observation (1-4 days).

8.4.3 ElectroCardioGraphy (ECG)

ECG is measured on all patients with the standard equipment at the sites. The standard routine in the EMU is followed.

Data is recorded continuously throughout the entire period, where the patients are under observation (1-4 days).

8.4.4 EDDI

The only investigational related activities for the patients are the mounting of an EDDI.

8.4.5 Overview of visits

In agreement with the established procedure the patient is firstly summoned to a talk with the physician (an investigator in the investigation) and possibly a nurse (also delegated to the investigation) regarding the purpose and the practicalities of the admission. During the talk with the physician, the patient will receive both oral and written information on the investigation.

The patient may give the written consent during the talk with the physician or during the possible talk with a nurse on the day of admission.

The clinical investigation starts at the same time as the other surveillance of the patient, in respect to the defined procedure in the EMU. In the same way the investigational part ends at the end of the admission of the patient.

8.5 Monitoring plan

The Device manufacturer will initiate the participating site(s) during an on-site visit.

The progress of the clinical investigation will be monitored by the Device Manufacturer, where the focus is to verify that data accrual is happening in concordance with the protocol to ensure conclusions based on the collected data are valid and that regulatory requirements are fulfilled.

The investigator documentation will be monitored for completeness including appropriately signed informed consent forms for all included subjects. Subject identification data, inclusion and exclusion criteria, the endpoint variables and AEs will be source data verified.

At the end of the clinical investigation, all participating sites will have a close out visit.

The sponsor shall assess the extent and nature of monitoring appropriate for the clinical investigation, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation. Results of this assessment shall be used to develop a monitoring plan.

8.6 Data collection

8.6.1 CRF data

The following information will be annotated in the CRF:

- Patient number
- Gender
- Age
- Diagnosis
- Monitoring, start and stop time
- For the seizures:
    - seizure type (Simple partial, complex partial, hypermotor, myoclonic, tonic, clonic, GTC, generalised – other than the above mentioned)
    - for the GTC seizure and PNES:

    - Date and time of start and stop of the seizure.
- Comments
- Investigation center
- AE type and description

8.6.2 Other parameters

- Seizure alarms recorded with EDDI (see section **Error! Reference source not found.**)
- EEG (see section 8.4.1)
- Video surveillance (see section 8.4.2)
- ECG (see section 8.4.3)

9. Statistical considerations

9.1 General considerations

A one group design is chosen due to the objective of estimation of sensitivity. No hypotheses are tested, but 95% two sided confidence intervals are constructed for the measure of sensitivity and specificity.

All patients enrolled who has been wearing the device, will be included in the Full Analysis Set (FAS) which forms the basis dataset for all analyses. No subgroup analyses are planned in advance. However if the final data end up showing equally distributed amounts of seizures from both kids and adults, we may study the result in the two subgroups.

The primary endpoint, the sensitivity, will be calculated as described in section 3.5.1 along with a 95% confidence interval (CI). The expectations for sensitivity (true positive assessments) are a lower limit of the two-sided 95% CI of more than 95% ± 5%.

The specificity is calculated and evaluate indirectly as the false detection rate (the number of false detections per hour). This parameter will be estimated along with 95% CI.

The effect of the GTC seizure alarm in a nocturnal situation (23:00 - 07:00) is found. Both the sensitivity and specificity will be calculated based on the data within this period of time (23:00 – 07:00) for each day and analyzed similarly to the analysis of the 24h periods.
Each false alarm is evaluated based on the video data to figure out, what may have caused it.

Adverse events (AEs) are summarized descriptively by type. Please refer to section 16 for details on AE collection types.

9.2 Sample size consideration for alarm correctness

With an expected sensitivity of 95%, a sample size of at least 19 patients with epileptic GTC seizures is needed. Based on this it has been chosen to include 20 patients with epileptic GTC seizures and furthermore 10 patients with PNES. To succeed in this inclusion, it is expected that about 80 patients will be included in total.

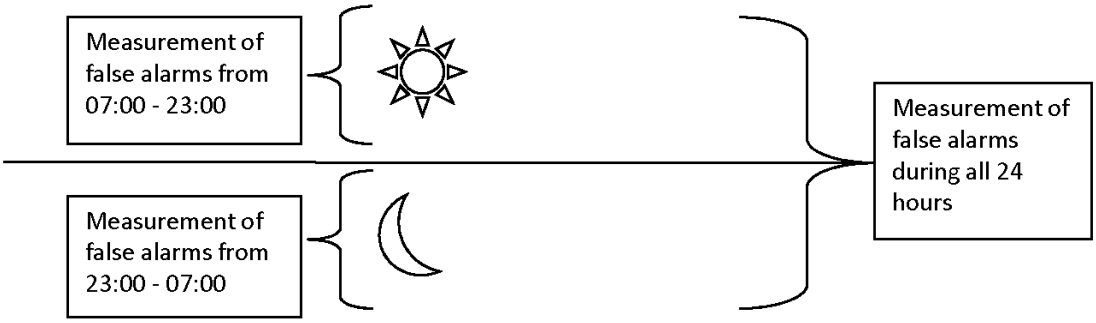
10. Data Management

Generally, data will be collected on CRFs and transferred to the database, which is maintained by the sponsor. Data (seizure times) from the EDDI are during the monitoring saved on SD-cards. When a patient is finished, all data in 8.6.1 is typed down in the CRF and sent to the sponsor. The SD-card is shipped to the Device Manufacturer, who will read out the seizure detection times, and sent them to the sponsor, who will collect them in a separate CRF. The sponsor is responsible for collecting all data in the two CRFs, and furthermore locks these two documents. A copy of the final two CRFs will be handed over to the Device Manufacturer.

Sponsor will keep data for 10 years.

10.1 Data analysis

The data analysis will be performed by the principal investigator. The sensitivity and specificity of the device will be calculated. Furthermore the specificity will be calculated explicitly during night time.



For each false positive the EEG and video should be checked to see if there is an explanation for the false alarming.
Also for each GTC seizure that is registered by the alarm the latency should be calculated from the onset of the tonic phase of the GTC seizure.
For the patients with PNES it should be calculated how many of the seizures are registered by the alarm. The number is expected to be 0.

11. Amendments to the CIP

Any variation in procedure from that specified in the Clinical Investigation Plan (CIP) may lead to the results of the Investigation being questioned and in some cases rejected. Any proposed CIP changes will be documented in a CIP amendment and this will be submitted to the Research Ethics Committee (REC) for approval prior to implementation.

12. Deviations from clinical investigation plan

Deviations from the CIP are not permissible (except in an emergency).

Any deviations are to be documented in the final Investigational Report.
Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC/Regulatory authorities.

Such deviations shall be documented to the sponsor and the EC as soon as possible and may cause amendment to the CIP.

13. Device accountability

Accountability of the device and related supplies will be kept by IctalCare and the investigational site(s). An accurate, timely record for the disposition of all devices and related supplies must be maintained as follows:

- Identification of the subject to whom which device(s) were allocated and used by
- The date(s) and quantity of device(s) and related supplies used by the subject
- The product lot/batch numbers

Records/tracks will be documented.

14. Statements of compliance

The investigation will be conducted in accordance with the ethical principles contained in the Declaration of Helsinki, the requirements of the Ethics Committees, and the European Medical Device Directive, EN ISO 14155-1, EN ISO 14155-2 and the CIP.

14.1 Approval of the ethics committee

The test will be reported to the local REC by the investigator(s).

14.2 Approval of the Danish Health and Medicines Authority

The EDDI is CE marked, and an approval from the Danish Health and Medicines Authority is thereby not necessary.

14.3 Danish Data Protection Agency

During the investigation information on private relations regarding the patient will be stored and processed, thus it is to comply with the regulations put forth in the Act on Processing of Personal Data.

15. Informed consent process

Prior to any investigational related procedures the information for the patient and the declaration of consent (approved by the local REC) are provided to the patients by an investigator delegated to the task. The information is given both in writing and orally in a, to the patient, understandable language. The written consent will be collected.

The oral information must be provided in an undisturbed room. The patient should have plenty of time to ask questions and may bring a companion to the conversation, which he/she should be informed about prior to the talk. The written consent is given based on both the written and oral information and may further be provided after some time to consider the information.

The original written consent is stored by the investigator. A copy of the written consent is provided to the patient.

The patient may at any time and without any explanation withdraw the written consent and thus withdraw from the investigation. This will not have any affect for the patient in the present or later treatments.

Children

When a child or a young person under the age of 18 participates in the investigation, the written consent is obtained from each of the persons holding the custody. The persons holding the custody are informed about the investigation both orally and in writing.
The child or the young person will also receive oral information on the investigation. The information will be given by a person, who has the preconditions to inform a child or young person, so that it is told in a way suited the age of the patient.
Possible expressions by the child or young person will have influence in the extent where it is relevant.

If a patient aged 15-17 wishes to have the information in writing, written information will be provided in a language adjusted to the age of the patient.

When including under-aged patients in the investigation, it requires that both possessors of custody give their written consent. This is not the case, when one parent has authorized the other in decisions regarding the child's participation in investigations.
The consent will express the interest of the under-aged patient. If the under-aged patient protests against the investigation, orally or physically, the investigation cannot be accomplished.
If the under-aged patient turns 18 within the investigational period, a written consent is to be obtained from the patient before the investigation continues.

The consent will be written, dated and signed based on the received written and oral information. The consent will be given to the person responsible for the investigation or the one who have been given the responsibility of providing the oral information. This person will be directly associated to the investigation. Original written consents will be stored by the person in charge of the investigation, and the patient or the persons holding the custody will be given a copy of the attested consent.

Mentally retarded adults

In the investigation it is the guardian, or the closest relative and the practicing doctor, or alternatively the National board of Health, who will submit the deputy consent.

The deputy consent will be obtained in cases where the patient is unfit/unable to give the consent themselves. This includes that the person giving the deputy consent must be informed of the investigation both in written and orally.

The mentally retarded adult patients, who are unable to give a written consent, will be informed and involved in the conversation on the investigation in a suited extent, unless it is damaging for the patients. The patient's expressions will be ascribed value in the amount it is relevant.

Regarding the closest relative: A specific evaluation will define who the closest relative is. This may be the patient's spouse, relative in straight line or siblings. Dependent on the circumstances, foster children will

often be considered as the closest relative, especially when there is no spouse or children. In such cases other relatives, which are tightly bound to the patient, will be seen as close relatives. Both the family relation and the tightness of the bound are considered. The person submitting the deputy consent will know the patient very well and hold the patient's trust. Thus a very close friend is able to give the deputy consent in some cases.

Regarding the practicing doctor or health inspector: The deputy consent from the practicing doctor will be submitted based on the doctor's knowledge of the patient, or the doctor's ability to become familiar with the patient or the patient's health relation, compared to the information on the investigation. The deputy consent of the doctor will be obtained to secure extra protection of the mentally retarded adult.
When the patient's doctor is absent, or the patients does not have a fixed doctor, the deputy consent must be submitted from the closest relative or the National Board of Health (health inspector).
The practicing doctor or the National Board of Health will, because of his/her education ensure that the consent is handled such that the patient is not harmed. This will be based on the doctor's knowledge of the patient or the doctor's ability to become familiar with the health of the patient.

Regarding the guardian: The guardian will submit the deputy consent, if the person to attend the investigation is under personal guardianship. This requires that the guardianship contains the authority to provide consent regarding participation in trials.

The deputy consent will express the patient's interest and the patient will receive information adjusted to the comprehension ability of the patient. Regardless of deputy consent, the investigation will not be conducted if the patient resists. This does not have to be formulated orally, but may also be expressed physically.
The consent will be written, dated and signed based on the received information; written and orally. The consent will be given to the person responsible for the investigation or the one who have been given the responsibility of providing the oral information. This person will be directly associated to the investigation. Original written consents will be stored by the person in charge of the investigation, and the patient or the persons holding the custody will be given a copy of the attested consent.

16. Adverse events, adverse device effects and device deficiencies

16.1 Adverse Event (AE)

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 investigated medical device. This includes events related to the investigational device. This includes events related to the procedures involved (any procedure in the clinical investigation plan).

16.2 Adverse Device Effect (ADE)

AE related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse.

16.3 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or user error and inadequate labeling.

16.4 Serious Adverse Device Effect (SADE)

A **Serious Adverse Device Effect** is an Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event (see 16.5). Added to that also **near-incidents** which are characterized by the fact that it would have led to above consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

16.5 Serious Adverse Event (SAE)

AEs that resulted in one or more of the following:

- Death
- Life-threatening injury or illness
- Permanent impairment of a body structure or body function
- Patient Hospitalization or prolongation of existing hospitalization
- Medical or surgical intervention to avoid the above

Fetal death, a congenital abnormality or birth defect in the fetus or any other negative effect on the fetus.

A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a SAE.

16.6 Unanticipated Serious Adverse Device Effect (USADE)

SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

16.7 Reportable events

The following events are considered reportable events

- any SAE or SADE,
- any Investigational Medical Device Deficiency (near-incident) that might have led to a SAE if
    - suitable action had not been taken or
    - intervention had not been made or
    - if circumstances had been less fortunate
- any new findings/updates in relation to already reported events.

16.8 Reporting timelines

The principal investigator at the sites is responsible for reporting all SAE or SADE at their own site.

The present study is a clinical investigation of a medical device, thus events related to the patient's daily or acute medication will not be reported. Adverse effects suspected to be caused by the patient's medication

will be reported in accordance with the normal obligation to report for medical personnel, established by the DHMA. This means all critical or unexpected adverse effects from medications are reported. Besides it is the medical doctors duty to report known or none critical side effects in the first two years the product is on the market:

http://laegemiddelstyrelsen.dk/da/topics/bivirkninger-og-forsoeg/bivirkninger/meld-en-bivirkning-eller-utilsigtet-haendelse/mennesker/meld-en-bivirkning-ved-medicin-til-menne---e-blanket

All events, which are not related to the medication of the patient, will be reported in the CRF from the time of inclusion to withdrawal of the patient.

All SAEs occurring from accept of the participation to the end of the investigation will be reported by filling in and sending in the SADE form to the Medical monitor of the sponsor. This is to take place within 24 hours from the point where the investigator has encountered that the event fulfills the definition of a SAE/SADE. After this initial SAE/SADE report has been filled in, the investigator is obligated to proactively communicate further information on the patient's condition. All follow up information must be submitted to the Medical Monitor, as soon as it is available. If there appear SAEs/SADEs after the end of the investigation, they must be reported if they are related to the investigation.

The obligation to report is also present for SAE or SADE caused by inaccurate or insufficient results from diagnostic equipment, e.g. a wrong diagnosis, a delayed diagnosis, delayed treatment or wrong treatment.

The Medical Monitor of the Sponsor must ensure, that it is carefully evaluated whether the SAE or SADE are caused by the medical device during the trials or consequences of the use of the medical device.

The Medical Monitor of the Sponsor must ensure that all information on the SAE or SADE are registered and submitted to the REC as fast as possible and within 7 days after the Medical Monitor of sponsor has become aware of the event. However the deadline is 2 days, if the incident constitutes an imminent risk of further deaths, serious injury or illness and which requires immediate action to other patients / subjects, users, or others.

The information must be reported on "Notification Form for Serious Adverse Events or near-incidents with Medical Devices during the clinical investigation", which can be found on the DHMA:

http://medicinskudstyr.dk/da/menu/klinisk-afproevning/ansoegning-om-klinisk-afproevning-af-med--nsk-udstyr

Every report must be followed by comments on possible consequences of the investigation.

All Follow-up information to an already reported SAE/SADE is to follow the same requirements of and timelines for reporting as the initial report.

All events occurring during the trials must be reported in the final report of the investigation. This will also include events, which are not critical.

For all occurring deaths, reported at any time, all available autopsy reports and relevant medical reports must be sent by fax to the Medical Monitor (in a blinded format with no patient names).

16.8.1 Follow-up on events

All events, regardless of the severity, will be followed till the events are resolved or stable or until the patient is no longer available for follow-ups. Subject follow-up is performed according to normal clinical procedures after a monitoring/hospitalization period.

17. Vulnerable population

Patients included in the investigation may be persons under the age of 18 (down to 3 years of age) and some of them (both children and adults) may be mentally retarded. In each case the responsible physician is to ensure that the information given and consent retrieved is in compliance with the ethical requirements.
There is nothing in the investigation which will cause a special risk to children or the mentally retarded in comparison to the legally competent adult volunteers.
All groups of patients described above are in the target group of patients who may potentially benefit from the results of this investigation in the future.
Overall it is believed that the investigation will not cause the patient any risk and it is therefore considered ethically responsible to conduct the investigation in all of the above mentioned groups of patients.

18. Suspension or premature termination of the clinical investigation

Participation in the investigation is strictly voluntary. Subjects are free to discontinue in the investigation at any time with or without giving any reason(s).

A subject is withdrawn from the Investigation in the event of any of the following:

- Withdrawal of consent
- Discontinuation of the monitoring/hospitalization
- Occurrence of a serious or non-serious Adverse Event, Adverse Device Effect or Device Deficiency that in the investigators opinion deems the subjects participation not safe
- No longer in compliance with in- and exclusion criteria
- Subject not in compliance (not able or willing to wear/use the device)

In case of premature withdrawal of a subject, this will be documented in the CRF.

Subject follow-up is performed according to normal clinical procedures after a monitoring/hospitalization period.

19. Publication policy

The investigator is obligated to publish negative as well as positive results. This should take place shortly after the investigation is finished, and at the same time in a professionally and sensible way corresponding to the law of data protection. If it is not possible to publish the results in a scientifically journal paper, it should be published in another way. It should be listed how this publication will take place.

The results of the study will be published in a pre-reviewed scientifically journal paper. Neither investigator nor sponsor may publish or submit the results without giving the other part 30 days to go through and

comment on the manuscript before submission. Investigator and sponsor will set down a work-group to settle on how the results are to be published.

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