

**RESEARCH PROTOCOL**  
**PROMISE study**  
(April 2018)

**PROTOCOL TITLE :**

“Promoting implementation of seizure detection devices in epilepsy care: the PROMISE study.”

<b>Short title</b>	The PROMISE study
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**LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

<b>ABR</b>	<b>ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)</b>
<b>AE</b>	<b>Adverse Event</b>
<b>AR</b>	<b>Adverse Reaction</b>
<b>CCMO</b>	<b>Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek</b>
<b>DSMB</b>	<b>Data Safety Monitoring Board</b>
<b>EEG</b>	<b>Electroencephalography</b>
<b>EU</b>	<b>European Union</b>
<b>EudraCT</b>	<b>European drug regulatory affairs Clinical Trials</b>
<b>FNAR</b>	<b>False negative alarm rate</b>
<b>GCP</b>	<b>Good Clinical Practice</b>
<b>IB</b>	<b>Investigator's Brochure</b>
<b>IC</b>	<b>Informed Consent</b>
<b>Kempenhaeghe</b>	<b>Academic Centre of Epileptology Kempenhaeghe</b>
<b>METC</b>	<b>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</b>
<b>QoL</b>	<b>Quality of Life</b>
<b>(S)AE</b>	<b>(Serious) Adverse Event</b>
<b>SDD</b>	<b>Seizure Detection Device</b>
<b>Sponsor</b>	<b>The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.</b>
<b>SEIN</b>	<b>Stichting Epilepsie Instellingen Nederland</b>
<b>SUSAR</b>	<b>Suspected Unexpected Serious Adverse Reaction</b>
<b>UMCU</b>	<b>University Medical Center Utrecht</b>
<b>Wbp</b>	<b>Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)</b>
<b>WMO</b>	<b>Medical Research Involving Human Subjects Act (in Dutch: Wet</b>

**Medisch-wetenschappelijk Onderzoek met Mensen)****SUMMARY**

**Rationale:** Various remote and wearable sensor devices have become available for the detection of potentially dangerous seizures, with limited impact on epilepsy care so far. Both our remote and our wearable seizure detection devices (SDDs) have been extensively tested and proven highly sensitive. Yet the home performance in children, an important target population, had been insufficiently studied.

**Objective:**

1. To test the performance of the wearable SDD (NightWatch) prospectively and the remote SDD (automated video and audio analysis) retrospectively in children in a family home setting. 2. To assess the feasibility, cost-effectiveness and cost-utility of NightWatch in children.

**Study design:** A multicenter home-based medical device intervention study with prospective validation of our wearable SDD.

**Study population:** 60 children (ages 4-16 years) with refractory epilepsy ( $\geq 1$  major nocturnal seizure per week) recruited from the outpatient clinics of one of the participating epilepsy centers (Stichting Epilepsie instellingen Nederland (SEIN), Academic Centre of Epileptology Kempenhaeghe (Kempenhaeghe), University Medical Center Utrecht (UMCU)).

**Intervention (if applicable):** Phase I: Two months of baseline (usual care); Phase 2: Two months of nocturnal seizure monitoring at home, using NightWatch and the remote SDD.

**Main study parameters/endpoints:** The diagnostic performance of NightWatch and the remote SDD algorithms, i.e. sensitivity, positive predictive value, false alarm rate and % time with uninterrupted signal output. We will evaluate feasibility of NightWatch through surveys on quality of life, sleep, parental strain, interviews with parents/guardians and neurologists, and a value sensitive design group session. We will also perform a cost-effectiveness and cost-utility analysis by medical consumption and costs questionnaires.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** Implementing SDDs will not pose any direct or substantial risk. Study participation can be a burden though, due to impact of the devices on privacy, number of false alarms and time spent on the questionnaires and interviews. Application of the SDDs, however, might offer better insight into the actual number of nocturnal seizures in a child, change in medical management and facilitate appropriate interventions in major motor seizures. If reliable, SDDs may improve the night rest of both patient and parents/guardians.



## 1. INTRODUCTION AND RATIONALE

Epilepsy impacts ~180.000 people in the Netherlands [1]. Despite advances in treatment, one third of all people with epilepsy continue to have seizures [2] that adversely affect quality of life (QoL) [3,4]. Poor seizure control is the major determinant of impaired QoL. Seizures impact not only individuals with epilepsy but also their guardians [5-7] as seizures are (1) unpredictable, (2) may cause loss of control and (3) cause life threatening situations, including injuries, status epilepticus and sudden unexpected death in epilepsy [8]. Convulsive seizures carry the greatest mortality risk, particularly those occurring at night, as these are often unwitnessed [9]. Childhood epilepsy has also a severe impact on parental QoL [10] and monitoring devices can help to improve parental anxiety levels, quality of sleep, and QoL [11]. Various non-EEG based signals have been assessed for the detection of potentially dangerous seizures [12]. Seizure detection devices (SDDs) have had, however, limited impact on epilepsy care so far. Barriers to SDD implementation include lack of external validation and high rate of false alarms. Most SDDs rely on a single modality. This approach likely explains limited sensitivity and specificity [12]. Previous studies validated multimodal algorithms for wearable sensors (accelerometry & heart rate) and demonstrated the feasibility of remote sensors (audio & video) to detect seizures [13-17].

Preliminary results indicate that the performance of the NightWatch is superior to a commonly used bed sensor, the Emfit. Our multicenter prospective trial in a residential population of adults with epilepsy and learning disabilities (LICSENSE trial, NTR4115) shows a median sensitivity per person of 85.7% with a positive predictive value of 49.3% and a median false negative alarm rate of 0.04 per person per night [18]. The interim analysis of our recent trial in 21 children (LICSENSE phase III) indicated that the algorithms needed an adjustment as in children higher heart rates are more common and less specific features for epilepsy appear thus increasing the number of false alarms. In response we updated our algorithm (with less emphasis on heart rate changes and more weight on movement changes). This approach still reach 80% sensitivity and 50% PPV in the majority (80%) of subjects (adults and children). This current prospective home-based trial is needed as a final validation step for the new algorithm in children and to evaluate feasibility of NightWatch. Former trials were performed without actual alarms. The current trial also enables us to get insight in the real life situation of children and their parents/guardians by focusing on feasibility. The literature has so far only discussed these needs with questionnaires but without insight into the home situation [19].

Remote SDDs may provide an alternative for wearable sensors, especially when they are not tolerated. We recently demonstrated the feasibility of video algorithms to detect convulsive seizures in a small clinical cohort (a learning set of 50 subjects with 72 convulsive seizures and a test set of 12 individuals and 50 seizures). Performance analysis resulted in 100%

sensitivity of detecting tonic-clonic seizures and 57% of detecting non-vital minor seizures. 67% of latencies were  $\leq 10$  seconds and the median false detection rate was 0.78 per night [13]. A previous study found a sensitivity of audio detection of 81% by analyzing seizure specific sounds in 10 subjects with 112 major seizures [15]. All false positive alarms (mean value: 1.29 per night) were due to minor seizures and 4 seizures (3%) were missed because of lack of sound and 10 (9%) because of sounds below the system's threshold. The company CLB Acoustic Monitoring has developed several acoustic monitoring devices for use in health care. They collected a large database of distinct sounds, including seizure related ones. For both remote SDD components (video and audio) long-term databases are needed to determine false alarm rates.

The current study will test (1) the performance of NightWatch with a fixed algorithm and (2) optimize the algorithms for the remote SDD (video and audio).

All studies on any SDD have been performed in a clinical (hospital/institution) setting. These study populations do not represent the general epilepsy population, and (sleep) settings in the hospital clearly differ from at home. Our study will test the SDDs in a family home setting and will be the first real field SDD implementation study. By focusing on the patient and family perspective, we will obtain crucial feedback on which performance is feasible for them and in which way parents/guardians experience support from an SDD. This study design will comply with the concepts of the Dutch Health Board's recommendations for novel devices [20].

## 2. OBJECTIVES

### Primary Objective:

Diagnostic performance of our wearable multimodal SDD (NightWatch) to detect major nocturnal motor seizures in children at home. Diagnostic performance of NightWatch will be measured prospectively by means of sensitivity, positive predictive value, false alarm rate and % time with uninterrupted signal output.

### Secondary Objectives:

- Diagnostic performance of our remote SDD (video and audio) to detect major nocturnal motor seizures in children at home. Diagnostic performance will be measured retrospectively by means of sensitivity, positive predictive value and false alarm rate and % time with uninterrupted signal output.
- Feasibility of NightWatch with a mixed methods approach focusing on Acceptability, Demand, Implementation, Practicality, Expansion and Limited-efficacy testing (caregiver strain (CSI), sleep (PSQI), QoL (EQ-5D-5L)) and impact of the SDD on parents/guardians and children (interview).
- Economic evaluation from a societal prospective of NightWatch involving a combination of a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). (*See 8.1.2. Methods*)

### 3. STUDY DESIGN

This is a home-based medical device intervention study, with prospective validation of our wearable device, including 60 children with refractory epilepsy ( $\geq 1$  major nocturnal seizure per week) from three epilepsy centers (SEIN, Kempenhaeghe, UMCU). Subjects will receive usual care during the first two months (non-exposure period), followed by home-based nocturnal monitoring for two months (exposure period) [See Figure 1]. In both periods parents/guardians will be invited to keep a seizure diary. The NightWatch wirelessly transmits sensor outputs to a monitor in the parents/guardians room to alert them in case of a suspected seizure [See Figure 2]. Simultaneous video and audio recordings will be stored and analyzed offline.[21] Both algorithms will generate marks in dataflow, but these marks will not be used to alert the parents/guardians and will only be examined by the researchers.[See figure 3] The video material will also be used to screen for false negative alarms and to improve the algorithm when necessary (comparable with the LICSENSE study design, NTR4115).

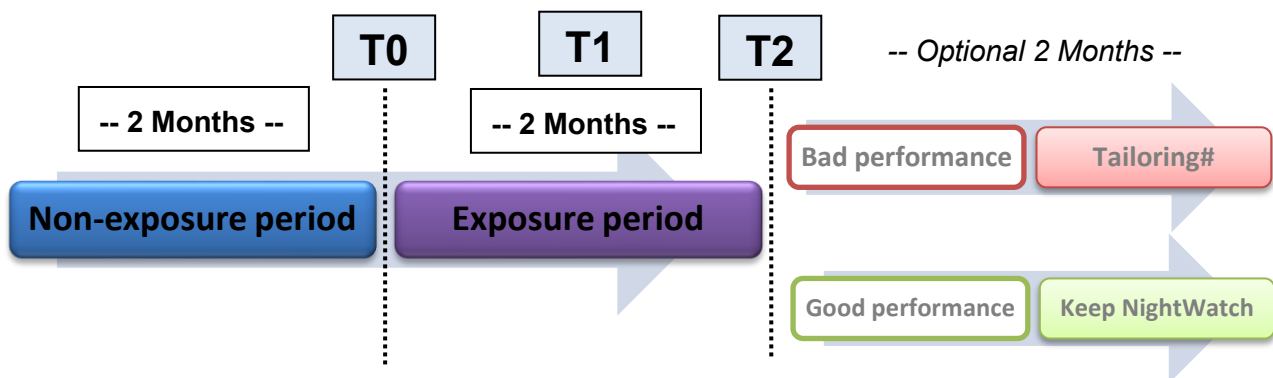
Trial nurses will check the validity of the generated alarms and marks in a blinded way and screen 5% of the nocturnal video recordings without alarms. The LICSENSE trial demonstrated a median false negative alarm rate (FNAR) of 0,03 per subject per night with 10% screening of all nights. We believe that 5% screening will also be feasible, but we will perform an interim analysis after inclusion of 20 subjects to see whether FANR is still reasonably low (below 0,1 per night). If this is not the case, we will increase screening to 10% of all nights. The LICSENSE trial found a high Cohen's kappa (0.77) for inter-observer agreement between trial nurses and neurologists. Therefore, this expert review of the nocturnal video recordings by the trial nurses will serve as the gold standard. Cases of doubt will be discussed with a neurologist. Seizures will be stratified according to type (tonic-clonic, >30 seconds tonic, hyper motor and major) and severity (minor/major).

Parents/guardians will be invited to articulate their user experiences at focus meetings. Video tracings of detected seizures of their child will be shown to the parents/guardians who will be asked to indicate whether they would want to be alerted for these events or not. Results from these meetings will be included in the discussion on which type of seizures should be alarmed by SDDs.

To evaluate SDD feasibility, we will compare parental strain, quality of sleep and QoL during the non-exposure period and exposure period [22]. Based on a survey after the exposure period, we will calculate retention rate.

After the exposure period, we will offer the parents/guardians and children  $\geq 12$  years of age two options, based on the diagnostic performance of the NightWatch in their child.

1. In case of bad performance, we will offer a second-2-month period of monitoring in case we noted that an individualized adjustment of the algorithm (i.e. threshold adjustments for heart rate & accelerometry settings) using the data from the exposure period results in a substantial improvement. We will prospectively test the diagnostic performance of the adjusted algorithm prospectively and compare results between both periods.
2. In case of good performance, we will offer the parents/guardians the possibility to keep the NightWatch for further use, under certain conditions. (See 11.4 Ethics)



**Figure 1: Study design.**

# If this results in a substantial improvement of the NW performance



**Figure 2: NightWatch around upper arm.**



**Figure 3: alarm system (left) and NightWatch (right).**

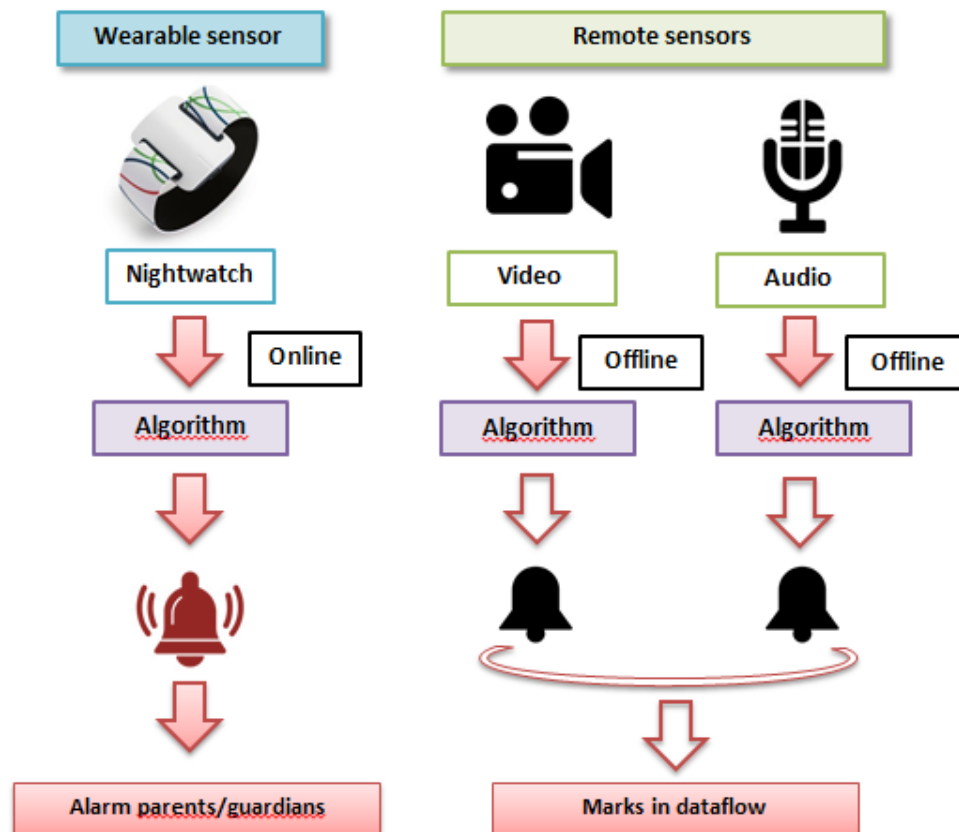


Figure 4: Overview of SDDs in study.

## **4. STUDY POPULATION**

### **4.1 Population (base)**

Around 20,000 children carry the diagnosis of epilepsy in the Netherlands [23]. Most children with severe or difficult to treat epilepsy are under specialized epilepsy care in SEIN, Kempenhaeghe or UMCU. This study will include 60 children with refractory epilepsy ( $\geq 1$  major nocturnal seizure per week) from one of the above epilepsy care facilities. There will be no restrictions on seizure etiology.

### **4.2 Inclusion criteria**

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age 4-16 years
- Diagnosis of refractory epilepsy with  $\geq 1$  major nocturnal motor seizure per week.
- Treated at one of the following epilepsy centers: SEIN, Kempenhaeghe or UMCU.
- Written informed consent by legal representatives (mostly parents) and also by the subject when aged  $\geq 12$  years and capable of signing informed consent.

### **4.3 Exclusion criteria**

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Intensive non-epileptic movement patterns such as severe choreatiform movements, intensive sleep walking, or frequent night terrors ( $> 1/\text{week}$ ).
- Minor motor seizures only, i.e. non-generalized or short ( $< 10$  sec.) tonic seizures or isolated myoclonias that are self-limited and do not require intervention.
- Presence of a pacemaker or cardiac arrhythmias that may generate false alarms (e.g. supraventricular tachycardia).
- Inability to comply to the trial procedure.
- Skin characteristics (e.g. dark skin color or tattoo) that may affect photoplethysmography and thereby influence performance of the NightWatch.
- Dependence on another SDD (e.g. Emfit or saturation monitor). Simultaneous use of a baby phone (or other types of microphones) is permitted.
- Subjects who are not sleeping alone in the bed (i.e. co-sleeping in the parents'/guardians' bed influences the remote SDD). We do not allow subjects and parents/guardians to change their sleeping habits for the duration of the study only.

#### 4.4 Sample size calculation

If 60 subjects are monitored for two months at minimal seizure frequency of 1 per week we will likely obtain around 540 seizures. To assess the diagnostic performance of the NightWatch this sample size seems sufficient. The detection algorithms aim to reach a sensitivity of 80% and a PPV of 50%. A sample size of 384 would be sufficient to reach a confidential interval of 5% (given a confidence level of 95%) [24]. A sample size of 60 subjects will allow us to intercept a drop-out rate of approximately 30% for the feasibility study.



**5 TREATMENT OF SUBJECTS**

Not applicable

**5.1 Investigational product/treatment**

Not applicable

**5.2 Use of co-intervention (if applicable)**

Not applicable

**5.3 Escape medication (if applicable)**

Not applicable

**6 INVESTIGATIONAL PRODUCT**

Not applicable

**6.1 Name and description of investigational product(s)**

Not applicable

**6.2 Summary of findings from non-clinical studies**

Not applicable

**6.3 Summary of findings from clinical studies**

Not applicable

**6.4 Summary of known and potential risks and benefits**

Not applicable

**6.5 Description and justification of route of administration and dosage**

Not applicable

**6.6 Dosages, dosage modifications and method of administration**

Not applicable

**6.7 Preparation and labelling of Investigational Medicinal Product**

Not applicable

**6.8 Drug accountability**

Not applicable

**7 NON-INVESTIGATIONAL PRODUCT**

Not applicable

**7.1 Name and description of non-investigational product(s)**

Not applicable

**7.2 Summary of findings from non-clinical studies**

Not applicable

**7.3 Summary of findings from clinical studies**

Not applicable

**7.4 Summary of known and potential risks and benefits**

Not applicable

**7.5 Description and justification of route of administration and dosage**

Not applicable

**7.6 Dosages, dosage modifications and method of administration**

Not applicable

**7.7 Preparation and labelling of Non Investigational Medicinal Product**

Not applicable

**7.8 Drug accountability**

Not applicable

## 8 METHODS

### 8.1 Study parameters/endpoints

#### 8.1.1 Main study parameter/endpoint

##### Performance of the NightWatch:

- Sensitivity;
- Positive predictive value;
- False alarm rate;
- % Time with valid signal allowing proper detection.

#### 8.1.2 Secondary study parameters/endpoints (if applicable)

##### 1. Validation of remote SDDs (video and audio):

- Sensitivity;
- Positive predictive value;
- False alarm rate;
- % Time with valid signal allowing proper detection.

##### 2. The feasibility of the NightWatch focusing on Acceptability, Demand, Implementation, Practicality, Expansion and Limited-efficacy testing [22].

### **Acceptability**

The parameter *Acceptability* is defined as:

*The extent in which the NightWatch is judged as suitable, satisfying, or attractive for people with epilepsy and their parents/guardians.*

Focusing on:

- Intent to continue use (survey T0)
- Expectations (survey T0)
- Satisfaction (Survey T2 and semi-structured interview with parents/guardians and subjects)

### **Demand**

The parameter *Demand* is defined as:

*The extent in which the NightWatch is likely to be used.*

Focusing on:

- Perceived demand (Survey T0)

- Actual use (Diary and semi-structured interview with parents/guardians and subjects)

### Implementation

The parameter *Implementation* is defined as:

*The extent in which the NightWatch can be successfully delivered to people with epilepsy and their parents/guardians.*

Focusing on:

- Degree of execution, (Diary, semi-structured interview with parents/guardians and subjects and survey T2)
- Success or failure of execution (semi-structured interview with parents/guardians and subjects and survey T2)
- Amount, type of resources needed to implement (semi-structured interview with parents/guardians and subjects)

### Practicality

The parameter *Practicality* is defined as:

*The extent in which the NightWatch device can be carried out in people with epilepsy and their parents/guardians using existing means, resources, and circumstances and without outside intervention?*

Focusing on:

- Factors affecting implementation ease or difficulty (semi-structured interview with parents/guardians and subjects and survey T2)
- Positive/negative effects on people with epilepsy and their family members (semi-structured interview with parents/guardians and subjects and survey T2)
- Ability of parents/guardians to carry out intervention activities (semi-structured interview with parents and subjects and survey T2)

### Expansion

The parameter *Expansion* is defined as:

*The extent in which the NightWatch can provide a new service to people with epilepsy and their parents/guardians.*

Focusing on:

- Fit with organizational goals and culture treatment of people with epilepsy (group session\* and interview with neurologists)
- Disruption due to expansion component (group session\* and interview with neurologists)

\*At the end of the study, we will evaluate the NightWatch by inviting a group of parents/guardians and professionals to a group session using the value sensitive design methodology.[26]

### Limited-efficacy testing

The parameter *Limited-efficacy testing* is defined as:

*The extent in which the NightWatch shows a promise of being successful on key intermediate variables (quality of life, stress, sleep, and strain) in people with epilepsy and their parents/guardians.*

Focusing on *Intended effects of the NightWatch on key intermediate:*

- Health-related QoL in people with epilepsy and their parents/guardians, including EQ-5D-5L [27] (Survey T0 and T2)
- Strain and sleep, including Caregiver Strain Index (CSI) [28] and Pittsburgh Sleep Quality Index (PSQI) [29] (Survey T0 and T2).

### 3. Economic evaluation of NightWatch

To evaluate the costs and effectiveness/utility of NightWatch for children and their parents/guardians from a societal perspective.

- Medical Consumption Questionnaire (MCQ) – adjusted version (T0 and T2)
  - Questions regarding the subject (to be completed by one or two parent(s)/guardian(s) together)
  - Questions regarding the parent/guardian (to be completed by one or both parent(s)/guardian(s) separately)
- Productivity Costs Questionnaire (PCQ) – adjusted version (T0 and T2)
  - To be completed by one or two parent(s)/guardian(s) separately.

### 4. Other secondary study parameters are:

- Compliance as indicated by frequency of use, i.e. hours per night that NightWatch is 'on'.
- Number and nature of interventions due to alarms.
- Effect of algorithm tailoring on performance of the NightWatch.

Table 1: Time schedule of surveys, questionnaires and interviews and feasibility domains.

Time period	Method	Duration	Topic
T0	Surveys T0	10 minutes	<ul style="list-style-type: none"> <li>- Personal/medical information subject and family (baseline)</li> <li>- MCQ and PCQ</li> <li>- <b>Acceptability:</b></li> <li>- <i>Intent to continue use;</i></li> <li>- <i>Expectations</i></li> <li>- <b>Demand</b></li> <li>- <i>Perceived demand</i></li> </ul>
	Questionnaires	30 minutes	<b>Limited-efficacy testing</b> <ul style="list-style-type: none"> <li>- <i>CSI: Parental strain/stress</i></li> <li>- <i>PSQI: Parental quality of sleep</i></li> <li>- <i>EQ-5D-5L: Parental and child quality of life</i></li> </ul>
T1	Diary		<b>Demand</b> <ul style="list-style-type: none"> <li>- <i>Actual use</i></li> </ul> <b>Implementation</b> <ul style="list-style-type: none"> <li>- <i>Degree of execution</i></li> </ul>
	Interview (subgroup)	60 minutes	<b>Acceptability</b> <ul style="list-style-type: none"> <li>- <i>Satisfaction</i></li> </ul> <b>Demand</b> <ul style="list-style-type: none"> <li>- <i>Actual use</i></li> </ul> <b>Implementation</b> <ul style="list-style-type: none"> <li>- <i>Degree of execution</i></li> <li>- <i>Success or failure of execution</i></li> <li>- <i>Amount, type of resources needed to implement</i></li> </ul> <b>Practicality</b> <ul style="list-style-type: none"> <li>- <i>Factors affecting implementation ease or difficulty</i></li> <li>- <i>Positive/negative effects on patients with epilepsy and their family members</i></li> <li>- <i>Ability of parents/guardians to carry out intervention activities</i></li> </ul>
T2	Surveys T2	10 minutes	<ul style="list-style-type: none"> <li>- MCQ and PCQ</li> <li>- <b>Acceptability</b></li> <li>- <i>Satisfaction</i></li> <li>- <b>Implementation</b></li> <li>- <i>Degree of execution</i></li> <li>- <i>Success or failure of execution</i></li> <li>- <i>Amount, type of resources needed to implement</i></li> <li>- <b>Practicality</b></li> <li>- <i>Factors affecting implementation ease or difficulty</i></li> <li>- <i>Positive/negative effects on patients with epilepsy and their parents/guardians</i></li> <li>- <i>Ability of parents/guardians to carry out intervention activities</i></li> </ul>
	Questionnaires	30 minutes	<b>Limited-efficacy testing</b> <ul style="list-style-type: none"> <li>- <i>CSI: Parental strain/stress</i></li> <li>- <i>PSQI: Parental quality of sleep</i></li> <li>- <i>EQ-5D-5L: Parental and child quality of life</i></li> </ul>
Optional	Group session	120 minutes	<b>Expansion</b> <ul style="list-style-type: none"> <li>- <i>Value sensitive design group session</i></li> </ul>

T0 = Before implementation of the SDDs;

T1 = Intervention (2 months);

T2= After implementation of the SDDs.

Table 2: Overview of questionnaires

Questionnaire	Domains	No. of items
<b>CSI</b>	Strain related to care provision. Major domains: Employment, Financial, Physical, Social and Time	13
<b>PSQI</b>	Quality of sleep. Major domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.	10
<b>EQ-5D-5L</b>	Quality of Life. Major domains: Mobility, self-care, usual activities, pain/discomfort, anxiety/depression.	5

### 8.1.3 Other study parameters (if applicable)

Not applicable.

### 8.2 Randomisation, blinding and treatment allocation

Not applicable

### 8.3 Study procedures

#### Inclusion & consent

(See 11.2 Recruitment and consent)

#### Run in period

During the first two months, there will be no home-based monitoring. Parent(s)/ representative(s) will complete the questionnaires and a subgroup will be interviewed.

#### Intervention

After two months, the researcher will visit the home to install the equipment. A camera and microphone will be placed on a pole, secured between floor and ceiling, next to the subject's bed. A suitcase containing a MacBook laptop and an external hard drive for data storage will be placed in the subject's room. The subject will be instructed to wear the NightWatch bracelet every night around the upper arm. When NightWatch is removed from its docking station, it will start running automatically. All recorded data (NightWatch, video and audio) will be stored automatically to the



MacBook and copied on hard drive. The researchers will replace the hard-drive every 2 weeks and store all recordings safely at SEIN or Kempenhaeghe for analysis. During the first weeks, the hard drive will be switched more often, in order to detect systematic errors in time.

In the morning, NightWatch must be connected to the docking station, when this happens, recordings stop automatically. During the study, subjects (or parent(s)/guardian(s)) do not have to switch any on/off button for the recordings. When NightWatch detects a seizure, it generates an alarm to the alarm station part of the NightWatch system at the parent(s)/guardian(s) bedroom. When the alarm goes off, the responding parent/guardian will check on their child and act upon the situation. He/she will keep a diary of all events. The SDD intervention period will last two months.

In case of technical problems, parent(s)/guardian(s) can contact the technical trial coordinator. If the parent(s)/guardian(s) give their consent, the coordinating investigator will be able to look into the study Macbook at their home from a distance true a secured program to solve technical problems. If the problem is not solved, the technical trial coordinator will visit the participant's home.

### **Questionnaires & interviews**

During the study (T0 and T2), parent(s)/guardian(s) will be asked to complete several questionnaires about their experiences with NightWatch, quality of life, stress and quality of sleep. This will take 40 minutes for each time period (T0 and T2). The questionnaires will be presented in an online tool. Parent(s)/guardian(s) will give their consent to use their email address for access to this tool. A subgroup of parent(s)/guardian(s) will be invited to participate in a semi-structured interview focusing on feasibility of NightWatch and the impact of the SDD on family life. This interview will take one hour. Parent(s)/guardian(s) can indicate their availability to participate on the informed consent form. Based on all evaluations, researchers will decide which perspective will gain deeper understanding about the feasibility and impact of NightWatch. The researchers will select parents/guardians based on maximum variation.

### **Optional phase**

Depending on the performance of NightWatch, parent(s)/guardian(s) will have different options. In case of bad performance, the researchers will offer them a second-2-month period of monitoring if an individually tailored adjustment of the algorithm could substantially improve performance. In case of good performance,

researchers we will offer the parent(s)/guardian(s) the possibility to keep NightWatch for further use. They can buy NightWatch at a 50% reduced rate of €750,-.

#### **8.4 Withdrawal of individual subjects**

Subjects can terminate the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons or important unforeseen events (e.g. material deficiencies). If the subject shows any signs of resistance to wear the device, the investigators are obliged to withdraw the subject from the study.

Researchers will ask for the reason of withdrawal, because this can give them information about the feasibility. Subjects and their parent(s)/representative(s) are not obliged to answer this question.

##### **8.4.1 Specific criteria for withdrawal (if applicable)**

#### **8.5 Replacement of individual subjects after withdrawal**

If a subject is withdrawn from the study within two weeks from inclusion, the subject will be replaced. After this time period, subjects will not be replaced.

#### **8.6 Follow-up of subjects withdrawn from treatment**

Not applicable.

#### **8.7 Premature termination of the study**

Not applicable.

## 9 SAFETY REPORTING

### 9.1 Temporary halt for reasons of subject safety

Not applicable

### 9.2 AEs, SAEs and SUSARs

Our wearable sensor (NightWatch) has been developed in cooperation with Livassured and a group of researchers, the Dutch Teleconsortium. After production of a prototype, different usability tests have been performed to examine the product. Special attention has been paid to patient safety.

NightWatch is CE certified as a Medical Device Class I.

#### 9.2.1 Adverse device events (ADEs)

Adverse device events (ADEs) are defined as any undesirable experience occurring to a subject during the study, causally related to the study device. All adverse device events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

#### 9.2.2 Serious adverse events (SAEs)

A serious adverse (device) event (SA(D)E) is a serious (leading to hospitalization or (near)-death) unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the clinical trial whether or not related to a failure of the device to alarm. A SAE will be reported within 7 days to the METC . All subjective or presumed complaints will be reported. We do not expect serious adverse events causally related to NightWatch (SADE). Previous trials (LICSENSE Phase I-III) have indicated that the NightWatch is tolerated well with respect to comfort and skin reactions.

#### 9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

### 9.3 Annual safety report

Not applicable.

**9.4 Follow-up of adverse events**

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

**9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]**

Not applicable.

## 10 STATISTICAL ANALYSIS

### 10.1 Primary study parameter(s)

Performance of the algorithms ( sensitivity, positive predictive value, false alarm rate and % time with valid signal allowing proper detection) will be expressed using descriptive statistics.

### 10.2 Secondary study parameter(s)

Methods triangulation will be conducted for this study, which means that there will be two or more research methods applied in one study [30,31]. After analysis the results will be combined, leading to a deeper understanding concerning the feasibility parameters.

Feasibility and utility of the NightWatch will be presented, using descriptive statistics (see table 3). To calculate differences in pre- and post-measurements, a paired samples T-test will be applied (in case of normal distribution). Multiple imputation test will be applied in case of missing data. Differences in outcome will be tested through a post-hoc test.

#### **Semi-structured interviews**

Data from the semi-structured interviews will be analyzed using a thematic analysis approach [32]. Thematic analysis is a flexible method for identifying and analyzing patterns within data. All interviews will be audiotaped, and transcribed verbatim; NVivo software (QSR International Pty Ltd, 2012) will be used in the analysis process. Thematic analysis consist of six steps: getting familiar with the data, generating codes, searching for themes, reviewing themes, defining theme, and representing results [32].

#### **Group session**

A focus group session with subjects, parents/guardians and professionals will be organized. After consent of the participants, the session will be recorded on video and transcribed verbatim will be used for further thematic analysis.

**Table 3. Analysis for feasibility parameters**

<b>Feasibility parameter</b>	<b>Source</b>	<b>Analysis</b>
<b>Acceptability</b>		
<i>Satisfaction</i>	- Survey T2 - Interview	- Descriptive statistics <sup>1</sup> - Thematic analysis
<i>Intent to continue use</i>	- Survey T0 - Interview	- Descriptive statistics <sup>1</sup> - Thematic analysis
<i>Expectations</i>	- Survey T0	- Descriptive statistics <sup>1</sup>
<b>Demand</b>		
<i>Actual use</i>	- Diary - Interview	- Descriptive statistics <sup>2</sup> - Thematic analysis
<i>Perceived demand</i>	- Survey T0 - Survey T2	- Descriptive statistics <sup>1</sup> - Descriptive statistics <sup>1</sup>
<b>Implementation</b>		
<i>Degree of execution</i>	- Diary - Interview - Survey T2	- Descriptive statistics <sup>2</sup> - Thematic analysis - Descriptive statistics <sup>1</sup>
<i>Success or failure of execution</i>	- Interview - Survey T2	- Thematic analysis - Descriptive statistics <sup>1</sup>
<i>Amount, type of resources needed to implement</i>	- Interview	- Thematic analysis
<b>Practicality</b>		
<i>Factors affecting implementation ease or difficulty</i>	- Interview - Survey T2	- Thematic analysis - Descriptive statistics <sup>1</sup>
<i>Positive/negative effects on people with epilepsy and their family members</i>	- Interview - Survey T2	- Thematic analysis - Descriptive statistics <sup>1</sup>
<i>Ability of parents/guardians to carry out intervention activities</i>	- Interview - Survey T2	- Thematic analysis - Descriptive statistics <sup>1</sup>
<b>Expansion</b>		
<i>Fit with organizational goals and culture treatment of people with epilepsy</i>	- Group session	- Videotaped and thematic analysis
<i>Disruption due to expansion component</i>	- Group session - Interview neurologist	- Videotaped and thematic analysis - Thematic analysis
<b>Limited-efficacy testing</b>		
<i>Health-related QoL</i>	- EQ-5D-5L	- Check on normally distributed data - Descriptive statistics <sup>3</sup> - Paired samples T-test
<i>Caregiver Strain Index (CSI)</i>	- CSI	- Check on normally distributed data - Descriptive statistics <sup>3</sup> - Paired samples T-test
<i>Pittsburgh Sleep quality index (PSQI)</i>	- PSQI	- Descriptive statistics <sup>3</sup>

- 
- Repeated measures ANOVA (if necessary multiple imputation)
  - post-hoc test (Turkey's HSD)
- 

1 = Median, mode, range, highest and lowest value

2 = Sensitivity, positive predictive value, false alarm rate (compared with results NightWatch analysis)

3 = Mean (with SD) or median (with IQR), mode, variance and range

### 10.3 Other study parameters

#### Economic evaluation NightWatch

This economic evaluation will involve a combination of a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). Additional costs and additional outcomes will be compared before and after implementation of NightWatch in a family home.

In the CEA, effects are presented in clinical outcomes and the incremental cost-effectiveness ratio (ICER). The primary outcomes measure for the cost-utility analysis will be QALYs, based on the EuroQol utility scores.[33]

We will assess intervention costs, healthcare costs, patient and family costs, and costs outside the health care sector. We have developed an adjusted version of the Medical Consumption Questionnaire (MCQ) and the Productivity Costs Questionnaire (PCQ) especially designed for parents or representatives of children with epilepsy.

The valuation of healthcare costs, patient and family costs will be based on the updated Dutch manual for cost analysis in healthcare research. This manual recommends using standardized cost prices.[34]

A baseline analysis will be performed to examine the comparability of groups at baseline for both costs and outcomes. If necessary, methods will be applied to control for differences in base. To investigate whether data are normally distributed a Kolmogorov-Smirnov test will be performed. Depending on the results either parametric (t-tests) or bootstraps will be used. The uncertainty of the Increment Cost Effectiveness Ratio (ICER) will be checked by non-parametric bootstrapping. The bootstrapped cost-effectiveness ratios will be subsequently plotted in a cost-effectiveness plane. The choice of treatment depends on the maximum amount of money that society is prepared to pay for a gain in effectiveness, which is called the ceiling ratio. Therefore, the bootstrapped ICERs will also be depicted in a cost-effectiveness acceptability curve showing the probability that NightWatch is cost-effective using a range of ceiling ratios. Additionally, to demonstrate the robustness of our base-case findings a multi-way sensitivity analyses will be performed.

**10.4 Interim analysis (if applicable)**

Not applicable.



## **11 ETHICAL CONSIDERATIONS**

### **11.1 Regulation statement**

The study will be conducted according to the principles of the Declaration of Helsinki (most recent version, date 19-10-2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

### **11.2 Recruitment and consent**

Subjects will be recruited in one of the epilepsy centers (SEIN, Kempenhaeghe, UMCU). The principal investigator will inform the neurologists from these centers about the study, before recruitment. After reviewing in- and exclusion criteria, the subject and/or parent(s) or guardian(s) will be informed about the study by their neurologist. All subjects and parent(s)/guardian(s) will receive an information letter with extensive information on the study, adjusted to age. Subjects and parent(s)/guardian(s) will be approached by researchers after a minimum of one week, to answer all questions and schedule an informed consent meeting (in person or by telephone) if they show interest. During this meeting, the researcher will explain everything about the study and parent(s)/guardian(s) can sign informed consent (with the researcher or at home, which will then be sent to the researcher). Subjects between 12 and 16 years will give a co-consent in addition to the informed consent of their parents/guardians, if they are able to do so.

### **11.3 Objection by minors or incapacitated subjects (if applicable)**

We will make sure that a minor or incapacitated subject will never be forced to participate in our trial. Subjects aged 12-16 must give a co-consent in addition to the informed consent of their parent(s)/representative(s). The subject can only participate if both parties have given consent. Younger subjects (age 4-12) will be informed about the study in the best way we can (by means of a specific information letter, adjusted by age). If a minor or incapacitated subject gives any objection against participation, the subject will not be included in the study. Next to that, all subjects will be able to stop participating in the study, at any moment during the study. When the subject is able to communicate this (non)verbally, the wish of the subject will be honored. If the NightWatch is experienced as a nuisance, or makes the subject uncomfortable, the device will be removed in consultation with the parent(s)/representative(s).

### **11.4 Benefits and risks assessment, group relatedness**

Implementing SDD is not considered to pose any substantial risks. Study participation can be a burden for the family (especially the parents/guardians) though, due to impact of the devices on privacy, impact of false alarms and time spent on the questionnaires &

interviews. Participation does, however, also offer better insight for the parents/guardians in the actual nocturnal seizure activity of their child, demonstrates the added value of the NightWatch and may help them to timely alert to a major seizure. When actual seizure activity is not consistent with the parent's expectations, this information can be confronting. All study results will be shared with the attending neurologists, so parents/guardians will be able to discuss this problem.

We will inform subjects and parent(s)/guardian(s) as good as possible on the impact of the study design on their privacy. It can be quite a burden to have a camera running in your (child's) room every night. To minimize this burden, we will give the subject and parent(s)/guardian(s) the opportunity to delete sensitive video or audio material from the storage data before it is sent to the researchers. To prevent the risk of data getting lost, we do not allow subjects or parent(s)/guardian(s) to delete the material themselves. Every 1-2 weeks, when a trial nurse comes to their home to switch the external hard disk for an empty one, they are able to delete any footage they want, without any consequences. If subjects or parent(s)/guardian(s) do not want the trial nurse to see or hear the sensitive material, they can simply refer to a specific night, or time-window during a night, which will then be deleted by the trial nurse. If they wish to stop the recordings, they can contact the researcher to discuss which recordings should be stopped and those will be switched off immediately.

If a high frequency of false alarms causes a big burden on parent(s)/guardian(s), they can contact the researcher to discuss this problem. The researcher can then offer them the possibility to switch off the audible alarms. Because the annotation process takes some time, we are not able to give feedback on the reason for these false alarms, and if they are really false alarms, at that time. When the analysis process is completed, the researchers will give the parent(s)/guardian(s) the opportunity to look at the recordings of their child to learn more about their seizures and reasons for false alarms.

At the end of the study, we will share the performance data of NightWatch with the subject's neurologist. He/she will invite the subject and/or his/her parent(s)/guardian(s) to discuss this performance and user experiences. As an objective third party, the neurologist can then advise them to keep NightWatch for further use or might advise to use another seizure detection device.

According to the performance of NightWatch, we will offer the following options at the end of the study:

In case of good performance, combined with satisfying use, NightWatch can give the family a benefit. In these cases, we would like to offer them the possibility to keep NightWatch for further use. We believe that offering NightWatch for free or a small amount of money can give an undesirable financial incentive to participate. It should be noted that currently none of the seizure detection devices are reimbursed. The most frequently sold seizure detection device (bed sensor) that was shown to have a poorer performance in our previous trial (LICSENSE NTR4115) has a higher cost price (€1700,-) compared to the NightWatch (€1500,-). For the above reasons, we found a 50% reduced rate of €750,- to be reasonable, since this is equal to the production costs. Besides, Livassured will offer a two year guarantee for the service and support of the device.

In case of bad performance, we will assess whether better performance can be obtained using a tailored algorithm. To this end we will review all trial data of the participant and evaluate the effects of altering the algorithm thresholds. If this is likely to result in a substantial improvement, we will offer participants a second 2-month intervention period with a tailored NightWatch algorithm. At the end of this trial we will once again share the results with the family and the treating neurologist. If the performance has improved we will offer the NightWatch at reduces rate of € 750,-.

### **Compensation for injury**

The investigator has a liability insurance which is in accordance with article 7 of the WMO.

SEIN has an insurance with HDI Global SE, the Netherlands, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

### **11.5 Incentives (if applicable)**

There will be no financial compensation for participation.

In case of good performance of NightWatch, we will offer participants NightWatch at a reduced rate of €750,-. (*See explanation above, 11.4*)

## **ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION**

### **11.6 Handling and storage of data and documents**

The processing of personal data in pursuit of this trial will be limited to those data that are reasonably necessary to investigate the efficacy, safety, quality and utility of the seizure detection sources used in this trial. The collected data contains not only figures and written observations, but also video-images. Subjects or their parents/guardians have the possibility to remove privacy-sensitive video-images from the trial data. They can indicate whether they want to remove video-images every time one of the researchers comes to their home to change the external hard-disk. The investigators will process the video-fragments with adequate precautions to ensure confidentiality and to protect the privacy.

All recordings will be stored safely at SEIN Heemstede and Kempenhaeghe for further analysis and a back-up of all data will be stored at SEIN Heemstede for 15 years after closure of the trial. Patient files will be coded and only the coordinating and principal investigator will have the key to this code.

No medical records will be shared with the sponsor or subsidizing parties. Only coded data from the study will be shared with LivAssured (the provider of the NightWatch) and CLB (provider of the audio algorithms) to optimize their algorithms.

The trial team ensures that the personal data are:

- collected for a specified and legitimate purpose;
- processed fairly and lawfully;
- accurate and up to date;
- not published or shown without prior explicitly written consent.

The trial team ensures that any audio fragments that could de-identify the subject (e.g. spoken language) will not be used for audio analysis by CLB. Prior to data exchange all audio fragments will be checked by the researchers.

Explicit consent for the processing of personal data will be obtained from the participating subject (or his/her legally acceptable representative) prior to any processing of personal data. All personnel whose responsibilities require access to personal data agree to keep the identity of trial subjects confidential. This confidentiality will be maintained throughout the complete data processing. Trial subjects will be entitled to request confirmation of the existence of personal data in the database and will have the right to rectify erroneous or inaccurate data.

### **11.7 Monitoring and Quality Assurance**

We will ask the Julius Center to monitor the trial according to the current Standard of Good Clinical Practice. One initiation, two monitoring, and one close out visit to both analyzing sites (SEIN and Kempenhaeghe) will be performed. Monitoring activities include: 1) monitoring rate of inclusion and dropout; 2) Checking availability and completeness of trial master file, informed consent forms, all SEAs, in- and exclusion criteria of a sample of subjects, query process and the presence of instructions for the execution of study procedures and if study personnel has been properly trained; 3) Verification of existence and identity of subjects and endpoints.

### **11.8 Amendments**

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

### **11.9 Annual progress report**

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### **11.10 Temporary halt and (prematurely) end of study report**

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the end of the monitoring period of the last included subject (except for subjects with early withdrawal).

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

### **11.11 Public disclosure and publication policy**

The study will be registered at [clinicaltrials.gov](https://clinicaltrials.gov).

For the disclosure of the results, we will submit our results for publication in peer-reviewed scientific journal. Involved companies will not have a say in the publication.

## 12 STRUCTURED RISK ANALYSIS

### 12.1 Potential issues of concern

### 12.2 Synthesis

Implementation of our wearable sensor device (NightWatch) is not considered to pose any substantial risk. Since the efficacy of NightWatch has not yet been proven in children in a family home setting, we cannot guarantee that subjects and parents/guardians can rely completely on this device. There is a chance that parent(s)/guardian(s) will become less alert during the study. To minimize this risk, we will give them extensive information that especially emphasizes this matter.

Study participation can be a burden for the family, due to the impact of the devices on their privacy, the impact of false alarms and the time spend on completing questionnaires, interviews and a diary. It does, however, also give the families better insight in seizure behavior of their child and shows them the possible utility of seizure detection.

If the NightWatch becomes uncomfortable or causes any distress, the wearable device will be removed and the subject will be withdrawn from the study. In case of alarm fatigue, the parents/guardians can stop the NightWatch measurements and contact the researcher to switch off the alarms. If the subject or parents/guardians wish(es) to stop the video registration for any reason, they can contact the researchers to switch off the video recordings or even all recordings.

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