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An economic evaluation of the NightWatch for children with refractory epilepsy: Insight into the cost-effectiveness and cost-utility

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ABSTRACT

Purpose: We performed an economic evaluation, from a societal perspective, to examine the cost-utility and cost-effectiveness of a wearable multimodal seizure detection device: NightWatch.
Methods: We collected data between November 2018 and June 2020 from the PROMISE trial (NCT03909984), including children aged 4–16 years with refractory epilepsy living at home. Caregivers completed questionnaires on stress, quality of life, health care consumption and productivity costs after two-month baseline and two-month intervention with NightWatch. We used costs, stress levels and quality-adjusted life years (QALYs) to calculate incremental cost-effectiveness ratios (ICERs). Missing items were handled by mean imputation. Sensitivity analyses were performed to examine the robustness of the results including bootstrap sampling.
Results: We included 41 children (44% female; mean age 9.8 years, standard deviation (SD) 3.7 years). Total societal costs of the baseline period (T1) were on average €3,238 per patient, whereas after intervention (T2) this reduced to 2,463 (saving €775). The QALYs were similar between both periods (mean QALY 0.90 per participant, SD at T1 0.10, SD at T2 0.13). At a ceiling ratio of €50.000, NightWatch showed a 72% cost-effective probability. Univariate sensitivity analyses, on the perspective and imputation method, demonstrated result robustness.
Conclusion: Our study suggests that NightWatch might be a cost-effective addition to current standard care for children with refractory epilepsy living at home. Further research with an additional target group for a large timeframe may support the findings of this research.

1. Introduction

Epilepsy is a significant health problem that imposes a substantial burden on individuals, their caregivers and health systems [1]. Seizures are unpredictable and may cause serious complications, including sudden unexpected death in epilepsy (SUDEP[1]) [1]. Having (generalised or focal to bilateral) tonic-clonic seizures, particularly if nocturnal and unattended, constitutes the most significant SUDEP risk factor [2–4]. This poses an opportunity for seizure detection devices (SDDs), which might lower the morbidity and mortality risk in epilepsy and potentially reduce the burden [5].

NightWatch is a multimodal wearable combining photoplethysmography and accelerometry to alert for nocturnal major motor seizures [6]. A previous prospective multicenter, video-controlled cohort study demonstrated good performance of NightWatch in adults, with 86% sensitivity and a median false alarm rate of 0.25 per person per night [6]. Yet economic studies addressing the cost-effectiveness of NightWatch and other SDDs are still lacking. Since no studies were found on this subject, this study aims to fill in that gap. As resources are scarce, evidence-based decisions on costs and effects are increasingly

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[1] SUDEP: Sudden unexpected death in epilepsy ; PROMISE: Promoting implementation of seizure detection devices in epilepsy care ; CSI: Caregiver Strain Index; iMTA MCQ: Institute for Medical Technology Assessment Medical Consumption Questionnaire; iMTA PCQ: Institute for Medical Technology Assessment Productivity Costs Questionnaire ; QoL: Quality of life ; ICER: Incremental cost-effectiveness ratio ; QALY: Quality-adjusted life year; CEAC: Cost-effectiveness acceptability curve ; CE: Cost-effectiveness; CHEERS: Consolidated Health Economic Evaluation Reporting Guidelines; SEIN: Stichting Epilepsie Instellingen Nederland; SDD: Seizure dectection device ; Hr-QoL: Health-Related Quality of Life

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important in current health care decision-making [7], particularly in the field of epilepsy, compromising 0.3% of the European total healthcare budget [8]. This is a pressing question as SDDs rapidly emerged in epilepsy care while costs of these devices are substantial and often not reimbursed, thus causing health inequality. We, therefore, aimed to perform an economic evaluation from a societal perspective to examine whether implementation of NightWatch is preferable over usual care in terms of costs, effects and utilities.

2. Methods

This study followed Dutch guidelines for economic evaluations [9] and the CHEERS reporting guidelines for economic evaluations [10].

2.1. Data collection

2.1.1. Target population and setting

We used data from a prospective multicenter home-based implementation study,the Promoting implementation of seizure detection devices in epilepsy care (PROMISE) trial; NCT03909984. PROMISE included 60 children aged 4–16 years with at least one major nocturnal motor seizure per week, living at home and treated at a tertiary epilepsy center in the Netherlands (SEIN, Kempenhaeghe or University Medical Center Utrecht). Background information from the children and caregivers participating in the PROMISE study was extracted from the PROMISE database (Table 1).

2.1.2. Study perspective and time horizon

The economic evaluation was executed from a societal perspective. This perspective accounts for both directs costs (i.e. health care costs) and indirect costs (i.e. lost productivity costs). The PROMISE study consisted of a two-month baseline period without any SDD used (comparator), followed by a two-month period with NightWatch use at home (intervention). Data for our analysis was collected between November 2018 and June 2020. The Research Ethics Committee of University Medical Center Utrecht approved the study (PROMISE: NL62995.041.17). The study devices and equipment were provided free of charge by the company that developed NightWatch (LivAssured). LivAssured had no role in the study design, analysis, or decision to submit for publication.

Table 1
Demographic characteristics of study particpants.

Baseline characteristics (*N*=41)	N	%
Characteristics of children		
Female	18	44
Mean age	9.8 (SD 3.7)	-
Mean age at seizure onset	2.8 (SD 3.3)	-
Epilepsy etiology		
Genetic	15	37
Structural	11	27
Unknown	15	37
Learning disability	29	71
Number of ASMs at start study		
None	1	3
One	7	17
Two	11	27
Three	14	34
Four	5	12
Five	3	7
Characteristics of caregivers		
Female	33	81
Mean age	40.9 (SD 6.2)	-
Marital status (living together)	28	68
Paid work	31	76
Mean no. of working hours/week	28.3 (SD 8.3)	-

*N: number; SD: standard deviation; ASMs: antiseizure medications.

2.1.3. Outcomes

Caregivers from the PROMISE study were asked to complete online questionnaires before the baseline period (T0), at the end of the baseline period (T1) and the end of the intervention period (T2). T0 included questions on baseline characteristics of the child and the caregiver. We used validated questionnaires to measure caregiver's stress (Caregiver Strain Index [CSI]), quality of life (EQ-5D-5L), medical consumption (Institute for Medical Technology Assessment Medical Consumption Questionnaire [iMTA MCQ]) and productivity (Institute for Medical Technology Assessment Productivity Costs Questionnaire [iMTA PCQ]) at T1 and T2. The iMTA MCQ and iMTA PCQ were specifically adjusted to the care situation of a child with epilepsy; the iMTA MCQ covered questions about the medical consumption of the child and the caregiver, while the other questionnaires focused only on the caregiver. We asked the caregiver that took primary care of the child to complete all questionnaires. An English version of the CSI and EQ-5D-5L, and the adjusted Dutch version of the iMTA MCQ and iMTA PCQ can be found in the Supplementary material.

2.2. Data analyses

2.2.1. Missing data

Missing items at T1 or T2 were handled by mean imputation, consisting of the mean score of the non-missing data [11]. At T1 data of two participants was missing (5% of the total study population). At T2 data of fifteen participants was missing (37% of the total study population).

2.2.2. Effectiveness

The effectiveness of the intervention, compared to the baseline period, was measured by the CSI questionnaire on caregiver's stress (Supplementary material 1). Individual CSI scores were calculated by adding up all questions answered with 'yes' (1 point per question).

2.2.3. Utility

The EQ-5D-5L questionnaire on caregiver's quality of life (QoL) [7] was used to measure the utility of the intervention, compared to the baseline period. The five dimensions of the EQ-5D-5L questionnaire were summed into a health state, with the help of the Dutch EQ-5D-5L utility values (Supplementary material 2) [12].

2.2.4. Societal costs

The iMTA MCQ (Supplementary material A.3,B.3) and the iMTA PCQ (Supplementary material 4) were included to measure the societal costs. A bottom-up approach was used to estimate the health care costs; information on each element of used service was multiplied by an appropriate unit cost (reference cost) and summed to provide overall costs [7]. The health care costs were extracted from national databases in line with the Dutch costing guidelines [9]. For a homeopathic consultation, the cost price stated by the Society of Homeopathy [Vereniging Homeopathie] was used [13]. The cost prices of respite care were calculated by comparing the cost prices of different respite care providers, and taking the average cost price [15]. Informal care costs were calculated by using shadow pricing, applying the general hourly minimum wages (Table 2) [9]. Productivity losses were estimated using the friction cost method, based on a mean added value of the Dutch working population [9]. Cost prices are expressed in euros in the year 2021. Existing cost prices were indexed to 2021 using the consumer price index (Table 2) [9,14].

2.2.5. Statistics

Statistical analyses were performed using SPSS V.27. We used non-parametric bootstrapping (1000 replications) to test for statistical differences in costs between the intervention and the baseline period. Microsoft Excel 2016 was used to quantify the uncertainty around the incremental cost-effectiveness ratio (ICER; 5000 bootstrap replications). The ICER represents the costs of an additional quality-adjusted life year

Table 2
Treatment costs per service and costs productivity losses in the Netherlands indexed for 2021.

Treatment	Costs in €
GP (per consultation)	
Occupational therapist	178.54
Usual consult	35.73
Home visit	54.13
Paramedical care (per session)	
Dietician	35.73
Physiotherapy	35.73
Speech therapist	32.28
Alternative cure (per session)	
Homeopath	67.50
Home care (per hour)	
Help in the household (i.e. domestic chores)	21.65
Home care (i.e. personal care)	54.13
Home nursing (i.e. hospital-based home care)	79.03
Mental health care (per session)	
Psychologist	69.29
Mental health care (GGZ)	18.41
Social worker	70.38
Hospital care	
Ambulance emergency transport	663.69
First aid	557.59
Night Hospital (weighted average)	515.36
Nursing day hospital (weighted average)	515.36
Outpatient clinic (weighted average)	98.53
Respite care (per hour)	
Respite care children	14.10
Respite care children learning disability	11.46
Respite care children night (24 hours)	174.51
Costs productivity loss	
Hourly wage (average)*	37.62
Hourly wage informal care	15.16

* For irregular working days, an average working day of 8 hours is assumed; GP: General practitioner; GGZ: Geestelijke gezondheidszorg [mental healthcare].

(QALY) gained, and was used to estimate the cost-utility of the intervention compared to usual care. ICERs were estimated by dividing the incremental costs by the incremental quality-adjusted life-year (QALY). The bootstrapped cost-effectiveness ratios were presented in a cost-effectiveness plane. The choice to implement the intervention depended on the maximum amount of money society is prepared to pay for a gain in QALYs (willingness-to-pay), determined as the '*threshold*'. As previously estimated in a Swedish study, we used a threshold (ceiling ratio) of €50,000 for refractory epilepsy per QALY gained [16,17]. We constructed a cost-effectiveness acceptability curve (CEAC) and calculated the incremental costs per responder to show the probability of a cost-effective intervention at different thresholds.

2.2.6. Sensitivity analysis

We performed three one-way sensitivity analyses to check the potential influence of base-case assumptions on the study findings. (1) To analyze the influence of our choice of perspective on the costs, we performed the data analysis from a health care perspective instead of a societal perspective [7]. (2) We tested a different imputation method (i.e. individual mean imputation), which replaces missing data by the individual mean score of a complete answered questionnaire at an earlier or later moment. (3) To test whether the mean imputation method was an appropriate way to handle missing data, all missing data ($n = 17$) were excluded from the analysis.

3. Results

We collected data from the PROMISE trial, including 60 participants, between November 2018 and June 2020, data from 41 participants was available for analysis. There were no statistically significant differences in characteristics (mean age, mean age at seizure onset, epilepsy etiology, learning disability (yes/no), number of anti-seizure medications at start study) between the dropped-out ($N = 19$) and included participants ($N = 41$), so no baseline corrections were performed.

3.1. Total resource use and total societal costs

Total societal costs of the baseline period were on average €3238 per patient (Table 3), whereas after intervention this reduced to €2463. During baseline, the health care costs (child and caregiver) accounted for 90% (€2910) of the total costs, compared to 91% (€2250) during the intervention. The productivity costs were respectively 10% (€328) and 9% (€212) (Table 3).

3.2. ICERs

3.2.1. Cost-utility

Fig. 1A illustrates the cost-utility analysis' cost-effectiveness (CE) plane from a societal perspective, representing the uncertainty surrounding the costs per QALY ratio. Based on the cost-utility analysis, the NightWatch was a cost-effective treatment compared to usual care alone (95% CI €19,387 - €28,182). The NightWatch is less expensive than usual care alone and equally effective in terms of QALYs (Table 3).

3.2.2. Cost-effectiveness

The incremental costs divided by the incremental effect (score on the CSI) resulted in an ICER of €846 per patient. The uncertainty analysis of this ICER is presented in a CE plane in Fig. 1C. Most ICERs lie in the dominant southeast quadrant (82%), indicating that the NightWatch is less expensive and more effective compared to usual care (95% CI €376–€7946).

3.2.3. Sensitivity analyses

Results from the sensitivity analyses are provided in Table 3. Looking at the costs per QALY from a health care perspective, instead of a societal perspective, the probability of NightWatch being cost-effective decreased by 2%. Using the individual mean imputation method, the cost-effectiveness probabilities of NightWatch decreased to 46%. This method resulted in higher caregivers' stress levels (8.02 vs. 7.11) and higher costs (3223 vs. 2463) during the intervention period, compared to the mean imputation method. By removing incomplete cases cost-effectiveness probabilities of NightWatch decreased to 33%. This method resulted in lower caregivers' stress levels (7.00 vs. 8.02) during the baseline period and higher stress levels (8.02 vs. 7.11) during the intervention period, compared to the mean imputation method. Also, costs decreased (2504 vs. 3238) during the baseline period using this method. From both a societal perspective and a healthcare perspective, most of the savings occur in healthcare costs (i.e. €659).

4. Discussion

4.1. Study findings

Our cost-utility and cost-effectiveness analysis suggests that a two-months intervention with NightWatch saves costs, reduces stress, and is equally effective in terms of QALYs, compared to usual care without an SDD.

4.2. Generalisability

We could not compare our results directly to others, as comparable studies are lacking. Some reports of the impact of wearables on caregivers' HR-QoL are available [18,19]. The caregiver burden scores from our study (mean QALY 0.90) were similar to the previously reported EQ-5D-5L scores of 86 caregivers of children with epilepsy (mean QALY 0.88) [18]. Another cross-sectional survey study examined the relation between SDD use and HR-QoL in 371 people with epilepsy and their

Table 3
Bootstrapped mean of the QALY, stress, and costs (€) per participant during the baseline period and the intervention.

	Bootstrap (*N*=41)			Sensitivity analysis					
				Healthcare perspective		Individual mean imputation		Only complete cases	
	Normal	Intervention	Difference	Normal	Intervention	Normal	Intervention	Normal	Intervention
Outcomes									
Caregivers' QALY*	0.9 (SD 0.12)	0,9 (SD 0.10)	0	0.9	0.9	0.9	0.89	0.92	0.9
Caregivers' Stress level	8.02 (SD 3.29)	7.11 (SD 2.74)	-0.91	8.02	7.11	7.51	8.02	7	7.96
Health care costs									
Intervention costs	0	49,67	49,67	0	49,67	-	-	-	-
Health care costs	2,910.13 (SD 3601.24)	2,200.9 (SD 1603.03)	-709.23	2,910.61	2,185.84	-	-	-	-
Costs in other sectors									
Lost productivity costs**	328.39 (SD 800.67)	212.46 (SD 391.53)	-115.93	-	-	-	-	-	-
Total costs	3,238.52	2,463.03	-775.49	2,910.61	2,235.51	3,307.39	3,223.48	2,504.47	2,325.94

* QALY, Quality Adjusted Life Year.
** Also includes costs for informal care (part of the patient and family costs).

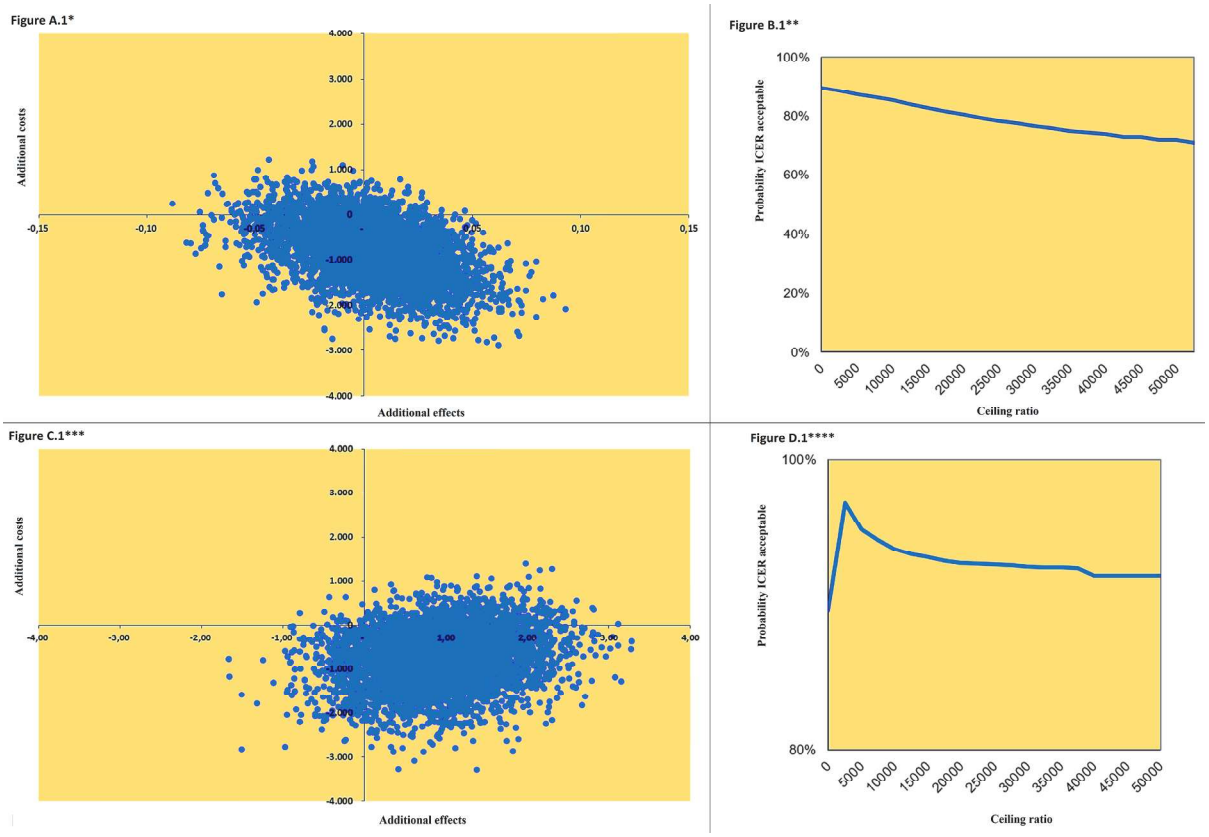

Fig. 1. Cost-effectiveness planes and cost-effectiveness acceptability curves for the NightWatch intervention.
**Fig. A.1. Cost-effectiveness plane, costs per QALY*
The horizontal axis represents the additional effects in Quality Adjusted Life Years [QALY] of the intervention (NightWatch) compared to baseline (usual care) (0); The vertical axis represents the additional costs of the intervention compared to baseline (€ -775,49); The blue dots represent the bootstrapped Incremental Cost-effectiveness Ratios [ICERs].
***Fig. B.1. Cost-effectiveness acceptability curve, costs per QALY*
The horizontal axis represents the ceiling ratio/threshold (for refractory epilepsy this is € 50.000); The vertical axis represents the threshold/willingness to pay; The blue line represents the probability of NightWatch being cost-effective (72% at a ceiling ratio of € 50.000).
****Fig. C.1. Cost-effectiveness plane, costs per stress score*
The horizontal axis represents the additional effects in stress of the intervention compared to baseline (-0,91); The vertical axis represents the additional costs of the intervention compared to baseline (€ -775,49); The blue dots represent the bootstrapped Incremental.
*****Fig. D.1. Cost-effectiveness acceptability curve, costs per stress score*
The hrizontal axis represents the ceiling ratio/threshold; The vertical axis represents the threshold/willingness to pay; The definition of the clinical outcomes, in this case stress levels, differs per study, we could not determine the ceiling ratio (threshold) for NightWatch. Therefore, it is not possible to interpret the probabilities of NightWatch being cost-effective in terms of costs and stress.

caregivers [19]. Compared with non-users, SDD users were significantly more likely to have been impacted by epilepsy in multiple HR-QoL domains. 80% of caregivers using an SDD (20% of total) reported a reduction in anxiety following SDD deployment. Of note, the SDD usage tended to be skewed toward younger age, and caregivers with higher-income, reflecting health care inequality. In-depth interviews with caregivers from the PROMISE study revealed that the amount of assurance NightWatch could offer, strongly depended on the ability to reduce their protective behavior as well as their resilience to handle the potential extra burden of care (e.g. due to false alarms or technical problems) [20].

The total price of NightWatch (€1500) is on the higher end of the spectrum compared to other SDDs. Yet, according to recently published standards, NightWatch' level of performance evidence is relatively high, and validation in adults support accurate detection of major nocturnal motor seizures [5]. Due to the wide variation in study designs, it is, however, hard to compare performances and estimate cost-effectiveness of other devices [3].

4.3. Limitations

The high probability of NightWatch being cost-effective (72%) found in our study might encourage NightWatch implementation. These results should, however, be interpreted with caution due to the small sample size and short time period. The cost-effectiveness of NightWatch was mainly due to the decrease in costs during the intervention, while effects on stress and QoL were less pronounced. Alternatively, the NightWatch is already manifesting its potential positive impact within this time frame but may be outweighed by alarm fatigue, thus resulting in unaltered levels of parental stress and QALY's. Although the EQ-5D-5L is an extensively validated questionnaire often used for the assessment of QoL in health technology assessment studies, it might not be discriminative enough to measure an effect in our study. The relatively small sample size might be another explanation for the lack of gain in QoL found in this study. Also, within this short time horizon it is uncertain whether the potential costs associated with the seizures are accurately captured. Another important unknown is the long-term retention rate (due to alarm fatigue) and the impact of NightWatch on SUDEP prevention, as this could significantly affect the cost-effectiveness. We speculate that alarm fatigue may vary over time particularly in periods with high parental care burden [20]. We lack prospective long-term data to monitor the impact of NightWatch or any other SDD on survival. A retrospective analysis in two residential units demonstrated that the center with the lowest grade of supervision had the highest incidence of SUDEP [3]. The significant contrast between sites was due to a central acoustic system, with only a minority of participants using additional SDDs. More economic evaluations on different SDDs could be helpful to get more insight in probabilities to improve the financial accessibility to SDDs. The overall burden for caregivers of children with epilepsy cannot be fully alleviated, but the use of SDDs such as NightWatch could decrease the burden. Another limitation of our short-term evaluation is that we could not study how much medication up titration NightWatch may create. NightWatch implementation may unveil a higher than previously reported seizure frequency and, in turn, impact epilepsy management. Despite these limitations, we found an evident effect in cost-effectiveness during the short time horizon and sensitivity analyses demonstrated result robustness. For further research we suggest to expand the time horizon and sample size to identify the long-term effects of SDD intervention, like SUDEP, visits the emergency room and alarm fatigue.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Declarations of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.08.003.

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