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An economic evaluation of a multicomponent self-management intervention for adults with epilepsy (ZMILE study)

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SUMMARY

Objective: The objective of this (trial-based) economic evaluation was, from a societal perspective, to compare the cost-effectiveness of a multicomponent self-management intervention (MCI) with care as usual (CAU) in adult patients with epilepsy over a 12-month period.

Methods: In a randomized-controlled trial, participants were randomized into intervention or CAU group. Adherence, self-efficacy (Epilepsy Self-Efficacy Scale [ESES]), quality-adjusted life years (QALYs), healthcare costs, production losses, and patient and family costs were assessed at baseline and during the 12-month study period. Incremental cost-effectiveness ratios (ICERs) (i.e., cost per increased adherence, self-efficacy, or QALY), and cost-effectiveness acceptability curves were calculated.

Results: In total, 102 patients were included in the study, of whom 52 were in the intervention group. Adherence rates over 6 months were 63.7% for the CAU group and 75.9% for the intervention group. Adherence, ESES, and quality of life did not differ significantly between groups. An ICER of €54 per point increase in ESES score at 6 months and €1,105 per point increase at 12-month follow-up was found. The intervention resulted in an ICER of €88 per percentage of adherence increase at 6 months. ICERs of €8,272 and €15,144 per QALY gained were found at 6- and 12-month follow-up, respectively.

Significance: Although no statistically significant difference was found after baseline adjustments, cost-effectiveness estimates for MCI appear promising. As rules of inference are arbitrary, it has been argued that decisions should be based only on the net benefits, irrespective of whether differences are statistically significant. Hence, the MCI may be a cost-effective addition to the current standard care for adults with epilepsy.

KEY WORDS: Epilepsy, Economic evaluations, Self-management, Adherence, Quality of life.

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KEYPOINTS

- This study examined the cost-effectiveness of a multi-component self-management intervention (MCI) for adults with epilepsy
- The MCI did not significantly improve self-efficacy, adherence, or (disease-specific) quality of life compared to usual care
- However, cost-effectiveness estimates for MCI appear to be promising
- Based on the net benefits, irrespective of whether differences are statistically significant, the MCI may be a cost-effective alternative

In Europe, the prevalence of epilepsy is estimated to be 5 per 1,000 inhabitants.¹ Because life expectancy is rising, resulting in an aging population, the expectation is that the number of people with a chronic condition such as epilepsy will increase.² In terms of economic impact on society, epilepsy is highly cost-intensive with respect to diagnosis, treatment, and hospitalizations due to seizures, as well as unemployment and household work.^{3,4} Furthermore, uncontrolled seizures negatively impact the quality of life (QoL) of patients with epilepsy.¹ Because the healthcare budget is insufficient to cover all healthcare expenses,⁵ economic evaluations are becoming a common requirement for reimbursement decisions.^{6,7} Budget constraints challenge policymakers to make the most cost-effective and health-producing decisions when allocating limited resources.

People with epilepsy are in many ways their own primary carers; well-controlled epilepsy often results in less productivity losses, hospitalizations, and other use of (healthcare) resources.⁸ Higher quality of self-care and reduced healthcare costs, provision of information, and adequate problem-solving skills are needed. Self-management education programs are designed to meet this need.⁹ Evidence from previous controlled clinical trials has indicated positive effects of self-management programs on improving clinical outcomes and their potential to reduce costs for chronic disorders.^{9,10} However, the Managing Epilepsy Well (MEW) Network has revealed a lack of evidence-based programs for epilepsy self-management education.¹¹ One of the mechanisms responsible for the improvements in health status, demonstrated by those attending self-management programs, is self-efficacy.⁹ Furthermore, the effectiveness of an antiepileptic drug (AED) treatment not only depends on the type of AED; the patients' attitude to it is also of great importance.¹² Hence, adherence, or more precisely, concordance, with medical treatment is closely linked to the patients' ability to self-manage their disease, and is shown to be an important factor in determining QoL.¹³ Concordance reflects a consensual agreement about taking AEDs that has been established between patient and practitioner.¹⁴

In this study, a full economic evaluation was performed that examined the cost-effectiveness of a multicomponent intervention (MCI) aimed at increasing self-management skills for people with epilepsy. Hence, the aim of this study was to compare, from a societal perspective, the cost-effectiveness (i.e., cost per improved adherence or self-efficacy) and cost-utility (i.e., cost per quality of life years [QALY] gained) of the MCI with care as usual (CAU) in adult patients with epilepsy over a period of 6 months with an extended follow-up of 12 months for the MCI group.

METHOD

Design

This trial-based economic evaluation was part of a randomized controlled trial (RCT) in which the clinical effectiveness of the MCI was assessed. Randomization was performed using sealed envelopes by an independent person. The study consisted of two parallel groups in which participants were randomly allocated to either the MCI group (a self-management education program with e-Health interventions) or CAU. The control group received CAU. Participants in the intervention group were followed for 12 months, and the CAU group for 6 months. After 6 months, patients from the control group were also given the opportunity of receiving MCI; this did not form part of the study. The protocol of this study has been described previously in Leenen and Wijnen et al. (2014).¹⁵ An overview of all relevant measurements for this economic evaluation is presented in Figure 1.

Participants and Setting

Adult patients, aged 18 years and over who were diagnosed with epilepsy, who lived at home, used AEDs, understood the Dutch language, and were willing and able (based on neurologists' opinion) to use e-Health devices belonging to the MCI, were eligible to participate in this study. Patients were excluded if they were not able or willing to function in group activities, or when it was expected, based on clinical judgment, they were not able to comprehend topics discussed within the MCI (e.g., patients with cognitive deficits). Patients were recruited in the outpatient clinics of Kempenhaeghe and by means of national epilepsy magazines and social media. The inclusion started in March 2014 and the last follow-up measurements were carried out in November 2016.

Multicomponent intervention

The MCI consists of the following: (1) group sessions, (2) the Medication Event Monitoring System (MEMS; Aardex Ltd., Switzerland); (3) a smartphone application "Eppy" (Epilepsy Foundation, The Netherlands); and (4) an Internet accessible patient database. The group sessions consisted of groups of three to five patients and additionally family

Figure 1.

Design of the ZMILE study (adapted version from Leenen and Wijnen et al.¹⁵)

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members and/or friends. During the first 5 weeks, group sessions took place once a week, followed by a booster session 4 weeks later. The group sessions lasted for 2 h and were led by two nurse practitioners, with experience in working in epilepsy patient groups. During the course, participants practiced with the five stages of proactive coping described by Aspinwall and Taylor¹⁶ and three fixed epilepsy-related themes.¹⁵ These five stages were (1) resource accumulation, (2) recognition of potential stressors, (3) initial appraisal, (4) preliminary coping efforts, and (5) elicitation and use of feedback concerning initial efforts. The three epilepsy-related themes were (1) self-monitoring and self-monitoring (e-Health) tools; (2) risk-management; and (3) shared decision-making/concordance. Patients were instructed to set goals and to proactively cope with possible pitfalls. The course was based on a self-management program for patients with type 2 diabetes, which was shown to significantly improve self-efficacy.¹⁷

The MEMS caps were electronic caps that fit on standard pill bottles. They registered the date and time every time the pill bottle was opened. In addition, the MEMS of the intervention group included an LCD screen that provided feedback on the number of times the bottle was opened on a particular day. Patients in the intervention group received feedback on medication adherence based on the MEMS reports during the group sessions and after 3, 6, 9, and 12 months of follow-up. Adherence was expressed as the percentage of days the MEMS bottle was opened according to the AED regimen, calculated as $100 \times (\text{number of days with number of openings as prescribed} / \text{number of monitored days})$.

The smartphone application “Eppy” was designed to register seizure frequency and other facts for persons with epilepsy. The Internet-accessible patient database consisted of a web-based interface and overview of the information gathered in “Eppy.”

Care as usual

Patients in the CAU group received no specific intervention; care was not intensified. The CAU group did not follow a standardized protocol. The CAU group also received the MEMS cap but without feedback about their behavior and without an LCD-screen providing feedback regarding the number of times it was opened on a particular day.

Outcomes

Self-reported questionnaires were administered to all patients at baseline, 3 months, and 6 months. The intervention group also completed the self-reported questionnaires at 9 and 12 months. Furthermore, adherence, used as a proxy for concordance, was monitored using the MEMS. The questionnaires included in the study were Epilepsy Self-Efficacy Scale-33 item (ESES), the Quality of Life in Epilepsy-31 Patient Weighted (QOLIE-31-P), the EuroQol 5 dimensions 5 levels (EQ-5D-5L), and a questionnaire regarding (healthcare) resource use over the last 3 months.

The ESES was used to assess the efficacy of self-management education program on epilepsy. Self-efficacy was defined as the confidence to carry out a behavior necessary to reach a desired goal.^{18–20} The items represent three dimensions of self-management: medication management, seizure management, and general management including safety and health. The total possible scores for the ESES range from 0 to 330. Higher scores correspond to higher levels of confidence in ability to manage epilepsy.²¹

The EQ-5D-5L was used to assess generic QoL expressed in a utility with a value between 0 and 1, where 1 means perfect health and 0 worst imaginable state of health.²² Utilities were derived using the Dutch tariffs.²³

Disease-specific quality of life was measured with the QOLIE-31-P, which consists of 38 items assessing 7 domains of epilepsy: seizure worry, overall QoL, emotional well-being, energy-fatigue, cognitive functioning,

medication effects, social functioning, and an overall score.²⁴ The final score ranges from 0 to 100, in which higher values indicate a better QoL.²⁵ Healthcare resource use and patient and family costs were measured using the Medical Cost Questionnaire, which was an adapted version of the Trimbos/iMTA questionnaire for costs associated with psychiatric illness. Productivity costs were measured with the Productivity Cost Questionnaire, both covering 3 months.

A detailed description of the measurement instruments can be found in Leenen and Wijnen et al.¹⁵

Costs

This economic evaluation was performed according to the Dutch guidelines for economic evaluations²⁶ and the Consolidated Health Economic Evaluation Reporting Standards.²⁷ A cost-effectiveness (CEA) and cost-utility analysis (CUA) were performed from a societal perspective to estimate the cost per QALY gain.

Costs were divided into four cost categories: intervention costs, healthcare sector costs, costs for patient and family, and productivity costs. The calculation was based on a detailed inventory covering all cost items composed of standardized cost prices from the Dutch manual for costing, and the calculated mean cost prices from the providers. To determine the costs of drugs, the website of the Dutch healthcare institute for the cost of pharmaceuticals (www.medicijnkosten.nl) was used. Intervention costs included the costs of the MEMS and costs associated with the MCI such as overhead costs, costs for instructors, costs of feedback sessions, and time costs for patients and relatives or friends (if a relative or friend was brought to the group sessions by a patient). Healthcare costs consisted of consultations with healthcare professionals, the use of diagnostic methods, and the frequency of inpatient stay and outpatient treatment. Patient and family costs included the use of formal (paid) care, informal care, and medical devices. The costs for unpaid care were valued using the proxy good method, which values the time spent on informal care at the labor market price of a close market substitute. Productivity costs included productivity losses due to absence from work and were valued using the friction cost method as recommended in the Dutch guidelines.²⁶ The friction cost method implies that long-term sick or absent employees will be replaced by employers after a specified friction period based on the average period an employer needs to replace a sick employee. In The Netherlands, a friction period of 85 days is recommended. All costs were indexed for the year 2015. Because the study follow-up was one year, no discounting was performed (for either costs or effects).

Analyses

Baseline differences in costs were checked with nonparametric bootstrapping, based on 1,000 bootstrap replications, as the data did not comply with the underlying assumptions

of parametric tests using Microsoft Excel 2010. ESES scores, QOLIE-31-P scores, utilities, and demographic variables were assessed for baseline differences using independent *t*-tests (for continuous variables) or Pearson's chi-square tests (for categorical variables) using IBM SPSS Statistics version 24. Adherence rates were compared using Wilcoxon rank test for repeated measurements. ESES, QOLIE-31-P, and utility follow-up scores were analyzed using multi-level analysis with a random intercept for each subject to account for repeated measurements, to correct for potential confounders (i.e., demographics, baseline depression, and anxiety scores), and to account for baseline differences (i.e., by including baseline values as an independent variable). Missing values (i.e., EQ-5D-5L, ESES, QOLIE-31-P, and costs) at baseline were managed using mean imputation ($n = 3$ for CAU group and $n = 1$ for intervention group) due to the low number of missing values and as no clinical information was available for these patients.

Missing data at follow-up measurements were dealt with using multiple imputation (5 times). Imputation was based on age, number of medications, employment, seizure frequency at baseline, seizure severity, self-efficacy score, randomization group, health care, patients and family, and productivity costs at each time point (for cost data only), EQ-5D-5L scores at each time point (for EQ-5D data only), ESES scores at each time point (for ESES data only), and QOLIE-31-P score at each time point (for QOLIE-31-P data only). To account for nonnormality of the cost data, predictive mean matching was used in which "real" observed values from similar cases were imputed instead of imputing regression estimates.^{28,29} QALYs were calculated by means of the "under the curve method," in which the time in a certain health state was multiplied by the utility of this health state.³⁰ Disease-specific QALYs were calculated based on the QOLIE-31-P by dividing the total QOLIE-31-P score by 100 to obtain disease-specific utility-like scores.

An intention to treat (ITT) analysis was used, meaning that all patients initially included in the study were included in the analyses. For the analysis of the MEMS, this implied that all patients who initiated the MEMS were included in the analysis. Analyses were carried out at 6 months (end of comparative phase) and after 12 months of follow-up. The CAU group was followed for only 6 months, and the results were extrapolated to 12 months, assuming this period was sufficient to obtain a representative estimation of 12-month follow-up costs. Because adherence was measured using MEMS caps in both groups, which may be seen as an intervention in both groups, the incremental cost-effectiveness ratios (ICERs) for adherence rates was calculated for only the comparative phase (6 months).

ICERs and incremental cost-utility ratios (ICURs) were calculated by dividing the incremental costs by the incremental effects, or QALYs, resulting in the costs per increased adherence, self-efficacy, QALY, or disease-specific QALY of the MCI as opposed to CAU. To quantify the

uncertainty around the ICER/ICUR, nonparametric bootstrapping was performed (5,000 times). To show the probability that the MCI is cost-effective, given different ceiling ratios, a cost-effectiveness acceptability curve (CEAC) was constructed.

In The Netherlands, the Council for Public Health and Health Care proposed an informal ceiling ratio for QALYs between €20,000 and €80,000 per QALY, depending on the burden of disease.³¹ Based on this proposition and the disability weight of (severe) epilepsy reported elsewhere,³²

one could assume that the maximum willingness to pay for one QALY is approximately €50,000.

A regression-based adjustment was performed to account for the difference in baseline costs, (disease-specific) utilities, and ESES scores between both groups.^{33,34}

One-way sensitivity analyses were performed by the following: (1) using disease-specific QALYs based on the QOLIE-31-P; (2) applying a healthcare perspective, instead of a societal perspective, as some European countries tend to adopt this; (3) excluding the costs of the MEMS for the

Table 1. (Baseline) characteristics of the population

Characteristics	Intervention group (n = 52)	Control group (n = 50)	Total (n = 102)
Gender			
Male	28 (53.9%)	22 (44%)	50 (49.0%)
Female	24 (46.2%)	28 (56%)	52 (51.0%)
Age in years (mean)	39.98 (SD: 13.1)	43.51 (SD: 15.4)	41.71 (SD: 14.7)
18–24	7 (13.5%)	7 (14%)	14 (13.7%)
25–44	23 (44.2%)	20 (40%)	43 (42.2%)
45–64	21 (40.4%)	18 (36%)	39 (38.2%)
≥65	1 (1.9%)	5 (10%)	6 (5.9%)
Marital status, n (%)			
Married/cohabiting	24 (46.1)	28 (56.0)	52 (51.0)
Living alone	15 (28.8)	11 (22.0)	26 (25.5)
Living with parents	7 (13.5)	8 (16.0)	15 (14.7)
Other	3 (5.8)	1 (2.0)	4 (3.9)
Missing values	3	2	5 (4.9%)
Education, n (%)			
No education	2 (3.8)	4 (8.0)	6 (5.9)
Primary school	1 (1.9)	3 (6.0)	4 (3.9)
Prevocational secondary school	29 (55.8)	30 (60.0)	59 (57.8)
Secondary school ^a	6 (11.5)	3 (6.0)	9 (8.8)
Higher education ^b	10 (19.2)	5 (10.0)	15 (14.7)
Other	2 (3.8)	3 (6.0)	5 (4.9)
Missing values	2	2	4 (3.9)
Daily life, n (%)			
Study	6 (11.5)	3 (6.0)	9 (8.8)
Work	20 (38.5)	11 (22.0)	31 (30.4)
Entrepreneur	4 (7.7)	0	4 (3.9)
Housewife/househusband	3 (5.8)	5 (10.0)	8 (7.8)
Unemployed	9 (17.3)	7 (14.0)	16 (15.7)
Incapacitated	5 (9.6)	16 (32.0)	21 (20.6)
Retirement or early retirement	2 (3.8)	4 (8.0)	6 (5.9)
Other	1 (1.9)	2 (4.0)	3 (2.9)
Missing values	1 (1.9)	2 (4.0)	3 (2.9)
Employment ^c			
Unpaid job/unemployed	27 (51.9%)	36 (72.0%)	63 (61.8%)
Employed	24 (46.2%)	11 (22.0%)	35 (34.3%)
Missing	1 (1.9%)	3 (6.0%)	4 (3.9%)
Mean number of seizures 4 weeks prior baseline	5.2 (SD: 13.2)	4.5 (SD: 7.8)	
Epilepsy Self-Efficacy Scale score ^c	243.8 (SD: 23.3)	230.4 (SD: 32.3)	
Hospital Anxiety and Depression Scale			
Total anxiety score	6.5 (SD: 3.4)	7.4 (SD: 3.4)	
Total depression score	4.8 (SD: 3.2)	5.2 (SD: 3.0)	
Medication Event Monitoring System (adherence rate)			
6 months of follow-up	75.9% (SD: 32.5)	63.7% (SD: 36.6)	
12 months of follow-up	71.0% (SD: 36.6)	–	

^aIncludes: General vocational school, preuniversity school, and secondary vocational education.

^bIncludes: Professional and academic higher education.

^cSig. difference between groups at 5% level.

CAU group, as patients in the CAU group did not receive any feedback from the MEMS and simply used the device for research purposes; and (4) by using the UK tariff to value the EQ-5D-5L health states.

RESULTS

Baseline characteristics

A total of 102 patients were included in the study, 52 of whom were in the intervention group. A large part of the patients reported to have an unpaid job or to be unemployed (61.8%). There was, however, a significant difference between the intervention group and the CAU group, indicating the intervention group had significantly more patients who had a paid job ($p = 0.02$). Furthermore the intervention group had a significantly higher score on the ESES ($p = 0.02$). Apart from employment rate and ESES score, no other baseline differences were found (see Table 1).

At baseline, healthcare costs and patient and family costs were similar between both groups. Productivity costs were, however, higher in the intervention group, leading to higher costs overall in the intervention group compared to the CAU group (i.e., €3,338 vs. €2,030). Although the two (95%) confidence intervals of total costs overlap marginally, a baseline correction was made. Unit prices are presented in Table S1.

Clinical effectiveness

There was a significant difference at baseline regarding ESES scores ($p = 0.020$). No significant differences between groups at 6 or 12 months of follow-up were found.

Mean adherence rates over 6 months, as measured with the MEMS, were 63.7% for the CAU group and 75.9% for the intervention group, which was not shown to be a significant difference. Adherence decreased slightly over time, resulting in an adherence rate of 71.05% at 12 months for the intervention group. In total, 18% of the subjects in CAU group and 4% of the subjects in the intervention group did not initiate the MEMS cap and were excluded from the analyses (resulting in 94 patients, 44 from the CAU group and 49 from the intervention group). Patients who were lost to follow-up or who did not use the MEMS caps were considered nonadherent. Utility scores derived from the EQ-5D-5L did not show significant differences at any of the follow-up measurements. Total QALYs at 6 months were 0.41 for both the intervention group and the control group using Dutch tariffs. Although baseline QOLIE-31-P scores differed, the difference was not significant between groups. At 3-month follow-up, the intervention group had higher QOLIE-31-P scores compared to CAU, and total disease-specific QALYs, as derived from the QOLIE-31-P, were higher in the intervention group (0.34) compared to the CAU group (0.32) at 6-month follow-up and at 12-month follow-up, but when adjusting for baseline differences, no significant differences were found between groups. Table 2

Table 2. Mean utility score and quality adjusted life years (QALYs) per group

	Intervention group (SD) (N = 52)			Care as usual (SD) (N = 50)		
	BS	FU3M	FU6M	FU12M	BS	FU3M
Epilepsy Self-Efficacy Scale	243.82 ^b (23.32)	253.16 (30.36)	263.16 (26.30)	263.03 (42.18)	230.42 ^b (32.31)	244.67 (32.14)
Epilepsy Self-Efficacy Scale_Adj			258.94 (23.76)	257.99 (37.19)		252.32 (32.83)
Utilities/ QoL						257.46 (23.03)
Utilities (NL-tariff)	0.82 (0.15)	0.85 (0.15)	0.85 (0.17)	0.85 (0.16)	0.83 (0.19)	0.81 (0.14)
Total QALYs (NL-tariff) ^c			0.42 (0.07)	0.85 (0.15)		0.41 (0.07)
Total QALYs (NL-tariff)_Adj ^c			0.42 (0.04)	0.85 (0.11)		0.41 (0.04)
Utilities (UK-tariff)	0.87 (0.12)	0.88 (0.13)	0.88 (0.14)	0.89 (0.12)	0.87 (0.16)	0.85 (0.14)
Total QALYs (UK-tariff) ^c			0.44 (0.06)	0.88 (0.12)		0.43 (0.06)
Total QALYs (UK-tariff)_Adj ^c			0.44 (0.05)	0.88 (0.12)		0.43 (0.05)
Visual analogue scale regarding quality of life (part of EQ-5D)	75.84 (14.93)	78.45 (11.68)	79.00 (12.66)	80.52 ^b (13.08)	73.63 (17.48)	74.71 (13.80)
QOLIE-31-P ^d	66.35 (10.10)	68.18 (8.33)	68.63 (9.60)	69.99 (10.90)	63.21 (11.39)	63.40 (13.18)
Total disease-specific QALY ^c			0.34 (0.04)	0.69 (0.08)		0.32 (0.05)
Total disease-specific QALY_Adj ^c			0.34 (0.02)	0.68 (0.05)		0.33 (0.03)
Epilepsy Self-Efficacy Scale						
Epilepsy Self-Efficacy Scale_Adj						
Utilities/ QoL						
Utilities (NL-tariff)						
Total QALYs (NL-tariff) ^c						
Total QALYs (NL-tariff)_Adj ^c						
Utilities (UK-tariff)						
Total QALYs (UK-tariff) ^c						
Total QALYs (UK-tariff)_Adj ^c						
Visual analogue scale regarding quality of life (part of EQ-5D)						
QOLIE-31-P ^d						
Total disease-specific QALY ^c						
Total disease-specific QALY_Adj ^c						

SD, Standard deviation; BS, baseline; FU, follow-up; 3M, 3 months; 6M, 6 months; QoL, quality of life; QOLIE-31-P, Quality of Life in Epilepsy-31-P; Patient Weighted; Adj, adjusted for baseline differences.

^aObservations at 6 months carried forward.

^bSig. difference between groups at 5% level.

^cTotal QALYs are calculated over 6 months (max QALY is 0.5).

^dDisease-specific QALY are calculated over 6 months, based on total QOLIE-31-P scores divided by 100 (max QALY is 0.5).

Table 3. Mean costs and bootstrapped 95% confidence intervals (CIs) after 6 months (end of comparative phase, no baseline adjustment)

	Intervention group (N = 52)		Care as usual group (N = 50)	
	6FU	12FU	6FU	12FU
Intervention costs	422	648	95	95
Healthcare costs				
GP visits	82	166	66	132
Specialist visits	139	494	324	649
Paramedic visits	279	579	183	366
Psychologist visits	62	175	99	198
Emergency department	108	303	109	217
Hospital stay	471	945	138	276
Epilepsy center	43	271	17	33
Daycare	0	19	121	242
Personal care	24	142	0	0
Prescribed medication	92	369	74	148
Total healthcare costs ^a (CI)	1292 (802–1918)	3109 (2189–4323)	1122 (737–1670)	2244 (1442–3335)
Patient and family costs				
Home care	88	158	176	352
Medical aids or transport costs	45	64	1	2
Total patient and family costs ^a (CI)	132 (25–284)	181 (46–337)	169	338 (83–639)
Productivity				
Absenteeism	811	1485	182	364
Presenteeism	1081	2219	631	1262
Unpaid work	778	1713	1268	2535
Total production losses ^a (CI)	2823 (1896–3877)	5378 (4007–6970)	2756 (1615–4100)	5512 (3318–7877)
Total costs (CI)	4491 (3395–5815)	9314 (7509–11,228)	4142 (2890–5568)	8189 (5661–10,750)
Total costs including baseline correction (CI)	4467 (3363–5662)	9014 (7241–11,006)	4345 (3199–5574)	8495 (6135–10,920)

^aFor the intervention group extrapolated to N = 52 and for CAU group to N = 50 based on multiple imputations; 6FU, results at 6 months of follow-up; 12FU, results at 12 months of follow-up; GP, general practitioner.

presents a detailed overview of the clinical effectiveness data.

Cost-effectiveness

The intervention costs were €422 and €648 for the intervention group at 6 and 12 months of follow-up and €95 for the CAU group. The intervention costs for the control group were mainly protocol driven costs attributable to the MEMS bottle. At 6 months, total costs were higher for the intervention group (€4,491) compared to the CAU group (€4,142). At 12 months, total costs were €9,314 for the intervention group and €8,189 for the CAU group. Total costs at 12 months of follow-up adjusted for baseline differences were €9,014 for the intervention group and €8,495 for the CAU group (see Table 3).

Looking at the ESES, the combination of effects and costs resulted in an ICER of €54 per point increase in ESES score at 6 months and €1,105 per point increase in ESES score at 12 months of follow-up. Concerning adherence, the intervention resulted in an ICER of €88 per percentage of adherence increase at 6 months. When looking at the QALYs (Dutch tariff), an ICUR of €8,272 per QALY gain was found at 6-month follow-up and an ICUR of €15,144 per QALY gained at 12-month follow-up. Results of the bootstrap replications of the ICERs/ICURs are presented in Figure 2, which presents the differences in costs and effects

between the MCI and CAU for each bootstrap replication (1,000 times).

The probability that the MCI is cost-effective given different ceiling ratios, as presented in CEACs, is shown in Figure 3. At a willingness to pay €2,000 per point increase on the ESES score, the probabilities of the MCI being cost-effective is 69% and 52% at 6 and 12 months of follow-up, respectively. In terms of QALYs, if one would be willing to pay €50,000 per QALY gained, the probability that the MCI would be cost-effective is 74% at 6-month follow-up and 76% at 12-month follow-up (see Fig. 3).

Sensitivity analyses

Disease-specific QALY: the ICURs at 6 and 12 months of follow-up, respectively, were €15,975 and €36,824 per disease-specific QALY gained. Applying a healthcare perspective instead of a societal perspective led to ICERs of €214 and €2,034 per score improvement on ESES score at 6 and 12 months, respectively. Looking at adherence, an ICER of €65 per percentage increase in adherence was found at 6 months. In terms of QALYs, the healthcare perspective led to an ICUR of €31,502 per QALY gained at 6 months of follow-up and €27,850 per QALY gained at 12 months of follow-up.

Excluding the costs of the MEMS for the CAU group resulted in an ICER of €93 per point increase in ESES score

Figure 2.

(A) Cost-effectiveness plane of ESES scores at 6 months of follow-up (costs per point ESES score increase); (B) cost-effectiveness plane of ESES scores at 12 months of follow-up (costs per point ESES score increase); (C) cost-effectiveness plane of percentage adherence at 6 months of follow-up (costs per percentage increase in adherence increase); (D) cost-effectiveness plane of QALY scores at 6 months of follow-up (costs per QALY gained); (E) cost-effectiveness plane of QALY scores at 12 months of follow-up (costs per QALY gained). *Epilepsia* © ILAE

at 6 months, €1,546 per point increase in ESES score at 12-month follow-up, and in ICER of €100 per percentage adherence increase. Excluding the cost of MEMS for the CAU resulted in an ICUR of €12,901 per QALY gained at 6 months of follow-up, and €20,363 per QALY gained at 12 months of follow-up.

Using the UK tariffs to value the EQ-5D-5L health states resulted in ICURs of €9,983 and €16,658 per QALY gained at 6 and 12 months of follow-up, respectively.

Finally, the analyses were performed without baseline adjustments. This resulted in an ICER of €48 per score improvement on ESES score at 6 months, an ICER of €105

per score improvement on ESES score at 12 months, and an ICER of €147 per percentage increase in adherence. In terms of QALYs, this led to an ICUR of €30,989 per QALY gained at 6 months of follow-up and €36,585 per QALY gained at 12 months of follow-up.

DISCUSSION

Cost-effectiveness estimates appeared to be promising. Unlike, QALYs, there is no willingness to pay threshold known for improvement on the ESES score, which makes it difficult to draw firm conclusions regarding cost-

Figure 3.

(A) Cost-effectiveness acceptability curve of costs per ESES score improved at 6 months; (B) cost-effectiveness acceptability curve of costs per ESES score improved at 12 months; (C) cost-effectiveness acceptability curve of costs per QALY gained at 6 months; (D) cost-effectiveness acceptability curve of costs per QALY gained at 12 months; (E) cost-effectiveness acceptability curve of costs per percentage increase in adherence at 6 months.

Epilepsia © ILAE

effectiveness. Regarding QALYs, considering a threshold of €50,000 per QALY gained, the probability that the MCI was cost-effective was estimated to be 74% at 6 months of follow-up and 76% at 12 months of follow-up. The MCI did not lead to significantly higher levels of self-efficacy. Furthermore, EQ-5D-5L score did not differ between the two groups. Total costs were higher for the intervention group compared to the control group.

The use of baseline corrections impacted the results as demonstrated by the sensitivity analyses. However, the imbalances in important baseline characteristics made us consider adjusting for them. It has been argued that imbalances in baseline measures could in fact matter without being statistically significant³⁵ and that baseline adjustments provide more precise estimates of a treatment effect.³⁴ Furthermore, although in contrast to, for example,

QALYs, baseline costs are not part of the total costs, one could still expect that patients' baseline costs will influence costs during the study. Hence, it is important to investigate this influence.³³

The lack of effectiveness of the MCI on the ESES and EQ-5D-5L may be explained by several factors. Of course, it could be that the intervention is not effective. However, this may be too short-sighted. For example, it is also possible, given the nature of the intervention, that we simply did not capture the effect or that the instruments were not sufficiently responsive. The first argument applies mainly to the ESES, as self-efficacy has been shown to increase in other studies investigating self-management programs.³⁶ The latter argument applies to the EQ-5D-5L, which has previously been reported not to be responsive in patients with epilepsy.⁴ However, it has been argued that rules of inference

are arbitrary and irrelevant to the decisions that clinical and economic evaluations claim to inform. Claxton et al.³⁷ argued that, if the objective is to maximize health gain for a given budget, decisions should be based only on the mean net benefits, irrespective of whether differences are statistically significant. This is because one of the mutually exclusive alternatives must be chosen and this decision cannot be postponed. By accepting the arbitrary rules of inference, one will impose costs that can be measured in terms of resources or lost health benefits.³⁷

This study is not without its limitations. First, an MCI tailored to specific patient populations may be more effective. For example, it has been shown that adults with lower education and income may be poorer self-managers than those with higher income and/or educational levels.³⁸ Second, because the interventions consist of multiple components, it is difficult to determine which aspect contributed to the effects found in this study. In addition, although the CAU group did not receive feedback on their use, both the CAU and the intervention group received the MEMS, which means CAU deviated from standard care. Third, patients were instructed to use the smartphone application “Eppy” (Epilepsy Foundation, The Netherlands). Because of financial constraints, Eppy was not maintained and updated, which meant that only a minority of the patients were able to use the app. Moreover, it was discontinued in early 2015 and removed from both the App store (Apple Inc., USA) and the Google Play store (Google Inc., USA). Fourth, the sample size of this study was based on a standard deviation for the ESES score of 7 points. However, the actual standard deviation found in this study was >30 points, which may have resulted in a decrease in study power. This may be a reason that we did not find statistically significant results. Finally, with regard to the 12-month sensitivity analyses, the CAU group was followed for only 6 months and the results extrapolated to 12 months. This implies that the 6-month follow-up of the CAU group was sufficient to obtain a representative estimation of 12-month follow-up costs.

In conclusion, although there was no statistically significant difference found after baseline adjustments, cost-effectiveness estimates appear to be promising. It has been argued that rules of inference are arbitrary and perhaps less relevant to the decisions that clinical and economic evaluations aim to inform. Further research should attempt to determine which factors of self-management contribute to an increased QoL in patients with epilepsy.

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DISCLOSURE OF CONFLICT OF INTEREST

All co-authors have been substantially involved in the study and/or the preparation of the manuscript. The authors declare no conflicts of interest. 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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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Overview of the most important cost categories of the ZMILE study.