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Methodological

Good Days and Bad Days: Measuring Health-Related Quality of Life in People With Epilepsy

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ABSTRACT

Objectives: Cost-effectiveness analyses typically require measurement of health-related quality of life (HRQoL) to estimate quality-adjusted life-years. Challenges with measuring HRQoL arise in the context of episodic conditions if patients are less likely—or even unable—to complete surveys when having disease symptoms. This article explored whether HRQoL measured at regular time intervals adequately reflects the HRQoL of people with epilepsy (PWE).

Methods: Follow-up data from the Epilepsy Support Dog Evaluation study on the (cost-)effectiveness of seizure dogs were used in which HRQoL is measured in 25 PWE with the EQ-5D at baseline and every 3 months thereafter. Seizure count is recorded daily using a seizure diary. Regression models were employed to explore whether PWE were more likely to complete the HRQoL survey on a good day (ie, when seizures are absent or low in frequency compared with other days) and to provide an estimate of the impact of reporting HRQoL on a good day on EQ-5D utility scores.

Results: A total of 111 HRQoL measurements were included in the analyses. Regression analyses indicated that the day of reporting HRQoL was associated with a lower seizure count ($P<.05$) and that a lower seizure count was associated with a higher EQ-5D utility score ($P<.05$).

Conclusions: When HRQoL is measured at regular time intervals, PWE seem more likely to complete these surveys on good days. Consequently, HRQoL might be overestimated in this population. This could lead to underestimation of the effectiveness of treatment and to biased estimates of cost-effectiveness.

Keywords: HRQoL, epilepsy, EQ-5D, seizures, episodic conditions, episodic diseases, episodic illness, utility, quality of life.

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Introduction

Cost-effectiveness analyses are often used by reimbursement agencies to inform decisions on whether or not to reimburse novel healthcare interventions. The outcome of a cost-effectiveness analysis is commonly expressed as the incremental costs per quality-adjusted life-year (QALY). QALYs are a function of both length of life and health-related quality of life (HRQoL). Estimation of the "quality" component can be achieved with a standardized measure of HRQoL such as EQ-5D.[1] EQ-5D is a widely used preference-based instrument which has country-specific scoring algorithms available for attaching a value between 1 (full health) and 0 (a state as bad as being dead) to the recorded health state. The resulting value is the EQ-5D utility score, which is often equated to HRQoL, and will also be the terminology in this article. EQ-5D is the preferred HRQoL measure of reimbursement agencies such as the National Institute for Health and Care Excellence in England and the National Health Care Institute in The Netherlands.[2-4] EQ-5D intends to capture self-reported health status on the day of completing the survey ("health today").

Although EQ-5D is widely applied in a variety of conditions and populations, challenges may arise in the context of its application to conditions which are characterized by considerable fluctuations in health, as in the case of migraine, multiple sclerosis, and epilepsy.[5-7] Recently, Sanghera and Coast[8] underlined the challenges in measuring HRQoL in fluctuating health states, arguing that HRQoL estimates may be biased if the timing of assessment and the recall period used do not properly account for the temporal nature of the symptoms.[8] That is to say, the symptoms may not have occurred in a representative manner within the recall period of the HRQoL instrument, because patients may be less likely—or even unable—to complete HRQoL surveys on days when an episode occurred. As a consequence, measured HRQoL may not adequately reflect (average) HRQoL and QALY estimations might be biased. This can be especially problematic when episodic symptoms are severe and infrequent, such as in epilepsy. In the context of cost-effectiveness analyses, this implies that measured

HRQoL differences between treatment groups may not reflect actual treatment effectiveness adequately, hence biasing cost-effectiveness estimates and potentially misinforming subsequent decisions. Nevertheless, so far, empirical evidence is lacking regarding the extent of the potential bias in HRQoL measurements in episodic conditions. This study is a first attempt to fill this gap for the episodic condition medically refractory epilepsy.

Measuring HRQoL in the Context of Epilepsy

Epilepsy is a neurological condition that is characterized by recurrent unpredictable seizures of various types and severities. The clinical presentation of a seizure depends on the area of the brain affected and may include unintentional body movements, unusual sensations, involuntary behaviors, and impaired consciousness.[9] The clinical spectrum of seizures encompasses focal aware or impaired awareness seizures, generalized seizures, and seizures with unknown onset. Reflecting the symptoms or signs occurring at the onset of the seizure, the seizure types can further be sub-classified as "motor" or "non-motor" and "intact awareness" or "impaired awareness" in the case of focal seizure.[10] Seizures generally last only seconds or a few minutes, and depending on the seizure type and severity, people with epilepsy (PWE) may recover quickly or need several hours or sometimes days to recover.[11] In the majority of PWE, seizures can be controlled using antiepileptic drugs (AEDs). Medically refractory epilepsy is the term used to describe epilepsy that cannot be controlled and occurs when patients fail to achieve seizure freedom with at least 2 appropriate and tolerated AED regimens.[12] This occurs in about one-third of the overall epilepsy population. Among people with medically refractory epilepsy, seizure frequencies may range from less than one per month to several seizures per day.[13,14]

A change in seizure frequency has traditionally been the main measure of efficacy for epilepsy treatments. To incorporate effects of treatment in cost-effectiveness analyses, changes in seizure frequency should be accompanied by changes in HRQoL, for treatment benefits to be captured in QALYs. Because PWE are generally not able to complete an HRQoL survey during a seizure or during the post-ictal period (ie, the altered state of consciousness after an epileptic seizure), surveys will typically be completed at another time. A study on 3 phase III trials in people with medically refractory epilepsy showed that of 1076 HRQoL surveys, only 82 were completed on a day during which seizures were present.[6] Indeed, PWE might be inclined to complete a survey on a good day (ie, a day when seizures are absent or low in frequency compared with other days) rather than on a bad day. If the HRQoL of PWE at the time of completing the HRQoL survey differs substantially from that around or during a seizure, the time since the last seizure and the applied recall period may have a considerable impact on the observed patients' HRQoL scores and implied cost-effectiveness of (novel) interventions.

Objective

The aim of this article is to explore whether HRQoL measured at regular time intervals adequately reflects the HRQoL of people with medically refractory epilepsy. In addition, we explored the impact of completing the survey on a good day on EQ-5D utility scores.

Methods

Data Source

Data from the Epilepsy Support Dog Evaluation (EPISODE) study were used.[15] The EPISODE study is a stepped-wedge randomized controlled trial that evaluates the effectiveness and cost-effectiveness of seizure dogs in people with medically refractory epilepsy. Seizure dogs are trained to detect seizures and to respond during or immediately after a seizure. Responses include, but are not limited to, summoning help by the activation of an alarm system or warning someone, helping PWE to a safe place or position during or after a seizure, blocking PWE during episodes of reduced awareness from walking into obstacles or traffic, and providing comfort or emotional support to PWE until the seizure subsides. The EPISODE study includes 25 adults with medically refractory epilepsy who have at least 2 seizures per week. The study adopts a stepped-wedge design, which means that all PWE start in the control arm and receive a seizure dog in a randomized order during the 3-year follow-up period. The primary outcome of the study is whether the placement of a seizure dog decreases seizure frequency. Secondary outcomes include HRQoL (generic and disease-specific), wellbeing, healthcare resource use, informal caregiver burden, societal participation, and productivity. More details on the rationale and design of the study are described in the study protocol.[15]

In the EPISODE study, seizure frequency is measured using a seizure diary. PWE record the daily seizure count per seizure type in a paper diary, of which they upload a photograph every week via a mobile phone application. PWE can distinguish up to 3 different seizure types in their seizure diary. Although the impact of different seizure types on HRQoL may vary, for this exploratory study, the seizure count consists of the sum of all seizures experienced on a given day (ie, all seizure types get the same weight). EQ-5D-5L, which has a recall period of "today," is measured as part of a comprehensive survey that is self-administered every 3 months.[1] EQ-5D utility scores were calculated using the Dutch tariff.[16] Before answering EQ-5D-5L, PWE are asked to record the present date. PWE are instructed to complete the survey preferably on the date indicated on the survey (the first day of the month), which is approximately 4 days after receipt. PWE are asked to return the survey in any case within 10 days after the indicated date, allowing them a window for completing the survey of roughly 2 weeks. This article uses the data collected during the first year of the study, which includes 5 EQ-5D assessments (at months 0, 3, 6, 9, and 12) and daily seizure count data for 13 months. Two of the 25 PWE received a certified seizure dog within this time frame, in month 10 and in month 11 of the 13-month follow-up period.

Statistical Methods

For each participant of the EPISODE study, a graphical display was made visualizing the timing of HRQoL reporting in relation to the seizure count pattern. Subsequently, regression analyses were conducted to test the association between HRQoL reporting and seizure count and to estimate the impact of reporting HRQoL on a good day on the EQ-5D score. It is anticipated that the marginal impact of an additional seizure will decrease as seizure count increases. Therefore, instead of estimating a linear disutility function, previous utility prediction models in epilepsy grouped seizure counts into a categorical variable.[6,17,18] Here, seizure counts were grouped based on quartiles.

The regression analyses followed a 2-step approach. First, a univariate random effects ordered logistic regression model was used to estimate the relationship between the day of reporting HRQoL and the seizure count quartile on that day (ie, are PWE are more likely to report HRQoL on a good day?). Second, we explored the association between seizure count quartile and EQ-5D utility score (ie, is the HRQoL estimate higher on a good day?). For this second analysis, 3 types of regression models were used:

Table 1. Patient characteristics.

Characteristics at baseline (first 28 days)	Number of patients (n = 25)
Age, mean (SD)	33.8 (12.3)
Female	11 (44)
Number of seizure types distinguished by the patient	
1	4 (16)
2	13 (52)
3	8 (32)
Daily seizure count at baseline	
Mean (SD)	3.59 (4.70)
Median (IQR)	3.86 (1.57-5.43)
Average daily seizure count at baseline categorized	
<1	11 (44)
1-3	6 (24)
4-6	3 (12)
7-9	3 (12)
10-19	1 (4)
20-29	1 (4)
Average number of seizure-free days per week at baseline	
<1	9 (36)
1-3	7 (28)
4-7	9 (36)
EQ-5D utility score, mean (SD)	0.72 (0.25)
EQ-5D VAS score, mean (SD)	66 (22)

Note: Values are number (percentage) unless indicated otherwise.
IQR indicates interquartile range; SD, standard deviation; VAS, visual analog scale.

generalized least squares (GLS) random effects regression, Tobit random effects regression, and repeated measures generalized estimating equations (GEE). GLS random effects regression was used because it is a common estimation method accounting for any potential impact of multiple observations from the same individual. The Tobit random effects model was used to censor predictions at the upper bound (1). GEE is a population-averaged panel-data model which accommodates both auto-correlated and non-normal data, such as the dependent variable EQ-5D utility score in this analysis. In the GEE model, a gamma distribution with a logarithmic link was used with disutility as outcome variable to have non-negative values (with disutility = 1—EQ-5D utility score). The mean absolute error (MAE) and root-mean square error (RMSE) were calculated to examine the differences between mean observed and predicted EQ-5D utility scores. The best performing models were selected on the basis of the lowest MAE and RMSE results, with the MAE as the decisive factor in case of contrasting results. Next, the best performing model was corrected for age and gender. Finally, sensitivity analyses were performed to assess the robustness of the findings; we explored different specifications of seizure count and used the EQ-5D visual analog scale (VAS) scores instead of the EQ-5D utility scores as dependent variable. Given the exploratory nature of the research questions and to avoid assumptions about missing observations and early patient dropout, multiple imputation of missing values was not conducted. Statistical significance was defined at the $P<.05$ level. All analyses were done in Stata 16 (StataCorp LLC, College Station, TX).

Results

Descriptive Statistics

The EPISODE study included 25 PWE at baseline, from whom at the time of analysis a maximum of 13 months of seizure data were collected. The mean age of the PWE was 34 years (Table 1). The daily seizure count over the first 4 weeks of the study was 3.59 (±4.70) on average, with a small proportion (8%) of the participants experiencing more than 10 seizures per day. A majority of the PWE had at least 1 seizure-free day per week (64%). The mean EQ-5D utility score at baseline was 0.72 (±0.25). On the EQ-5D VAS, PWE scored on average 66 (±22) at baseline.

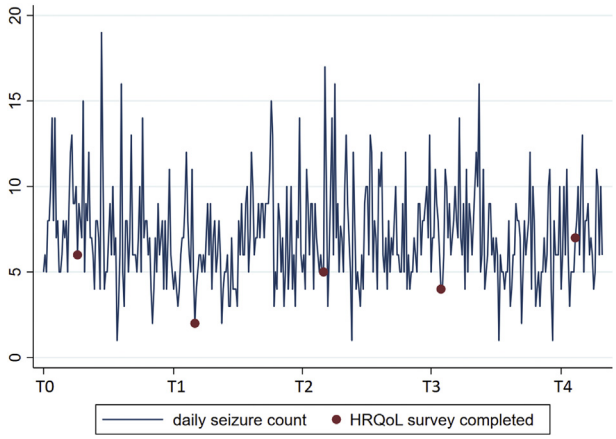
Complete HRQoL data (ie, a set of data on EQ-5D-5L, date of reporting and seizure count) were collected for all 25 PWE for up to 5 assessments (baseline, n = 23; month 3, n = 23; month 6, n = 22, month 9, n = 22; month 12, n = 21). The main reasons for missing complete HRQoL data included withdrawal from the study, no survey returned, or incomplete responses. Over all assessments, EQ-5D utility scores ranged from −0.15 to 1, with 13 observations (12%) of EQ-5D utility scores equal to 1 (ie, perfect health). In total, 53 EQ-5D observations (48%) were taken on

Table 2. Average seizure count on day of HRQoL reporting relative to the average over the preceding period.

Seizure count	Total (assessment 1 to assessment 4)		Assessment 1 (t = 3, n = 23)		Assessment 2 (t = 6, n = 22)		Assessment 3 (t = 9, n = 22)		Assessment 4 (t = 12, n = 21)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
On day of reporting HRQoL	2.98 (5.35)	1.00 (0.00-4.00)	2.61 (4.46)	1.00 (0.00-3.00)	3.55 (5.84)	0.50 (0.00-5.00)	1.73 (2.80)	0.00 (0.00-3.00)	4.10 (7.42)	1.00 (0.00-5.00)
Preceding 7 days	3.61 (5.41)	1.14 (0.29-5.00)	3.79 (5.13)	1.00 (0.29-5.43)	4.20 (6.56)	1.21 (0.29-6.00)	2.47 (3.25)	0.93 (0.29-2.86)	4.01 (6.37)	1.29 (0.57-4.43)
Preceding 14 days	3.66 (5.37)	1.07 (0.43-5.00)	3.38 (4.90)	1.14 (0.34-4.93)	4.17 (6.50)	0.82 (0.50-6.21)	3.01 (3.92)	1.01 (0.29-4.58)	4.10 (6.13)	1.01 (0.64-5.07)
Preceding 28 days	3.62 (5.22)	1.03 (0.48-4.89)	3.37 (4.94)	1.11 (0.36-4.82)	3.95 (5.90)	0.82 (0.47-6.36)	3.21 (4.03)	1.31 (0.39-4.89)	3.98 (6.13)	1.00 (0.54-4.39)

Note: The baseline HRQoL observations (assessment 0, t = 0, n = 23) are not included in the descriptive statistics as no preceding seizure count data were available for this measurement.
HRQoL indicates health-related quality of life; IQR, interquartile range; SD, standard deviation.

Figure 1. Example of the seizure pattern and timing of HRQoL reporting in a patient with daily seizures.

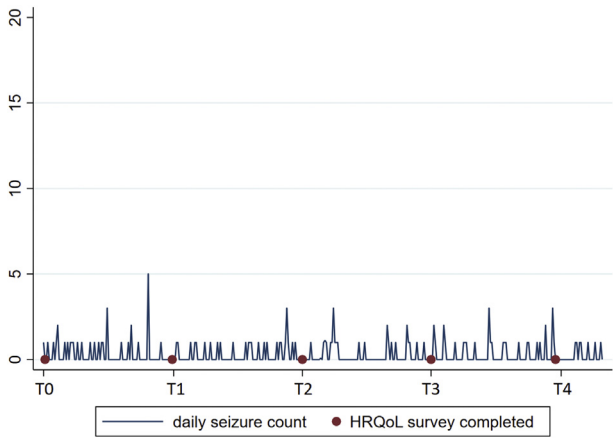


HRQoL indicates health-related quality of life.

seizure-free days. Five PWE (20%) completed all surveys on a seizure-free day, whereas for 8 PWE all EQ-5D observations were taken on days when at least one seizure occurred (32%). Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.001 presents an overview of the timing of HRQoL reporting relative to the indicated date on the survey. Table 2 shows the average seizure count of PWE on the day of reporting HRQoL for the surveys completed at months 3, 6, 9, and 12 (n = 88), as well as the average seizure count over the preceding 7, 14, and 28 days. In general, the mean and median seizure count of the sample appears lower on the day of reporting HRQoL than the average daily seizure count over each preceding period. This is confirmed when the analysis is repeated on data without outliers in seizure count (Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.001).

For illustration, 2 examples of the timing of HRQoL reporting relative to seizure patterns are presented in Figures 1 and 2. These PWE record only one seizure type. The days which were indicated as the preferred date for completing the survey are shown as T0 to T4. Figure 1 shows data from a participant who has daily seizures, who appears to complete the surveys on a day during which the seizure count is relatively low. Figure 2 shows data from a participant who has seizures a few times per week, who completed all surveys on a seizure-free day.

Figure 2. Example of the seizure pattern and timing of HRQoL reporting in a patient with occasional seizures.



HRQoL indicates health-related quality of life.

Regression Analyses

Table 3 shows the distribution of observations over the seizure count quartiles, as well as the mean seizure count and mean EQ-5D utility score within the quartiles. The mean seizure counts of these subgroups were 0, 1, 3, and 13. On days of reporting HRQoL, the seizure count falls most often in the lowest quartile (seizure-free). The EQ-5D utility score is higher for observations taken on a seizure-free day than for observations taken on a day when seizures occured. Ordered logistic regression showed that reporting HRQoL was associated with a significantly lower probability of a higher seizure count quartile that day (odds ratio 0.64; $P<.05$) (MAE 0.017; RMSE 0.159).

The 3 regression models for predicting the EQ-5D utility score from the seizure count quartiles performed broadly similarly, with MAE scores ranging between 0.184 and 0.187 and RMSE scores ranging from 0.239 to 0.241. All models showed a significant negative association between each of the 3 seizure count quartiles and the EQ-5D score compared with the first seizure count quartile (seizure-free) ($P<.05$). The Tobit model performed best, followed by the GEE model, and the GLS random effects model performed least well (Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.001). The performance of the Tobit model increased by including demographic factors (MAE 0.169; RMSE 0.232). The details of the best performing model are given in Table 4. Several sensitivity analyses have been performed to assess the robustness of the findings. These analyses, which explored the impact of different specifications of seizure count and investigated the EQ-5D VAS score as outcome variable to test for sensitivity, were in line with the observation from the main analysis that a lower seizure count is associated with a higher HRQoL estimate ($P<.05$) (Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.001).

Discussion

Obtaining reliable estimates of HRQoL in the context of an episodic condition such as medically refractory epilepsy can be challenging, because the symptoms may not have occurred in a representative manner within the recall period of the HRQoL instrument. Using data from the EPISODE study, our analyses indicated that people with medically refractory epilepsy seem more likely to complete HRQoL surveys on good days rather than bad days in terms of seizure count. Sanghera and Coast illustrated that, at the time of HRQoL assessment, people with episodic conditions may be either at the worst or best point of the fluctuation in symptoms or at some point in between.[8] Graphical displays of the EPISODE data showed that PWE seem to complete the HRQoL survey at a relatively good point of the fluctuation in seizures, and this hypothesis was confirmed by statistical analysis. Regression analysis revealed that HRQoL reporting was associated with a lower seizure count on that day, and that a lower seizure count was associated with a higher HRQoL score. Therefore, it is possible that when HRQoL is measured at regular time intervals, the assessments result in an overestimation of average HRQoL in the medically refractory epilepsy population and, consequently, an underestimation of the potential effect of seizure control on HRQoL. This might help to explain why some studies in epilepsy treatments failed to detect a significant difference in HRQoL when

Table 3. Distribution of observations over quartiles.*

Seizure count quartile (daily seizures)	Mean seizure frequency (SD)	Proportion of all observations, percentage (n = 9199) (%)	Proportion of observations on days of reporting HRQoL (n = 111) (%)	Mean EQ-5D utility score (SD)
Q1 (seizure-free)	0	41.37	47.75	0.80 (0.16)
Q2 (1 seizure)	1	14.46	9.91	0.64 (0.29)
Q3 (2-5 seizures)	3.28 (1.14)	21.53	26.13	0.58 (0.30)
Q4 (6 or more seizures)	12.85 (7.33)	22.64	16.22	0.56 (0.27)

HRQoL indicates health-related quality of life; Q, quartile; SD, standard deviation.
*The 4 groups are not balanced despite the distribution over quartiles; for example, 41% of observed seizure counts was 0.

measured with EQ-5D, even when a clinically meaningful treatment effect in terms of seizure frequency (ie, a 50% reduction) was observed.[6,19,20]

Our analyses have a number of limitations, which should be considered in interpreting these results. First of all, the current study did not differentiate for seizure severity. Seizure types vary, from muscle twitches or short absences to drop seizures, and may not all have a similar impact on HRQoL. The majority of PWE in our study distinguish their seizures into different types when completing their seizure diary, which indicates that using an unweighted total seizure count as indicator for disease severity on a given day likely constitutes an oversimplification of the burden they experience. In addition to seizure count, the type of seizures and the time intervals between seizures will likely have an impact on HRQoL on a given day and on the ability or motivation of a person to complete an HRQoL survey. Second, the EQ-5D observations were matched with the seizure count recorded in the seizure diary as a proxy for seizures that occurred within the EQ-5D recall period, which is "today." Nevertheless, seizures may still have occurred on that day *after* completing the survey. Thus, the seizure count from the seizure diary presents the maximum amount of seizures that could be reflected in the EQ-5D utility scores, but likely is an overestimation. In contrast, it may occur that the prolonged aftermath of a severe seizure on the days preceding HRQoL observation is captured within the EQ-5D utility scores, for example, because of a long recovery period or because of injuries incurred. Moreover, because we had EQ-5D observations on both seizure-free days and days with at least one seizure for a part of our (already limited) sample, the ability to perform within-subject analyses was limited. Therefore, utility differences between different seizure count quartiles should be interpreted with caution, as what might be considered a good day by one person might be perceived as a bad day by another person. Finally, our study had a limited sample size which brings a higher likelihood of observing coincidental findings. This article reports findings of a secondary analysis on data collected for a (cost-) effectiveness study, and, therefore, power calculations were not performed for the current analyses.[15] Hence, this study should be considered as explorative. Nonetheless, the sensitivity analyses that were conducted confirm the results regarding the impact of seizure count on the day of completing EQ-5D on HRQoL estimates.

Table 4. Regression coefficients and predictive performance of best performing utility model.

Tobit model, right-censored at 1	
Parameter estimate (SD)	
Seizure count Q2 (1 seizure)	−0.13* (0.06)
Seizure count Q3 (2-5 seizures)	−0.17† (0.05)
Seizure count Q4 (6 or more seizures)	−0.19‡ (0.07)
Age	−0.00 (0.00)
Gender	−0.18* (0.09)
Constant	0.87† (0.14)
Predictive performance	
MAE	0.169
RMSE	0.232
Estimates within ±0.05 of true value	25.23%
Estimates within ±0.10 of true value	34.23%
Estimates within ±0.25 of true value	57.66%

CI indicates confidence interval; MAE, mean absolute error; Q, quartile; RMSE, root-mean square error; SD, standard deviation.
*$P<.05$.
‡$P<.01$.
†$P<.001$.

The issue of measuring HRQoL in episodic conditions has been previously described mainly from a theoretical point of view, and this study is a first attempt to explore this issue in practice, by investigating the timing of reporting HRQoL relative to symptom severity within our epilepsy trial. For a better understanding of the impact of fluctuating symptoms on HRQoL estimates in PWE, it would be interesting to investigate the impact of using modified recall periods. Moreover, experimenting with consecutive measurements over a period of time (ie, intensive longitudinal assessment) might contribute to a better understanding of how HRQoL fluctuates within PWE and provide more insight into HRQoL on bad days and into the extent of overestimation of HRQoL when the timing of reporting HRQoL relative to the occurrence of seizures is not accounted for. Findings in medically refractory epilepsy are not necessarily generalizable to other episodic conditions. Hence, future research may help identify for which episodic conditions the timing of completing the survey is particularly relevant, by considering disease characteristics such as the frequency, duration, severity, and time intervals of symptom episodes.

Conclusion

This exploratory study showed that PWE are more likely to complete HRQoL surveys on relatively good days in terms of seizure counts. If seizures do not occur in a representative manner within the recall period of a HRQoL instrument, the observed impact of seizures on HRQoL may be biased. In particular when treatment reduces the frequency or intensity of bad days, HRQoL

measured at regular time intervals may not be sufficiently responsive to changes in seizures over time, especially when measured with instruments with a short recall period such as EQ-5D. Not accounting for the finding of this study that HRQoL reporting in the context of medically refractory epilepsy is more likely on relatively good days may result in a biased estimation of the HRQoL of PWE and, consequently, in a biased estimation of the (cost-)effectiveness of interventions in this patient population.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.05.001

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