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From clinically relevant outcome measures to quality of life in epilepsy: A time trade-off study☆

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ABSTRACT

Objectives: A proposed method for bridging the gap between clinically relevant epilepsy outcome measures and quality-adjusted life years is to derive utility scores for epilepsy health states. The aim of this study is to develop such a utility-function and to investigate the impact of the epilepsy outcome measures on utility.
Methods: Health states, based on clinically important epilepsy attributes (e.g. seizure frequency, seizure severity, side-effects), were valued by a sample of the Dutch population (N = 525) based on the time trade-off method. In addition to standard demographics, every participant was asked to rate 10 or 11 different health state scenarios. A multilevel regression analysis was performed to account for the nested structure of the data.
Results: Results show that the best health state (no seizures and no side-effects) is estimated at 0.89 and the worst state (seizures type 5 twice a day plus severe side-effects) at 0.22 (scale: 0–1). An increase in seizure frequency, occurrence of side-effects, and seizure severity were all significantly associated with lower utility values. Furthermore, seizure severity has the largest impact on quality of life compared with seizure frequency and side-effects.
Conclusions: This study provides a utility-function for transforming clinically relevant epilepsy outcome measures into utility estimates. We advise using our utility-function in economic evaluations, when quality of life is not directly measured in a study and hence, no health state utilities are available, or when there is convincing empirical evidence of the insensitivity of a generic quality-of-life-instrument within epilepsy.

1. Introduction

Quality of life (QoL) is a very important outcome measure, not only for patients, but also as an input for cost-utility analyses. A cost-utility analysis is a form of economic evaluation in which costs and benefits of alternative interventions are compared to see whether the investigated intervention offers good 'value for money'. The benefits of a cost-utility analysis are expressed in Quality Adjusted Life Years (QALYs), which incorporate effects in terms of both QoL (utilities) and survival (life-years gained). The value a person assigns to a particular health state (i.e. description of a particular set of symptoms which is common to a particular disease) is commonly referred to as a utility, and lies on a scale where death and full health are assigned values of 0 and 1, respectively. Using utility values one can calculate QALYs by multiplying the numbers of life-years gained by the utility of those added life-years. However, the essential utilities are not always available. Especially in case of model-based, cost-utility analyses, where researchers are dependent on the published literature, suitable utilities for certain health states are often hard to find.

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Obviously, as utilities are used to calculate QALYs, they need to be measured in a methodologically sound and preferably uniform manner. Hence, the ISPOR Task force regarding the measurement of utilities, called for the use of direct utility elicitation methods, such as the standard gamble (SG) or time trade-off (TTO) exercises (Ramsey et al., 2005).

Problems in gathering utility values may occur because clinical trials and clinical evaluations measure the effects of interventions with common clinically relevant measures, rather than with QoL-measures.

Within the field of epilepsy, three disease-specific clinical outcome measures are often used to reflect patients' health, namely; seizure frequency, seizure severity and side-effects due to antiepileptic drugs (AEDs). Frequency and severity of seizures in people with epilepsy vary from one individual to another. In some people, seizures are very severe and occur frequently despite treatment with AEDs. In others, seizures are mild, less frequent and more easily controlled by AEDs. Seizure severity is measured using standardized questionnaires. One of the most frequently used seizure severity questionnaires focusing on the clinical events of a seizure, is the National Hospital Seizure Severity Scale (NHS3), a revised and simplified version of the Chalfont scale (O'Donoghue et al., 1996).

In order to bridge the gap between clinical trials, which measure clinical outcomes, and economic evaluations, which require utility values, it would be preferable if one could make clinically relevant epilepsy outcome measures applicable to cost-utility analysis by deriving utility scores for the epilepsy outcome measures. For this purpose, the TTO method was used, in which participants are asked to determine how many life years one is willing to give up in order to avoid a particular health state (Drummond et al., 2005). This method has been used before in four other studies which elicited utilities for epilepsy health states. Firstly, Messori et al. (1998) interviewed a small series of refractory epilepsy patients (N = 81) and asked them how much of their current state of health they would be willing to give up in order to live the remaining years in excellent health. Secondly, Forbes et al. (2003) executed a TTO experiment among a smaller group of epilepsy patients (N = 43). However, only seven patients understood the exercise (Forbes et al., 2003). Thirdly, Carroll and Downs (2009) interviewed a large group of parents (N = 4016) to obtain their assessment of various health states while imagining that it would be one of their children who was experiencing the health state under consideration. Lastly, Kang et al. (2014) asked the general population (N = 300) to assess three epilepsy health states. These published TTO-studies elicited utilities for a very small number of specific health states (i.e. 1–5); furthermore, in these studies, seizure severity and side-effects were not (fully) included in the health state description.

To overcome this gap, the objective of this study is twofold: first of all, to create a reliable utility-function to transfer clinically relevant epilepsy outcomes to health state utilities based on preferences of the general public measured with the TTO method, and secondly, to investigate the impact of the separate clinically relevant outcome measures on health state utility. Preferences of the general public are used in economic evaluations as policy decisions are often made on societal level. Hence, it is stated within health economics, that the population potentially affected by resource allocation decision should be polled, and that the general public is supposed to value policy decisions with the most benefit for society as a whole (McDonough and Tosteson, 2007). In addition it has been demonstrated that 'outsiders' may be more able to differentiate across treatment groups than patients are themselves (De Wit et al., 2000).

Seizure frequency:
You will experience one seizure a day
Side-effects:
You will experience moderate side-effects
Seizure severity:
The attack occurs without warning, and results in sudden falling to the ground, but you will recover within a few seconds. You will often cut your head deeply as a result.

Fig. 1. Example of a health state description.

2. Methods

2.1. Study participants

Participants from the general population aged >18 years without epilepsy were recruited using e-mail, personal communication and social media. A link was provided to participants, which gave access to the online questionnaire. As part of this communication, we asked the participants to forward our invitation to participate in the study to their family and friends (again aged >18, without epilepsy). Participants who did not fully complete the questionnaire were excluded from the analyses. Participants were told that if they decided to complete the questionnaire, they thereby consented to participate in the study. In addition, information was provided that participation, and/or forwarding the invitation to friends and family, was completely voluntary and anonymous. This consent procedure was approved by the medical ethical committee of the epilepsy center Kempenhaeghe.

2.2. Attributes and levels

Health states were developed based on three clinically important disease-specific outcome measures (i.e. attributes): seizure frequency, seizure severity and treatment-related side-effects. These attributes were selected based on expert advice and commonality of use within the clinical epilepsy setting. Table 1 presents the three attributes and their levels. The attribute "seizure frequency" comprises 6 levels ranging from no seizures to two seizures per day. The levels of "seizure severity" were based on the description of seizures used in the valuation study of the National Hospital Seizure Severity Scale-3 (NHS3) (O'Donoghue et al., 1996). The attribute "experience of side-effects" was categorized into three levels: no or mild, moderate and severe side-effects. Fig. 1 presents an example of a health state to be valued by participants.

2.3. Valuation exercise

Preferences of a sample of the general population were elicited through a time trade-off (TTO) exercise for each of the epilepsy health states. The TTO was based on a process of outward titration to select a length of time in a health state with full health which they regarded as being equivalent to 10 years in an epilepsy health state. In other words; participants were asked which life they thought would be better, life A or life B (or are the two equivalent)? Life A: living for 10 years within the presented epilepsy health state; life B: living t = 5 years in perfect health. In the case that the participant prefers life A to life B, t is increased by 1 point (maximum t = 10), until the participant becomes indifferent to whether it is life A or life B. The other way around, if a participant prefers life B to life A, t is decreased (minimum t = 0), until the participant becomes indifferent to whether it is life A or life B. The smaller the 'equivalent' number 't', the worse the epilepsy health state. If a respondent was willing to sacrifice all t years in full health to avoid a certain epilepsy health state, then the participant valued the epilepsy health state as being equivalent to death.

A (nearly) full factorial design was used which resulted, after removing all unrealistic scenario's (i.e. all combinations of "no