Quality-of-Life–Adjusted Hazard of Death: A Formulation of the Quality-Adjusted Life-Years Model of Use in Benefit-Risk Assessment

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ABSTRACT

Background: Although the quality-adjusted life-years (QALY) model is standard in health technology assessment, quantitative methods are less frequent but increasingly used for benefit-risk assessment (BRA) at earlier stages of drug development. A frequent challenge when implementing metrics for BRA is to weigh the importance of effects on a chronic condition against the risk of severe events during the trial. The lifetime component of the QALY model has a counterpart in the BRA context, namely, the risk of dying during the study. Methods: A new concept is presented, the hazard of death function that a subject is willing to accept instead of the baseline hazard to improve his or her chronic health status, which we have called the quality-of-life–adjusted hazard of death. Results: It has been proven that if assumptions of the linear QALY model hold, the excess mortality rate tolerated by a subject for a chronic health improvement is inversely proportional to the mean residual life. Conclusions: This result leads to a new representation of the linear QALY model in terms of hazard rate functions and allows utilities obtained by using standard methods involving trade-offs of life duration to be translated into thresholds of tolerated mortality risk during a short period of time, thereby avoiding direct trade-offs using small probabilities of events during the study, which is known to lead to bias and variability.

Keywords: benefit-risk assessment, hazard function, mean residual life, quality-adjusted life-years, tolerated risk.

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Introduction

The concept of quality-adjusted life-years (QALY) has been routinely used to guide health care policymaking since its inception some 30 years ago. QALYs provide a very intuitive way of combining the two main components of health, namely, life duration and quality of life (QOL), into a single index. In its simplest form, which is linear with respect to time, the QALY model is formulated as $QALY = T / g(Q)$, where $T$ is the life duration and $g$ is a utility function over the health states.

More recently, regulatory agencies, pharmaceutical companies, and other groups have begun to discuss and explore methods to improve and standardize the benefit-risk assessment (BRA) performed throughout all drug development phases and during the assessment of a marketing authorization application. In this context, three detailed reviews of quantitative methods with potential use during BRA have been published [1–3]. Some of the models and metrics proposed for BRA, such as relative value-adjusted number needed to treat, global benefit risk, and multi-criteria decision analysis, share the idea of combining risks and benefits into a single index by incorporating patients’ or decision makers’ preferences [4–6]. These models do not necessarily decompose the subject’s outcomes into the two dimensions of the QALY model but are often based on a set of clinical trial end points selected for each evaluation.

Although the Work Package 2 report of the European Medicines Agency Benefit Risk Methodology Project concluded that regulators still find QALY insufficiently comprehensive for drug-related BRA, the existence of aspects common to QALY and other BRA models that deserve further research was acknowledged [2]. Herein, we concentrate on the inverse relationship between the life duration component of the QALY model and the risk of death during a clinical trial and use the hazard function, which is a key concept in time-to-event models, to establish a line of communication between the two frameworks.

Utilities in the QALY Model

In the QALY model, a chronic health state $Q_0$ is quantified on a 0 to 1 scale, with 1 representing perfect health and 0 representing death. Two common ways to elicit the utility of health status $Q_0$ are standard gamble (SG) and time trade-off (TTO).

SG is the most classical method for quantifying preferences in decision theory. With the SG probability equivalent (PE) method, decision makers are asked to fix a probability $p$ such that they are
Weights for Benefit-Risk Metrics

To compare both frameworks, in this section we define a simple weighted-sum multicriteria decision analysis model for BRA over two clinical trial end points, namely, the chronic health state achieved at steady state Q1 and the risk of death during the study D. If the variable Q has two possible values, Q0 and Q1, preferred to Q0, the model can be expressed by

\[ \text{Score} = w \cdot P(Q_1) - P(D) \]  

(1)

where \( P(Q_0) \) is the probability of achieving health state Q0 and \( P(D) \) is the probability of death during the study. This simple BRA metric requires the fixing of a weight \( w \) that represents the importance of a swing from the chronic health state Q0 to Q1 with respect to a swing from Q0 to death during the study period. By using a PE gamble, decision makers might be asked to fix a probability \( p \) such that they are indifferent between a certain consequence of a chronic health state Q0 at steady state in the clinical trial and a lottery in which the patient will achieve health state Q1 with a certain probability \( q \) or will die during that period of time with the opposite probability \( (1 - p) \). If they accept a probability of death \( q = 0.03 \) (3%), then a swing from 0% to 3% in the percentage of subjects dying during the study will be concluded to have the same importance as a swing in the chronic health state from Q0 to Q1, leading to a weight \( w = 0.03 \).

One aspect that deserves attention is the fact that the quantification of preferences for the decision models proposed for BRA have often required trade-offs using small probabilities [13–15]. Individuals, however, are not perfect von Neumann–Morgenstern agents, and PE gambles that handle probabilities close to 0 are known to provide biased and variable quantifications [7,8,16–18].

Herein, we propose to avoid trade-offs that use low probabilities of events during the study and to focus on trade-offs of life duration. This article proposes a procedure to translate these TTO utilities into weights that could be useful for BRA metrics.

The Quality-of-Life–Adjusted Hazard of Death

In survival analysis, the term baseline hazard is used to represent the risk of death estimated for a subject or group of similar subjects over time and, as such, related to our knowledge of their diseases and demographic characteristics. The baseline hazard function \( h_0 \) is associated with a probability distribution of lifetimes \( L_0 \).

A quality-of-life-adjusted hazard of death (QAHD) function is defined as a hazard function of death, \( h(t) \), that a person is willing to accept at any time \( t \), instead of his or her baseline hazard of death \( h_0(t) \), to improve his or her health status from any given level \( Q_0 \) to any other level \( Q_1 \). In other words, \( h(t) \) is the QAHD for an improvement from \( Q_0 \) to \( Q_1 \) if that person is indifferent between being in health state \( Q_0 \) with its baseline lifetime probability distribution \( L_0 \), for the rest of his or her life and being in health state \( Q_1 \) with distribution \( L_1 \), where \( h_0(t) \) and \( h(t) \) are the hazard functions associated with probability distributions \( L_0 \) and \( L_1 \), respectively. We intentionally restrict the definition of QAHD to lifetime distributions \( L_1 \) that meet the condition whereby if a subject survives to an interim

The Hazard Function and the Mean Residual Life

The hazard function \( h(t) \), also known as failure rate or hazard rate, is a key concept in time-to-event statistics that represents the instantaneous risk of suffering the event of interest at time \( t \) for a subject who has survived to that moment in time. The hazard rate quantities are not probabilities but range from 0 to infinity and depend on both the strength of the risk and the time units used. For example, both a mortality hazard rate of 0.015 deaths per subject-month and 18 deaths per 100 subject-years represent the same instantaneous risk at a given time \( t \) but expressed in different units. The hazard function \( h(t) \) of a random variable \( T \) is formally defined as

\[ h(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \leq T < t + \Delta t | T > t)}{\Delta t} \]  

(2)

Another function that deserves special attention here is the mean residual life (MRL), also called expected remaining lifetime. The MRL provides the expected value for the lifetime remaining at any time \( t \), given that the subject is known to have survived to \( t \). Although two different random variables \( T \) and \( T' \) may share the same expected value \( \mathbb{E}(T) = \mathbb{E}(T') \), the complete MRL(t) function over time uniquely defines the probability distribution of a random variable \( T \). The MRL is given by

\[ \text{MRL}(t) = \int_t^{\infty} \frac{S_r(x)}{S_r(t)} \, dx \]  

(3)

where \( S_r(t) \) is the survival function, that is, defined as \( S_r(t) = \mathbb{P}(T > t) \).

In expected utility, a subject is said to be risk-neutral with respect to the remaining life duration if he or she is indifferent over any lotteries with the same expected value. If lotteries over life duration are formulated in terms of hazard functions, risk neutrality over life durations is given by a subject being indifferent to any two hazard functions \( h_0 \) and \( h_1 \) that provided the expected remaining lifetime is the same.

A risk-neutral 30-year-old subject would be indifferent between the two lotteries of lifetime durations \( L_0 \) and \( L_1 \) associated with the two hazard functions of death \( h_0 \) and \( h_1 \), illustrated in Figure 1, because both have the same expected value (52.3 years) when the subject is 30 years old. The same two hazard functions can be used to represent not only the lotteries at an initial time \( t = 0 \) but also the subsequent lotteries \( L_0(t) \) and \( L_1(t) \) for subjects who survive to later times. If the same risk-neutral subject survives to the age of 70 years and is again asked to choose between these two hazards, he or she will prefer the lottery represented in Figure 1 by the solid line because this function provides a higher MRL at this later age.

The importance of a swing from the chronic health state requires the both downward and upward biases might cancel out, thereby compatibility effects [7,9]. It has also been hypothesized that to life duration curvature, whereas others have suggested a warned of a possible downward bias of TTO utilities, mainly due to life duration is assumed to be linear, the utility of health state Q, on the 0 to 1 scale, where 0 is death and 1 is health state Q. SG utilities are believed to be upward biased due to loss aversion and probability weighting effects [7,8].

The TTO method asks for the duration (T0) that yields indifference between living T0 years in Q0 status and living T1 years in another health status Q1, that is preferred to Q0. When utility of life duration is assumed to be linear, the utility of health state Q0 with respect to Q1 is calculated as u = T0/T1. Some authors have warned of a possible downward bias of TTO utilities, mainly due to life duration curvature, whereas others have suggested a possible upward bias caused by loss-aversion and scale-compatibility effects [7,9]. It has also been hypothesized that both downward and upward biases might cancel out, thereby possibly explaining empirical evidence suggesting the greater accuracy of TTO when it comes to reflecting preferences over other methods such as SG [7–12].
time point \( t \) he or she would still be indifferent between living in health status \( Q_0 \) versus \( Q_1 \) under the two new probability distributions of remaining lifetime durations obtained from \( h_0 \) and \( h_1 \), respectively, conditioned to survival to time \( t \). This definition cannot be applied to compare a reference health state \( Q_4 \) considered better than death with another health state \( Q_0 \) regarded worse than death because such states violate the mutual utility independence assumption and thus for any hazard functions \( h_0(t) \) and \( h_1(t) \) the subject will always prefer \( \{Q_1, h_1(t)\} \) over \( \{Q_0, h_0(t)\} \).

If \( h_1(t) \) is a QAHD for a chronic condition \( Q_0 \), we define the maximally tolerated excess mortality risk function for an improvement from \( Q_0 \) to \( Q_1 \) as the difference between the QAHD function and the baseline risk and express it as \( \lambda(Q_0, t) \). A general form for the QAHD is then given by \( h_1(Q_0, t) = h_0(t) + \lambda(Q_0, t) \). Below, two possible behaviors are presented concerning how the tolerated excess mortality risk for an improved chronic health condition might change as the subject’s baseline risk varies over time. In the next section, we will prove that the QALY model represents a middle ground between these two assumptions.

- **Constant additive trade-off of mortality rate** would hold if the excess mortality risk \( \lambda \) that a person is willing to add to his or her baseline hazard of death to improve his or her health status from any given level \( Q_0 \) to any other level \( Q_1 \) is constant over time. Under the constant additive trade-off of mortality rate assumption, the QAHD function is expressed as \( h_1(Q_0, t) = h_0(t) + \lambda(Q_0) \).

- **Constant proportional trade-off (CPTO) of mortality rate** would hold if a person is willing to increase his or her baseline hazard of death multiplicatively from \( h_0(t) \) to \( h_0(t) \times k \) to improve his or her health status from any given level \( Q_0 \) to any other level \( Q_1 \). Under the CPTO of mortality rate assumption, the QAHD function is given by \( h_1(Q_0, t) = h_0(t) \times k_{Q_0} \) and the tolerated excess mortality risk function can be expressed as \( \lambda(Q_0, t) = [h_0(t) - 1] \times k_{Q_0} \).

Because a 90-year-old subject from the general population has an approximately 300 times higher mortality rate than when aged 30 years [19], it might be difficult to assume that a person’s tolerated excess mortality risk for a chronic health state improvement remains constant after this remarkable change in baseline risk. Moreover, it may also be unrealistic to assume that both baseline risk and tolerated risk have a strictly proportional relationship; that is, if the baseline risk is multiplied by 300, the risk of death tolerated for an improvement in chronic health status is also multiplied by 300.

**The QAHD under the QALY Model**

The CPTO of life duration assumption is said to hold if the number of remaining years of life that a person is willing to give up to improve his or her health status from any given level \( Q_0 \) to any other level \( Q_1 \) is a fixed ratio of the absolute number of remaining life-years. This assumption is typical of the QALY model and does not characterize the risk attitude of the subject but rather how the trade-offs of riskless life durations and QOL change as the duration used as reference varies. Multiple studies have checked this assumption empirically and found mixed results, suggesting not only that this assumption might not perfectly hold but also that the deviations from this behavior might not be large [12,20,21].

**Theorem**

If a subject in a chronic condition \( Q_0 \) has a baseline hazard rate of death \( h_0(t) \) and all three conditions of the linear QALY model (mutual utility independence, CPTO of remaining life duration, and risk neutrality over lotteries in life duration) hold, then the hazard function \( h_1(t) \) that the subject is willing to accept at any time \( t \) to improve his or her health status from level \( Q_0 \) to another level \( Q_1 \) is given by

\[
h_1(Q_0, t) = h_0(t) + \left( \frac{1}{MRL_{Q_0}(t)} - 1 \right) \frac{1}{MRL_{Q_0}(t)}
\]

where \( MRL_{Q_0}(t) \) is the MRL function derived from \( h_0(t) \), and \( u \) is the utility of \( Q_0 \) with respect to the reference state \( Q_1 \) consistent with the linear QALY model.

**Demonstration**

Let \( h_0(t) \) be the baseline death hazard function defined over any \( t \geq 0 \) for a subject in health state \( Q_0 \) and \( MRL_{Q_0}(t) \) be the subject’s mean residual life function associated with this hazard function. At \( t = 0 \), life expectancy is denoted simply as \( T_0 \). If \( T \) and \( Q \) are mutually independent, there should be a lifetime \( T_1 > 0 \) for which living \( T_1 \) years in health state \( Q_0 \) is indifferent to living \( T_1 \) years in health state \( Q_1 \). The utility \( u \) of health state \( Q_0 \) is defined as the ratio \( T_1/T_0 \). If risk neutrality over lotteries in life duration holds, this indifference is maintained if, instead of offering fixed (riskless) life durations, two lotteries \( h_0(t) \) and \( h_1(t) \) are proposed with life expectancies \( T_0 \) and \( T_1 \), respectively. In addition, the CPTO of remaining life guarantees that if the lottery \( h_1(t) \) is chosen to maintain the indifference between \( h_0(t) \) in health state \( Q_0 \) and \( h_1(t) \) in health state \( Q_1 \) also at later times \( t > 0 \), then \( MRL_{Q_0}(t)/MRL_{Q_1}(t) \) should equal \( T_1/T_0 \) at any \( t \geq 0 \). The appendix
The assumptions of the QALY model result in subjects eager to tolerate higher increases in their mortality rate as their baseline risk increases (or lower increases if the baseline risk decreases), although such increases (or decreases) are not proportional to the change in baseline risk but inversely proportional to the remaining life expectancy. Because one of the key assumptions of the linear QALY model is the CPTO of life duration, it is not surprising that the resulting form of the QAHD under this model resembles the hazard function of Oakes and Dasu’s proportional MRL model [22].

Corollary
If all three assumptions of the linear QALY model hold and the hazard function is nondecreasing, then the QAHD has a lower bound given by \( h_0(Q_1) ≤ h_0(t)/u \), where \( u \) is the utility of \( Q_0 \) with respect to the reference state \( Q_1 \). Demonstration is trivial because \( h_0(t) ≤ 1/MRL(t) \) at any \( t \).

Example: Tolerated Risk in Crohn’s Disease
The solid line of Figure 2 shows the estimated mortality risk versus age for patients with Crohn’s disease [19,23]. A group of decision makers can define a combined metric for BRA in this indication by using existing evidence suggesting that the moderate symptoms status (\( Q_0 \)) might have a utility of about 0.9 on the 0 to 1 scale, where 0 means death and 1 relates to the remission status (\( Q_1 \)) that they want to use as reference [24].

If all three conditions of the linear QALY model hold, we can conclude that patients with Crohn’s disease would be willing to tolerate, for an improvement from \( Q_0 \) to \( Q_1 \), an excess mortality rate of \( 1/0.9 - 1 = 0.11 \) times the inverse of the MRL, which is represented in Figure 2 as the difference between the solid line and the dotted line. Table 1 shows that the resulting excess risk tolerated by these subjects increases with age when expressed additively with respect to the baseline risk but decreases when stated as the ratio of the baseline risk.

The challenge here is that the tolerated risk depends on a subject’s MRL, which is not the same for all subjects, changes over time, and may be difficult to estimate [25]. The above corollary allows the utility of 0.9 to be translated into a generalizable lower limit of tolerated mortality risk (dashed line), with the only condition that the population risk of death increases over time, which is a reasonable assumption in many populations. We can therefore conclude that, for any subject, a swing in the QOL attribute from moderate to remission status would be regarded at least as important as a 1.11-fold increase in the risk of death.

The lower limit should, however, be used cautiously because it may be too conservative. It notably underestimates the tolerated risk of death for an improvement in their health status for the younger subjects of Figure 2. It might also be anticonservative, and thus inappropriate, in indications in which the main benefit of a new drug is an increase in life expectancy and a worsened QOL is the price to pay for that benefit.

Conclusions
Quantitative models and metrics for BRA often require quantifying the patients’ tolerance to risk for an improvement in their chronic condition. As such, BRA models need to pay more attention to the effect, in term of bias and noise, of asking patients or decision makers to make trade-offs by using small probabilities of suffering unfavorable events during the study.

Herein, we have proposed an alternative solution comprising the use of trade-offs of life duration. In this regard, we have related the well-known concept of QALYs to the hazard rate function and have introduced a new concept, namely, the hazard rate of death that a subject is willing to accept to improve his or her chronic health status, instead of the baseline hazard, which we have called the QAHD. Furthermore, we have shown that if usual assumptions of the linear QALY model hold, the excess

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**Table 1 – Tolerated excess mortality rate in Crohn’s disease.**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline hazard of death*</td>
<td>0.08</td>
<td>0.61</td>
<td>24.37</td>
</tr>
<tr>
<td>QAHD for ( u = 0.9 )</td>
<td>0.30</td>
<td>1.13</td>
<td>28.14</td>
</tr>
<tr>
<td>Absolute difference (QAHD − baseline)*</td>
<td>0.22</td>
<td>0.52</td>
<td>3.78</td>
</tr>
<tr>
<td>Relative difference (QAHD/baseline)</td>
<td>3.98</td>
<td>1.86</td>
<td>1.16</td>
</tr>
</tbody>
</table>

* Units are deaths per 100 subject-years.

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**Fig. 2 – Baseline and quality-of-life adjusted hazard of death in Crohn’s disease.** * Quality-of-life adjusted hazard of death for a chronic health state improvement with utility \( u = 0.9 \).
mortality risk that a subject maximally tolerates to improve his or her health status is inversely proportional to the remaining life expectancy. This result leads to a new representation of the linear QALY model, for the simple case in which an individual is in the same state for the remaining years of his or her life, in terms of hazard rate functions. We have shown how to transform utilities obtained from trade-offs of life duration into tolerated excess mortality rates that can be used in BRA models defined over a short evaluation period, thereby avoiding the need for direct trade-offs using low probabilities of death during the study. This procedure assumes CPTO of life duration, an assumption that might not perfectly hold but still appears more prudent and supported by previous literature than other assumptions such as constant or proportional trade-off of mortality rate.

Although we have focused herein on the risk of death during the study, models for BRA often include other severe but nonfatal events. In these situations, it may still be useful to initially obtain a weight for death to be used as a reference and then estimate weights for other nonfatal severe events, for example, a nonfatal myocardial infarction, by quantifying the loss of QOL and life expectancy caused by this event with respect to the total loss implied by the subject’s death.

One important limitation of this article is its focus on the most conventional QALY model that assumes the same health status maintained over the remaining life, risk neutrality, and no discounting. Further research is recommended to extend this new proposed formulation in terms of hazard rate functions and to investigate other potential uses of this representation not only in the field of BRA but also in other areas.

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Supplemental Materials

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REFERENCES