Exploring a Markov Model Framework to Quantify Societal Preferences, Concerning Age and Severity of Disease, for Health Resource Allocation

Zsombor Zrubka

Health Economics Research Center, University Research and Innovation Center,
Óbuda University, Bécsi út 96/b, 1034 Budapest, Hungary
zrubka.zsombor@uni-obuda.hu

Zoltán Hermann

Institute of Economics, Centre for Economic and Regional Studie, Tóth Kálmán u. 4, 1097 Budapest, Hungary, and Institute of Economics, Corvinus University of Budapest, Fővám tér 8, 1093 Budapest, Hungary, hermann.zoltan@krtk.hu

Márta Péntek

Health Economics Research Center, University Research and Innovation Center,
Óbuda University, Bécsi út 96/b, 1034 Budapest, Hungary
pentek.marta@uni-obuda.hu

Levente Kovács and Dániel András Drexler

Physiological Controls Research Center, University Research and Innovation Center, Óbuda University, Bécsi út 96/b, 1034 Budapest, Hungary
kovacs@uni-obuda.hu; drexler.daniel@nik.uni-obuda.hu

Mariann Békésy

Innovation Management Doctoral School, Óbuda University
Bécsi út 96/b, 1034 Budapest, Hungary, bekesy.mariann@phd.uni-obuda.hu

László Gulácsi

Health Economics Research Center, University Research and Innovation Center, Óbuda University, Bécsi út 96/b, 1034 Budapest, Hungary, gulacsi@uni-obuda.hu

Abstract: Certain health problems are considered as a normal part of ageing, hence are more acceptable at older, rather than at younger ages. In the context of this research, acceptability has been defined as the proportion of the general population who consider a certain health state acceptable for a given age. We propose a Markov model framework to quantify societal preferences concerning the severity of the health state and age of the affected individuals. Health states in each model cycle are split to acceptable and not acceptable proportions, with different priority weights. Health gains originated from the shifts between health states, are expressed in Quality Adjusted Life Years (QALYs). Using the Hungarian acceptability set and value set of the EQ-5D-3L health status measurement tool, we compare health gains in four priority function scenarios with and without adjustment for acceptability. The analysis on selected health states suggested, that priority scenarios valuing both time in acceptable health and health gains in not acceptable health, reflect several societal preferences, related to healthcare resource allocation. However, more theoretical and empirical research is needed before this method can be implemented in real-life decision-making.

Keywords: acceptability; EQ-5D; quality of life; QALY; Markov model; economic evaluation; resource allocation

1 Introduction

Before the COVID-19 pandemic, health care expenditure has been growing faster than the general economy in most European countries, putting health financing decision makers under increasing pressure [1]. While the pandemic demanded extra public health expenditure under the conditions of declining economic performance [1], it also facilitated the uptake of advanced technologies [2] [3], and the scope of technologies competing for public reimbursement has broadened with digital health interventions in many countries [4]. The increasing pressure on health financing decision makers calls for the rigorous assessment of the efficacy and value of novel technologies seeking public financing [5] [6]. Health technology assessment (HTA) is “a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system” [7]. The European Network for HTA (EUnetHTA) has structured HTA in nine core domains including economic evaluation (EE), defined as a “comparative analysis of alternative courses of action in terms of both their costs and consequences” [8] [9]. EE informs value-for-money judgements by comparing the costs and health outcomes of alternative treatments [8]. Among various EE methods, cost-utility analysis (CUA) provides comparable results between disease areas, as health outcomes are summarized in quality adjusted life years (QALYs) [8] combining both the quality and length of life in a single figure [10]. The results of CUA are expressed as the incremental cost-effectiveness ratio (ICER) [11]. In QALY-based CUA studies the literal meaning of ICER (eq. 1) is the cost of producing one additional QALY when choosing health technology “A” versus “B”.

$$ICER = \frac{Cost_A - Cost_B}{QALY_A - QALY_b} \tag{1}$$

When evaluating cost-effectiveness, ICERs are compared to the societal willingness to pay (WTP) threshold for a unit of outcome, using techniques outside the scope of this paper. EEs are usually performed using decision-analytic models, with cohort state transition models (Markov models) among the most frequently used techniques [8] [12].

This paper is motivated by the discrepancies between the normative theories behind QALYs and actual preferences of the society about the distribution of scarce resources. QALYs have long been criticized for imperfectly reflecting societal preferences that may matter in decision-making [13-15]. Notably, when allocating scarce health resources, people would consider the age and disease severity of the affected population in question [16] [17], while QALYs are invariant to these parameters [15]. Building on the observation that certain health problems become increasingly acceptable with age [18-21], acceptability (i.e., the proportion of the general population who consider a certain health state acceptable for a given age) has been proposed to quantify societal preferences concerning age and disease severity [22]. In this paper we propose a discrete-time Markov model framework for health resource allocation, using acceptability-adjusted QALYs (aQALYs) to quantify societal preferences about age and disease severity. Also, without proposing a normative framework, we explore different scenarios for aQALY adjustments using empirical data.

The structure of this paper is the following. The literature review introduces the measurement methods and theoretical background for using aQALYs in EE. In the methods section we introduce Markov models, demonstrate the construction of aQALYs, and explore the implications of acceptability on possible model transitions to death. In the results we explore aQALYs using empirical data, followed by discussion and conclusion.

2 Literature Review

2.1 EQ-5D-3L

Acceptability studies were mainly conducted using the descriptive system of the EQ-5D-3L questionnaire [18-23], the most frequently used instrument for the calculation of QALYs [24]. EQ-5D-3L describes patient-reported health problems in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) in three levels (1 - no problems, 2 - moderate problems, 3 - severe problems), distinguishing 243 (3^5) health profiles [25]. Health profiles attach the problem levels of the five dimensions into five-digit numbers. For example, 21131 denotes moderate problems with mobility, extreme pain / discomfort and no problems in the other three dimensions.

For the measurement of the quality-of-life component of QALYs, quantified societal preferences (utilities) are attached to all EQ-5D-3L health profiles (denoted as value set) [26][27]. By definition, the utility of full health (11111) is 1, the utility of death is 0, and health profiles perceived as worse-than-death have negative utilities. The lowest value of the Hungarian EQ-5D-3L value set is -0.865 for the health profile 33333 denoting severe problems in all five dimensions [28]. Utilities are the same for a given health profile regardless the age, gender, specific disease etc. of the individual [29].

2.2 Acceptability

With ageing, certain health problems become acceptable in the general population and chronic patients [18-21, 30]. Acceptability is a measurable rating for complex subjective judgements [31], such as the overall “goodness” of a health state. Since acceptability reflects the preferences of the general population, it may be a suitable for resource allocation purposes. Conveying as much information about a population’s judgements as a rating scale, acceptability is evaluated via binary yes/no survey items [32]. While the EQ-5D-3L value set attaches a single utility to health profiles, acceptability (i.e., proportion of the population) is reported for six ages from 30 to 80 years in 10-year-steps [22].

2.3 The Normative Theories of Applying Acceptability for Resource Allocation Decisions

Health economic models are generally based on utilitarianism and egalitarianism, by aiming to maximize a value function (health gains from a unit resource), while treating individuals equally by some criteria [33] [34]. Egalitarian theories vary in terms of what should be the basis of equity (e.g., health, resources, or access to treatment) [35] [36]. Some countries also incorporate the principle of prioritanism by favoring individuals in poorest health [34] [37].

The normative background of using acceptability for resource allocation has been explored by Wouters at al [38], following the tenets of sufficientarianism [39]. Sufficientarians assert that the equal distribution of goods is not important, but everyone should have enough [40]. The positive thesis poses that it is morally relevant to live above the sufficiency threshold, while the negative thesis rejects the relevance of other theories of justice [38] [41]. The shift thesis suggests that the priorities to benefit individuals change beyond the sufficiency threshold, without specifying the priority functions below and above the threshold [42]. While sufficientarianism is focused on well-being, acceptability is concerned with quality of life [38], suggesting resource allocation priorities above and below the reference threshold of acceptable health should differ [23] [38]. In practice, acceptability should be applied jointly with other theories of distributive justice [19, 23, 38].

2.4 Alternative Approaches to QALY Estimation in Decision-Analytic Models

Recognizing the discrepancies between standard QALY estimates and societal preferences [17] [43], several modelling studies proposed using the alternative QALY estimates. In a systematic review, Carlson et al. have identified 28 alternative models based on nine strategies [43]. The feasibility of these approaches was evaluated based on the availability of supporting data and compatibility with existing model structures. Only three strategies deemed feasible: A) utilities elicited from patients; B) life years gained; and C) equity weighting using three approaches: 1) weighting based on baseline utility (i.e., favoring those with more severe disease), 2) weighting based on fair innings (favoring those who have not yet achieved a fair amount of healthy lifetime), 3) weighting based on proportional QALY shortfall (the proportion of lost QALYs due to the disease compared to the general population). The five alternative approaches were tested on nine diseases. All of them affected the model results, with greatest negative impact on health gain estimates if utilities were assessed by patients [43]. Other model experiments aimed at extending the assessment of health gains beyond the health sector [44]. Altogether, despite their technical feasibility and plausibility from theoretical standpoint, neither of these methods have been implemented in the usual practice of resource allocation, mainly due to lingering methodological concerns and lack of consensus about the appropriate inputs [43].

3 Methods

3.1 Markov Models

Markov models (cohort state transition models) are among the most frequently used tools for health economic evaluations to support financing decisions in healthcare [45]. Markov models are composed of states, transitions, an initial state vector, transition probabilities, cycle length (i.e., the time elapsing between state transitions), and state values (e.g., utilities or costs attached to the states). The possible health states (e.g., S_1, S_2,…, S_n) in a disease including death (D), and possible transitions (e.g., $\tau_{11}, \tau_{12, \ldots,} \tau_{nn}$) are depicted in state transition diagrams. An example of a state transition diagram is shown in Figure 1.

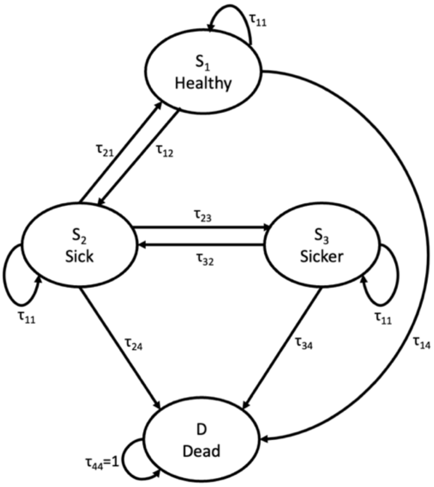

Figure 1
Example of a state transition diagram

In its general form, health outcomes of treatment "A" over the modelling time horizon ($QALY_A$) can be summarized for a homogenous cohort as

$$QALY_A = \sum_{i=1}^{m} \boldsymbol{p_{i-1}} \boldsymbol{T_{Ai}} \, \boldsymbol{u}^{\mathrm{T}} \frac{1}{(1+d)^{i/q}} \tag{2}$$

where $m=tq$ with t denotes the model time horizon in years and q denotes the number of model cycles per year. The actual model cycle is denoted by i, $\mathbf{p_i}$ is a n-dimensional row vector representing the distribution of patients in the n possible health states in the model including death as the n^{th} state $(S_k \in \{S_1, S_2, \ldots S_{n-1}, D\})$. The time preference of the decision-maker is reflected by the annual discount rate d [46]. The distribution of the baseline population over model states is provided in

p₀. $\mathbf{T}_{\mathrm{Ai}}$ is an $n\times$ matrix representing the transition probabilities characterizing treatment “A” in cycle i.

$$T_{Ai} = \begin{pmatrix} \tau_{A11i} & \cdots & \tau_{A1ni} \\ \vdots & \tau_{Akli} & \vdots \\ \tau_{An1i} & \cdots & \tau_{Anni} \end{pmatrix} \tag{3}$$

where τ_{Akli} $(k,l \in \{1, 2, \dots n\}, i \in \{1, 2, \dots m\})$ are transition probabilities from health state k to health state l in cycle i characterizing treatment “A”. Transition probabilities are usually derived via systematic evidence synthesis of clinical study results. Age-specific mortality is denoted by $\tau_{Akni} = \lambda_{Ak}\mu_i$, $(i \in \{1, 2, \dots m\}, k\in \{1, 2, \dots n\})$, with μ_i taken from mortality tables of the general population [47] adjusted for the model cycles and the age of the cohort at cycle 0. For patients receiving treatment “A” in disease state k, λ_{Ak} denotes the relative mortality, versus the general population. Due to the age-specific mortality values, the transition matrix changes over time in most decision modelling situations in healthcare. However, for health state transition probabilities, the assumption is often $\tau_{Akli} = \tau_{Akl}$ [48]. The elements in each row of $\mathbf{T}_{\mathbf{Ai}}$ add up to 1. Death is an absorbing state with $\tau_{Anli} = 0$ if $l\neq n$ and $\tau_{Anni} = 1$. The utility values of the n health states including death are contained by the n-dimensional transposed row vector denoted with $\boldsymbol{u}^{\mathrm{T}}$. The utilities of the n health states have to be corrected by the number of model cycles per year.

$$\mathbf{u} = \left(\frac{u_1}{q}, \frac{u_2}{q}, \cdots \frac{u_n}{q}\right), u_n = 0 \tag{4}$$

A consequence of the time-invariant property of QALYs is that **u** is constant over the entire model time horizon. For inhomogeneous populations containing a variety of cohorts in terms of demographic characteristics or risk, the results of cohorts have to be aggregated as

$$QALY_A = \sum_{j=1}^{k} \sum_{i=1}^{m} \pi_j \boldsymbol{p}_{\boldsymbol{i-1},\mathbf{j}} \boldsymbol{T}_{\boldsymbol{Aij}}\, \boldsymbol{u}' \frac{1}{(1+d)^{i/q}} \tag{5}$$

where π_j is the proportion of cohort j $(j \in \{1, 2, \dots k\})$ in the population. Consequently, mortality values have to be adjusted to the age and other relevant risk factors for the decision situation, leading to cohort-specific patient vectors ($\mathbf{p}_{\mathbf{ij}}$). Health gains for the comparator treatment ($\mathrm{QALY_B}$) are calculated similarly, replacing $\mathbf{T}_{\mathbf{Ai}}$ with $\mathbf{T}_{\mathbf{Bi}}$ reflecting transition probabilities specific to treatment “B”. For accurate results, a half-cycle correction is applied to the first and final cycle, for details, see [45]. In probabilistic sensitivity analyses models are run multiple times with parameters randomly drawn from appropriate distributions [45].

3.2 Defining a Continuous Acceptability Function

Acceptability is defined as the proportion of the general population, who consider a health profile acceptable for a given age [22]. The acceptability set for EQ-5D-3L has been determined for 1458 health profile-age combinations of the 243 health profiles H_χ $(\chi \in \{1, 2, ... 243\})$ and six ages x $(x \in \{30, 40, ... 80\})$, formally written as

$$A(H_\chi, x) = P \tag{6}$$

$$(\mathit{being\ in}\ H_\chi\ \mathit{is\ acceptable\ by\ a\ person\ in\ the\ general\ population}\ \big|\ \mathit{age} = x)$$

For details, see Hermann et al. [22]. Acceptability evaluations reflect the preferences of the general population concerning chronic health states, and *x* refers to the age of a patient for whom acceptability is evaluated. As health states in a model usually represent a group of patients in a certain severity group (e.g., mild or severe cases with corresponding health profile distributions), the acceptability of health state *S* for age *x* is given by the formula in eq. 7.

$$A(S, x) = \sum_{\chi=1}^{243} \pi_\chi\, A(H_{\chi,} x), \qquad \sum_{\chi=1}^{243} \pi_\chi = 1 \tag{7}$$

Within health state *S* the proportion of patients with each health profile are denoted by π_χ.

For practical applications it is convenient to derive acceptability as a continuous function of utility and age, using the fact that each *H* health profile of EQ-5D-3L is mapped to a corresponding utility value by a value function $(u_\chi = U(H_\chi),\ \chi \in \{1, 2, ... 243\})$. For details of the Hungarian EQ-5D valuation study, see Rencz et al. [28]. The utility function for health state *S* is defined as the expected value of the individual utilities of patients within health state *S* as

$$u(S) = \sum_{\chi=1}^{243} \pi_\chi\, U(H_\chi), \qquad \sum_{\chi=1}^{243} \pi_\chi = 1 \tag{8}$$

where the proportion of patients with health profile H_χ is denoted by π_χ. Combining (7) and (8), the continuous acceptability function can be defined as follows.

$$A(u, x) = \{A(S, x) \mid u(S) = u, \mathit{and\ age} = x\},\ A(u, x) \in [0,1] \tag{9}$$

A(u,x) is interpreted as the proportion of the population who consider utility *u* acceptable for age *x*. The definition suggests that although acceptability is measured and defined for discrete health profiles [22], the continuous acceptability function for utility *u* and age *x* assumes the mean acceptability of a group of individuals in health state *S* with mean utility *u* and age *x*. In practice, *A(u,x)* can be estimated from the acceptability set [22], mean utilities are reported for various disease health states in quality-of-life studies [49-51], and age is modelled in the Markov model.

3.3 Incorporating Acceptability in a State Transition Model

The normative assumption is that the priority of financing treatments for acceptable and not acceptable health states should differ in health resource allocation [38].

Therefore, for a health state with utility u, the acceptability-adjusted utility in age x can be calculated using eq. 10.

$$\upsilon(u,x) = A(u,x)p(u) + [1 - A(u,x)]q(u), \qquad u(x) \leq 1 \tag{10}$$

Where $p(u)$ and $q(u)$ denote the priority functions for utilities considered respectively as acceptable or not acceptable by individuals of the general population. Through the priority functions, various principles of distributive justice can be implemented in combination with acceptability. We propose to keep the convention that priority-adjusted utility and acceptability-adjusted utility should be maximized at 1, for full health (eq. 11).

$$p(1) = q(1) = \upsilon(1,x) = 1 \tag{11}$$

We note that in the state transition model age x is expressed as a function of the model cycle i. The acceptability-adjusted utility vector for model cycle i is

$$\boldsymbol{\upsilon_i} = \left(\frac{\upsilon_{1i}}{q}, \frac{\upsilon_{2i}}{q}, \cdots, \frac{\upsilon_{ni}}{q}\right),\ \upsilon_{ni} = 0 \tag{12}$$

We assign zero utility value to death in all model cycles ($\upsilon_{ni} = 0$). The aQALY formula for treatment “A” is

$$aQALY_A = \sum_{i=1}^{m} \boldsymbol{p_{i-1} T_{Ai}\, \upsilon_i}' \tag{13}$$

and the acceptability adjusted QALY gain when using treatment “A” vs treatment “B” is $\mathrm{aQALY_A}$ - $\mathrm{aQALY_B}$.

3.4 Constructing Priority Functions

Following the work of Wouters et al. [38] the priority functions of acceptable and not acceptable health states should satisfy the following properties:

a) For the same health state with utility u, the priority-adjusted utility should be the same or greater if the health state is considered acceptable compared to when the health state is not acceptable.

b) When transitioning between two health states, if neither health states are acceptable, priority-adjusted health gains should be the same or greater than if the same health states are both acceptable.

c) The utility of full health is 1, and full health is always acceptable. Formally: for every u, $p(u) \geq q(u)$ and $0 \leq p'(u) \leq q'(u)$, and $p(1)=1$, where $p'(u)$ and $q'(u)$ denote the derivatives of $p(u)$ and $q(u)$, respectively.

In Figure 2 we explore four parametrization scenarios for the priority functions.

Following the priority weighting scenarios explored by Wouters et al, scenario “A” corresponds to the “strict sufficientarian weighting”: the priority-adjusted utilities of acceptable and not acceptable health states are 1 and 0 respectively, with no value attached to health gains that do not cross the acceptability threshold. Scenario “B” is similar to “modest sufficientarian weighting”: the priority-adjusted utility of acceptable health states is 1 with no value of further health gains. However, all health gains below the acceptability threshold are valued without adjustment. When crossing the acceptability threshold, the priority-adjusted utility jumps to 1. We add scenario “C” to illustrate a possible implementation of “shift sufficientarian weighting”, reflecting twice as great priority for health in not acceptable health states than for health gains in acceptable health states, with an abrupt increase in priority-adjusted utility when crossing the acceptability threshold. Scenario “D” depicts a “mixed sufficientarian-prioritarian weighting”. The priority function is non-linear, greater slopes attach greater weights to health gains in lower utility ranges, with a sudden increase of priority-adjusted utility, whenever the acceptability threshold is crossed.

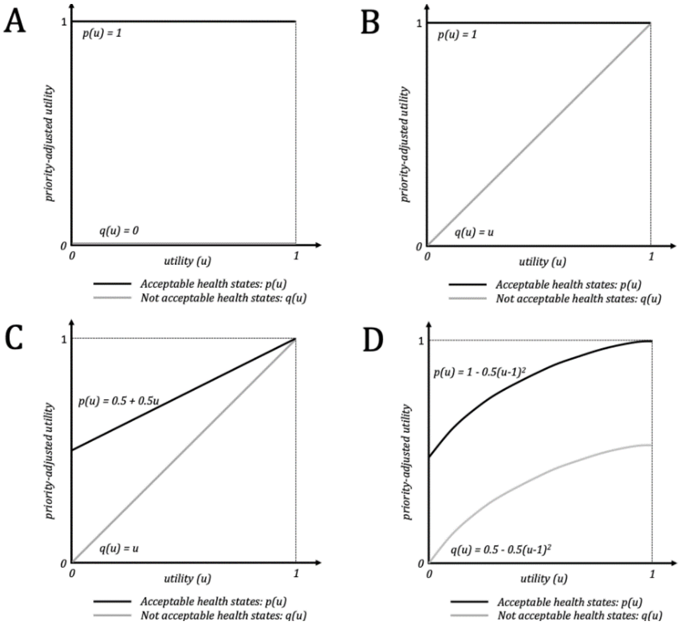

Figure 2

Four parametrization scenarios for the priority functions

3.5 Modelling Transitions to Death

The fact that some health states are perceived as worse than death has been long described in the QALY literature [29]. The utility value of death is zero by convention. Therefore, these health states are associated with negative utilities [52]. Although the various valuation techniques for negative utilities have shown to be inconsistent [53], negative utilities corresponded poorly with the affected individuals' actual well-being [54], and ethical concerns have been raised about using negative utilities in health economic evaluations [55], the tacit consequence of current practice using negative utilities is that death from a worse-than dead health state is accounted as a QALY gain [8, 56]. In aQALY models death may occur from acceptable or not acceptable health states with either positive or negative utility values [22], resulting in four possible transitions to death. While a recent report on the value of death [57] and the vast literature on the preferences about euthanasia and end-of life care [58-61], suggests that death may be acceptable in certain health states and / or age, the current framework ignores this possibility.

3.6 Exploring Priority Functions on Empirical Data

We explore four priority function scenarios depicted in Figure 2, using four health profiles with different severity levels. The choice of parameters was arbitrary. Due to the linear properties of Markov models, the priority shifts of single health profiles provide good insights about aggregate-level changes of the entire model when replacing QALYs with aQALYs.

The availability of both a value set and an acceptability set for EQ-5D-3L from the Hungarian general population allows the exploration of priority function scenarios on empirical data. The Hungarian value set for EQ-5D-3L was estimated on a representative survey of the Hungarian adult population (N=1000) using computer-assisted personal interviews [28]. The acceptability set for EQ-5D-3L has been determined first for the Hungarian population via an online survey involving 1375 respondents [22] [23].

The four selected health states included full health ($H_1=11111$), moderate health problems in two dimensions ($H_2=21121$), a health profile with both moderate and severe problems ($H_3=21131$) and a worse-than dead health state with severe problems in multiple domains ($H_4=31133$).

For the four priority function scenarios in ages 50 (middle age) and 80 years (old age), we tabulated the utilities, acceptability, acceptability adjusted utility, and health gains (i.e., changes in utility) from transitions between health states and transitions to death. To help the interpretation of findings, we calculated relative priority (RP_σ) in the four scenarios ($\sigma \in \{A, B, C, D\}$) for each health gain as

$$RP_\sigma(\%) = \frac{\Delta\upsilon/\bar{\upsilon}_\sigma}{\Delta u/\bar{u}} = \frac{\Delta\upsilon\bar{u}}{\Delta u\bar{\upsilon}_\sigma}, \sigma \in \{A, B, C, D\} \tag{14}$$

Mean utility was denoted by $\bar{u}$, the unadjusted health gain was denoted by Δu, and the priority of health gains within each scenario was calculated relative to the mean utility of the scenario ($\Delta u/\bar{u}$). The scenario-specific acceptability-adjusted mean utilities, health gains and priorities are denoted by $\bar{\upsilon}_\sigma$, $\Delta\upsilon$ and $\Delta\upsilon/\bar{\upsilon}_\sigma$, respectively. *RP* is the ratio of the priorities of health gains between the adjusted and unadjusted scenarios. *RP > 100%* or *RP< 100%* indicate that transitions have respectively greater or lower priority in the acceptability adjusted- compared to the unadjusted base scenario.

4 Results

The mean utility of the health profiles in the four scenarios was the same ($\bar{u} = \bar{u}_A = \bar{u}_B = \bar{u}_C = \bar{u}_D = 0.56$). However, the mean acceptability-adjusted utility differed between the four scenarios ($\bar{\upsilon}_A = 0.44, \bar{\upsilon}_B = 0.62, \bar{\upsilon}_C = 0.59, \bar{\upsilon}_D = 0.50$). Health gains and their relative priorities are summarized in Table 2. The acceptability-adjusted priority increased for transitions to death in most scenarios, suggesting that acceptability weighting would favor life-extension over improvements in quality-of-life. The utility gains associated with death from “worse than dead” health states were reversed or mitigated in most scenarios.

Table 2

Transitions between health states in four priority function scenarios

Scenario	Age (x_ξ)	EQ-5D-3L Profile (H_χ)	Utility U(H_χ)	Accept-ability $\alpha(H_\chi, x_\xi)$	Accept-ability adjusted utility $\upsilon(x)$	Transitions between health profiles				Transitions from health profiles to death			
						Transi-tion	Δu	$\Delta\upsilon$	RP_σ	Transi-tion	Δu	$\Delta\upsilon$	RP_σ
A	50	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.909	942%	$H_1 \to D$	-1	-1	226%
		H_2=21121	0.878	0.091	0.091	$H_3 \to H_2$	0.258	0.066	32%	$H_2 \to D$	-0.878	-0.091	23%
		H_3=21131	0.620	0.025	0.025	$H_4 \to H_1$	1.264	0.993	99%	$H_3 \to D$	-0.620	-0.025	9%
		H_4=31133	-0.264	0.007	0.007	$H_4 \to H_2$	1.142	0.084	9%	$H_4 \to D$	0.264	-0.007	-6%
	80	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.153	159%	$H_1 \to D$	-1	-1	226%
		H_2=21121	0.878	0.847	0.847	$H_3 \to H_2$	0.258	0.461	226%	$H_2 \to D$	-0.878	-0.847	218%
		H_3=21131	0.620	0.386	0.386	$H_4 \to H_1$	1.264	0.821	82%	$H_3 \to D$	-0.620	-0.386	141%
		H_4=31133	-0.264	0.179	0.179	$H_4 \to H_2$	1.142	0.668	74%	$H_4 \to D$	0.264	-0.179	-153%
B	50	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.111	82%	$H_1 \to D$	-1	-1	161%
		H_2=21121	0.878	0.091	0.889	$H_3 \to H_2$	0.258	0.260	90%	$H_2 \to D$	-0.878	-0.889	163%
		H_3=21131	0.620	0.025	0.630	$H_4 \to H_1$	1.264	1.255	89%	$H_3 \to D$	-0.620	-0.630	163%
		H_4=31133	-0.264	0.007	-0.255	$H_4 \to H_2$	1.142	1.144	90%	$H_4 \to D$	0.264	0.255	155%
	80	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.019	14%	$H_1 \to D$	-1	-1	161%
		H_2=21121	0.878	0.847	0.981	$H_3 \to H_2$	0.258	0.215	75%	$H_2 \to D$	-0.878	-0.981	180%
		H_3=21131	0.620	0.386	0.767	$H_4 \to H_1$	1.264	1.038	74%	$H_3 \to D$	-0.620	-0.767	199%
		H_4=31133	-0.264	0.179	-0.038	$H_4 \to H_2$	1.142	1.019	80%	$H_4 \to D$	0.264	0.038	23%
C	50	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.116	90%	$H_1 \to D$	-1	-1	169%
		H_2=21121	0.878	0.091	0.884	$H_3 \to H_2$	0.258	0.259	95%	$H_2 \to D$	-0.878	-0.884	171%
		H_3=21131	0.620	0.025	0.625	$H_4 \to H_1$	1.264	1.260	94%	$H_3 \to D$	-0.620	-0.625	171%
		H_4=31133	-0.264	0.007	-0.260	$H_4 \to H_2$	1.142	1.143	95%	$H_4 \to D$	0.264	0.260	167%
	80	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.070	55%	$H_1 \to D$	-1	-1	169%
		H_2=21121	0.878	0.847	0.930	$H_3 \to H_2$	0.258	0.236	87%	$H_2 \to D$	-0.878	-0.930	179%
		H_3=21131	0.620	0.386	0.693	$H_4 \to H_1$	1.264	1.151	86%	$H_3 \to D$	-0.620	-0.693	190%
		H_4=31133	-0.264	0.179	-0.151	$H_4 \to H_2$	1.142	1.081	90%	$H_4 \to D$	0.264	0.151	97%
D	50	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.462	422%	$H_1 \to D$	-1	-1	199%
		H_2=21121	0.878	0.091	0.538	$H_3 \to H_2$	0.258	0.098	42%	$H_2 \to D$	-0.878	-0.538	122%
		H_3=21131	0.620	0.025	0.440	$H_4 \to H_1$	1.264	1.295	114%	$H_3 \to D$	-0.620	-0.440	142%
		H_4=31133	-0.264	0.007	-0.295	$H_4 \to H_2$	1.142	0.833	81%	$H_4 \to D$	0.264	0.295	223%
	80	H_1=11111	1	1	1	$H_2 \to H_1$	0.122	0.084	77%	$H_1 \to D$	-1	-1	226%
		H_2=21121	0.878	0.847	0.916	$H_3 \to H_2$	0.258	0.295	127%	$H_2 \to D$	-0.878	-0.091	23%

		$H_3=21131$	0.620	0.386	0.621	$H_4 \rightarrow H_1$	1.264	1.209	107%	$H_3 \rightarrow D$	-0.620	-0.025	9%
		$H_4=31133$	-0.264	0.179	-0.209	$H_4 \rightarrow H_2$	1.142	1.125	110%	$H_4 \rightarrow D$	0.264	-0.007	-6%

Scenario “A” valued only life years spent in acceptable health. This would favor transitions to perfect health in the middle-aged group, and transitions to milder health problems among the elderly. In both age groups health gains from the worst health states would have lower value compared to health gains from better health states. The priority of life extension in the middle-aged group would decrease markedly in this scenario. Scenario “B” valued both life years in acceptable health and health gains in not acceptable health. This scenario would reduce the priority of quality-of-life improvement in the elderly slightly more than among middle aged individuals, with marked priority reduction for transitions from mild health states to perfect health among the elderly. Conversely, the priority of life extension would increase, slightly favoring older individuals with severe health problems compared to the middle age group. The overall profile of scenario “C” was similar to scenario “B” with milder priority changes compared to unadjusted utilities. The mixed weights in scenario “D” resulted in varying priority changes favoring both the transitions to acceptable health states and improvements from the worst health states. Surprisingly, compared to the unadjusted scenario, the relative priority of treating middle aged individuals in worst health states would decrease. Furthermore, this scenario attached greater utility gain to death from the most severe health states. If left unadjusted, this scenario would favor less efficacious treatments with greater mortality risk for individuals in the worst health states.

5 Discussion

In this paper we introduced a Markov model framework that incorporates acceptability and quality adjusted life years to quantify societal preferences concerning age and severity of disease for health resource allocation. Using empirical data from the Hungarian value set and acceptability set for EQ-5D-3L, this paper is among the first to explore acceptability adjusted QALYs for decision modelling [22] [28]. The relative priorities for health gains were compared between unadjusted and acceptability-adjusted utilities in four priority-function scenarios.

We demonstrated that using aQALYs is a feasible decision-analytic model framework, as it can be implemented in a standard model structure and data are available for acceptability adjustments [43].

Acceptability adjustments in scenarios “B” and “C”, which valued both time in acceptable health and health gains in non-acceptable health, shifted relative priorities in accordance with frequently documented societal preferences [16]: the importance of life-extension increased in comparison to quality-of-life improvements, the priority slightly shifted towards younger individuals, and the priority of improving mild problems decreased compared improving severe problems. Scenario “A” valuing only acceptable time provided results that contradict several of the above listed priorities. Also, in scenario “D”, the theoretically promising model of mixing acceptability and prioritarian weighting brought counter-intuitive results. Although the existence of the acceptability threshold is well documented [18, 20-22, 62], more research is needed to determine optimal parameter settings and priority function forms that match the societal preference patterns for resource allocation.

Our exploration also highlighted the diversity of possible transitions from health states to death. The question remains if the acceptability of death in certain health states or ages is a plausible assumption. While it would reflect the evolving complexity of our notion about death and death systems in contemporary medicine [57], the theoretical and methodological challenges of a feasible modelling solution are far-reaching, and beyond the scope of this paper. Societal preferences about the end-of-life have been shown to change, albeit with mixed results [16]. Also, the relative position of health problems to death seems to be influenced by their severity and duration, which is not described adequately by the current QALY model [63] [64]. On the other hand, several methodological studies have convincingly concluded that death should positioned at zero utility to preserve the ratio-scale properties of QALYs [65]. Therefore, death may be used as an anchor when estimating the various priority functions in empirical studies. Also, it remains an elusive question, if acceptability of a health state implies strictly positive utility valuation. Altogether, the valid and feasible acceptability-based adjustments for modelling transitions to death require further research.

We are aware of two modelling studies, which applied an acceptability or sufficiency threshold for quality of life or well-being. In a previous study, we explored the application of acceptability adjusted life years in a published model for Crohn’s disease [19], using acceptability data from a convenience sample [23] and utilities of the UK value set [66]. In this model, two strict priority functions were explored: one that values only time in acceptable health, and the other that values only QALY gains in not acceptable health states. Adjusted QALY gains between competing biologic treatments were explored over the age spectrum. Maximum differences from the unadjusted model were observed around 80 years of age, with opposite direction: acceptable life years favored while QALY gains in not acceptable health disfavored older cohorts. Furthermore, we are aware of one study that proposed the sufficient capability threshold concept for the evaluation of health interventions [67]. The levels of sufficient capability were arbitrarily chosen using the ICECAP-O capability of wellbeing instrument [68-70], which was rescaled to cap weights for individuals in sufficient capability. Life years gained in sufficient capability were calculated for a cohort of patients undergoing hip replacement surgery.

The strength of our study is that beyond demonstration of the technical feasibility of a Markov model framework, the applied acceptability thresholds and utility values were derived from representative samples of the Hungarian population, reflecting relevant preferences for decision-making.

However, our study has a number of limitations. First, acceptability adjustments have changed the mean utilities across the included health profiles. This suggests, that depending on the applied priority functions, the WTP threshold for acceptability adjusted economic models should be different from the threshold applied for models using unadjusted QALYs. Also, the acceptability function is yet to be estimated, and the relevant priority functions and their parameters for the Hungarian population have yet to be determined. Each priority scenario assumed an abrupt utility change (i.e., “jump”) when the acceptability threshold is crossed. In our examples the difference between acceptable and not acceptable health profiles was chosen arbitrarily. Furthermore, the adequate utility values for transitions to death require further exploration. Also, despite the evaluation of four health states provided good insights into the expected changes, to generalise the results, acceptability adjustments should also be tested in full models in a variety of patient cohorts, to explore the aggregated effects in various patient-cohorts. Finally, while other model structures are also used in EE, this paper introduced the implementation of a QALYs only on the example of Markov models.

Conclusions

The application of acceptability adjusted QALYs, are feasible in a Markov modelling structure. The evaluation on selected health profiles suggested, that the priority scenarios valuing both time in acceptable health and QALY gains in not acceptable health reflected several societal preferences, concerning health resource allocation. Altogether, while the concept of using acceptability adjusted QALYs, for health resource allocation is promising, more theoretical and empirical research is needed before this method can be implemented in real-life decision-making scenarios.

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