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The QALY model and individual preferences for health states and health profiles over time: A systematic review of the literature

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Aki Tsuchiya, PhD †
Centre for Well-being in Public Policy, School of Health and Related Research, University of Sheffield.

Paul Dolan, D. Phil
Centre for Well-being in Public Policy, University of Sheffield.

† **corresponding author**
Aki Tsuchiya, CWiPP, School of Health and Related Research, 30 Regent Street, Sheffield, S1 4DA
Tel: 0114.222.0710 Fax: 0114.272.4095 e-mail: a.tsuchiya@sheffield.ac.uk

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ABSTRACT

The numbers of quality-adjusted life years (QALYs) gained are increasingly being used to represent the gains in individual utility from treatment. This requires that the value of a health improvement to an individual is a simple product of gains in quality of life and length of life. The paper reports on a systematic review of the literature on two issues: whether the value of a state is affected by how long the state lasts; and by states that come before or after it. It was found that individual preferences over health are influenced by the duration of health states and their sequence. However, whilst there is much variation across individual respondents, the assumptions tend to hold much better when valuations are aggregated across respondents, which is encouraging for economic evaluations that rely on using average (mean or median) values.
(139 words)

Key Words: QALYs; individual preferences; utility measurement

The QALY model and individual preferences for health states and health profiles over time: A systematic review of the literature

1. INTRODUCTION

Since people experience health benefits as improvements in their quality of life and/or as increases in their length of life, the quality-adjusted life-year (QALY) attempts to combine the value of these attributes into a single index number. At a broad conceptual level, the value of a QALY is the value of one year spent in full health. This is then taken as a benchmark value against which all other health profiles (of whatever duration, in whatever combination through time) are valued. However, since there are an infinite number of such combinations of health states, establishing the benchmark value of each in QALY terms would be quite impractical, and some simplifying assumptions are introduced.

In this paper, we present the results from a systematic review of the literature that was designed to examine the extent to which people’s preferences satisfy some of the key assumptions of the QALY model explained below. Our aim has not been to be prescriptive about which elements of the QALY approach *should be* adhered to, and we leave it for others to make their judgements about the normative significance of some of our findings. We also consider this to be a review of empirical tests of QALY assumptions and, while we present a summary of study design (such as the sample size and composition, and the country of origin), we have made no attempt to assess the quality of empirical studies. Because people's preferences are so heavily influenced by the ways in which questions are put to them, it has not really been possible to systematically assess the quality of the empirical evidence. For instance, there are no obvious criteria that allow us to rank between a marginally poorly designed postal survey with a large and representative sample and a marginally better designed interview with a small and non-representative sample. This is in contrast to trial evidence, for example, where the criteria for assessing the quality of studies are well established.

In what follows, section two sets out the QALY model and the assumptions that are tested here. Section three describes how the systematic review was undertaken and presents some summary data about the studies included in the review. Section four discusses the empirical evidence and section five provides a summary of the findings and some conclusions.

2. THE QALY MODEL AND ITS ASSUMPTIONS

In the simplest case, with no uncertainty, no temporal discounting, and no changes in health over time, the value of a health gain from treatment for an individual, $QALY_G$, can be represented as:

$$QALY_G = T_1Q_1 - T_0Q_0, \quad [1a]$$

where T is the number of years of survival, Q represents health state values, and the subscripts 1 and 0 represent health with and without treatment, respectively (1).

Alternatively, introducing uncertainty and temporal discounting, and assuming discrete time so that changes in health occur only when moving from one period to the next, the expected net gain of a treatment to any one individual can be expressed as:

$$QALY_G = \sum_h \sum_t p_{1ht}Q_{ht} - \sum_h \sum_t p_{0ht}Q_{ht}, \quad [1b]$$

where p_{1ht} and p_{0ht} represent the probabilities of an individual finding himself in health state h in time period t with and without treatment, respectively. Q_{ht} is the value of health state h at time t (the subscript t here allows for constant rate temporal discounting so that $Q_{ht} = \frac{Q_h}{(1+r)^t}$, where r is the discount rate).

This algorithm – the QALY model – is an expression of the value to an individual associated with a given intervention. If the quality of life associated with 'full health' were to be assigned a value of 1, then the algorithm could be considered to express health gains measured in 'objective physical units' i.e. life years. Any state of health less than this is adjusted for its quality and hence assigned a lower value. Against a background based on expected utility theory, Pliskin and colleagues first set out a set of sufficient assumptions for this simple model to represent individual utility over health states and duration (2). For health profiles of constant quality (i.e. "chronic" states), these are mutual utility independence between quality of life and duration, constant proportional trade-off, and risk neutrality over life years. Bleichrodt and colleagues have presented a smaller set of sufficient assumptions consisting of risk neutrality and the "zero condition" (which implies that for a duration of zero life years, all health state values are equivalent) (3). Alternatively, Miyamoto and colleagues further demonstrated that, with non-linear utility functions, this set becomes the zero condition and "standard gamble invariance" a special case of the utility independence of duration of survival from quality of life) (4).

On the other hand, besides risk attitude and time preference (which are issues not specific to health and QALYs), the empirical literature on whether the QALY model holds have typically addressed one or both of the following two questions:

1. Is the value of a state affected by how long the state lasts?
2. Is the value of a state affected by the states that come before or after it?

The first question is related to three concepts: utility independence of quality of life from the duration of survival, constant proportional time trade-off, and maximum endurable time. The first two terms both mean that the value of a health state is independent of its duration (2;5;6). *Utility independence* here means that values elicited using Standard Gamble (SG) with some given fixed duration are unaffected by this specific choice of duration. *Constant proportional time trade-off* means that values elicited using Time Trade-Off (TTO) are not affected by duration i.e. the same proportional amount of time is traded-off independently of the absolute duration presented in the scenario. When these concepts are applied to VAS (Visual Analogue Scale) values, they mean that VAS scores should not be affected by how long the state lasts. *Maximal endurable time* means that, for some severe states (independent of which method is used to value them), the value of those states becomes negative after some threshold duration. When maximal endurable time takes effect, utility independence and constant proportional time trade-off are violated.

The second question can be broken down into two issues. The first is whether or not *additive separability* holds; that is, the value of a health state should be independent of what precedes or follows it (7). Under zero discounting, additive separability means that the value of a complete health profile would be equal to the sum of the value of individual health states that make up that profile, irrespective of the order of the states. Obviously, the present value of the two profiles will not coincide under non-zero discounting, but then, the difference should be a function of a positive discount rate alone. The second is whether or not *preference independence* holds. This requires that "given two profiles that have the same health state during interval *i*, preference between them does not depend on the level of health during interval *i*" (8). The testing of this concept does not rely on any assumptions concerning time preference. However, there is a large literature in experimental psychology that addresses the issue of how people's perceptions are affected by "troughs and peaks", or sequence effects (see (9) which includes a brief review). This suggests that additive separability and preference independence in the context of QALYs may not be satisfied.

Thus, this paper reports on a systematic literature review on these two questions. As can be seen, these two questions are taken from the set of sufficient assumptions set out in the literature. As they are individual assumptions within sets of sufficient assumptions, demonstrating that any one of these is satisfied individually will not validate the QALY model (although it may count as additional piece of evidence in favour of the validity of the model). On the other hand, since each of these assumptions is also a necessary assumption, demonstrating that any of these are not satisfied has the potential to invalidate the QALY model.

3. THE LITERATURE SEARCH

The aim of the search strategy was to identify systematically all issues relating to the two topics of the review through the retrieval of published and unpublished papers. A method called 'citation pearl growing' (10) was employed, using the citation search facility of the Institute of Scientific Information (ISI) citation indexes and through reference list searching (as also used in (1)). These databases cover the science (including biomedical science), social sciences (including economics) and arts and humanities literature. In addition the websites, publication lists and research registers of relevant organisations were searched and relevant experts were consulted. The process of citation searching begins from an initial list of relevant references, which were put together from the authors' own collections. Finally, a keyword search strategy was developed, based on the indexing terms of included studies, in order to check the completeness of the primary search method. The search was restricted to papers in the English language, dated 2002 or earlier.

After three rounds of searching, no additional unique references were retrieved. This provided 601 references. Using the titles and abstracts of retrieved references the first author undertook the first stage of assessment for inclusion, and then the second author checked a sample of the references excluded at this stage. Full papers were assessed for inclusion independently by both authors. Through this process, 71 papers were identified as relevant, including 20 with empirical data. Table 1 provides information on the empirical studies, in terms of study design, sample population and sample size. It can be seen from this table that most of the empirical studies have used structured interviews with students or patients, and have often had sample sizes less than 100. The table also shows the country in which the study was conducted. Most of the studies have been carried out in North America, followed by the UK and Europe.

4. EMPIRICAL EVIDENCE ON THE QALY MODEL

4.1 Is the value of a state is unaffected by how long the state lasts?

4.1.1 Utility independence

McNeil and colleagues interviewed 37 volunteers (25 executives and 12 fire-fighters) and asked them to value speech loss for various lengths of time (11). They found that, while respondents on average accepted a 14% risk of death to avoid speech loss, none accepted a positive risk of death when survival was shorter than 5 years. Bleichrodt and Johannesson asked 172 students to fill in a questionnaire with SG questions of 10 and 30 year durations, followed by death (6). The authors conclude that utility independence is violated at the aggregate level, with 10-year SG values higher than 30-year SG ones. Bala and colleagues interviewed 114 elderly people using 20-year SG and a 1-year SG, both followed by death (12). About 25% satisfy utility independence but there is no systematic pattern in the responses of those who do not.

4.1.2 Constant proportional time trade off

Several studies have shown constant proportional time trade off to be a pretty good approximation of preferences at the aggregate level. In a questionnaire survey, Pliskin and colleagues asked 10 respondents (physicians, economists, and statisticians) the number of years they will sacrifice to avoid severe or mild angina pain (2). The same question was asked with 5-year and 15-year survival baselines. At the individual level, most respondents violated constant proportional time trade-off. However, at the aggregate level there is little difference between the trade-offs from the 5-year TTO and the 15-year TTO. Cook and colleagues interviewed over 500 patients with gallstone disease and, at the aggregate level, trade-offs for states lasting 12 months and 12 years followed by death were not significantly different from one another (13). Bleichrodt and Johannesson found that 10-year TTO and 30-year TTO values (followed by death) did not differ from one another at the aggregate level (6).

However, other studies have shown constant proportional time trade off to be violated. All of these except the one by Unic and colleagues have found that shorter periods of time are associated with less trade-offs (i.e. higher implied health state values) (14). Sackett and Torrance interviewed 246 members of the public and 29 patients on home dialysis (15). They asked respondents to value 15 scenarios covering various health conditions from tuberculosis to kidney transplant, with durations of 3 months, 8 years, and the life expectancy of a respondent, all followed by death. They found that values declined with duration. In a study on utility independence of duration on quality of life where 64 hospital inpatients with a range of conditions were interviewed, Miyamoto and Eraker also explored constant proportional time trade off, and report that about 25% of respondents did not trade off any time to improve their current health when the duration was under 1 year, whilst time was traded off when the duration was over a year (16).

Stalmeier and colleagues asked four groups of university and high school students (total respondents 176) to rank two scenarios, one living for a longer time with a severe health condition and dying, and another living for a shorter time with the same health condition and dying (17). The proportion of those who ranked the shorter scenario over the longer one varied from 44% to 71%. The vast majority of these (73% to 94%) displayed a *preference reversal*, where their TTO value for the shorter scenario was lower than that for the longer scenario. Furthermore, regarding those respondents whose preferences were not reversed, the authors go on to discuss the possibility of a “proportional heuristic” in the TTO. When respondents are asked to give the number of healthy years that is equivalent to living in a given state for 10 years, and then the same for 20 years, respondents may give proportional answers not because they satisfy constant proportional time trade off but because they see that the nummeraire of the exercise has been doubled. Since this indicates that certain tests of constant proportional time trade off may be too easy to pass, this has important implications for earlier studies that demonstrated satisfaction of this requirement.

Buckingham and colleagues conducted a postal survey of over 4000 members of the public, with over 1500 usable replies (18). They report aggregate results from three different TTO formats for a condition that lasts for the rest of one's life. These were: a daily TTO which was about trading off the number of hours awake per day; a yearly TTO which was about trading off the number of active days per year; and the lifetime TTO which was about trading off years of life expectancy. Assuming that time spent sleeping, 'lost' days and lost years are all valued at zero, constant proportional time trade off will require that the proportion of a day that is traded off is equal to the proportions of a year and of a lifetime that are traded off in exchange for full health. The study found that the yearly values are the highest and the daily values the lowest. This suggests that the relationship between the length of the period and the size of the trade off may not be linear. There has been one study that has looked at the effect of duration on VAS responses. From interview with 236 members of the general public, Dolan reports values for health states lasting for one month, one year and ten years "and what happens thereafter is not known and should not be taken into account". (19). In general, the shorter the duration, the higher the value. Olsen has presented a method whereby positive implicit time preference rates can be derived for such responses (20).

4.1.3 Maximal endurable time

Sutherland and colleagues interviewed 20 health professionals (physicians, biophysicists, biologists) and asked them to value 7 states, each lasting for 3 months, 8 years, and the respondent's life expectancy, each followed by death, using the SG (21). They were also asked for the preference between each scenario and death. A maximal endurable time was observed for up to 75% of respondents, depending on the health state. The worse a health state was considered to be the more respondents indicated maximal endurable time. Stalmeier and colleagues asked three groups of female university and high school students (totalling 86 respondents) to value breast cancer related health states (22). 58% indicated maximal endurable time such that 25 years with metastasised breast cancer (implicitly followed by death) was preferred to 50 years in the same state (again implicitly followed by death). However, 74% of these also indicated preference reversals in TTO such that the number of healthy years equivalent to 25 years with metastasised breast cancer was proportionally smaller than that for 50 years in the same state.

4.2 Is the value of a state is unaffected by the states that come before or after it?

4.2.1 Additive separability

Richardson and colleagues interviewed 63 women who did not have breast cancer to value four breast cancer related health scenarios using VAS, TTO and SG (23). Three scenarios consisted of a single health state while the last one was a profile combining these three states in deteriorating order followed by death. Using a 3% and a 9% discount rate, they found that the number of QALYs calculated indirectly from the individual health states was 30-50% higher than number of QALYs calculated from the direct value of the profile. The authors argue that "the knowledge of future death casts a shadow over, or devalues, the enjoyment of earlier life years". Thus, there is the possibility that the results are driven by the dread of suffering and death at the end of the scenario in addition to a systematic violation of the additivity assumption.

Kuppermann and colleagues interviewed 121 pregnant women and asked them to value (using VAS and SG) eight "paths", involving two prenatal diagnostic tests for chromosomal abnormalities of the foetus at different stages of the pregnancy, different test results, and outcomes including spontaneous abortion of the foetus possibly related to the test and the effect on the woman's fertility afterwards (24). The paths were then broken down into discrete states, and the direct valuation of the paths was compared to the indirect values calculated from the values of the discrete states, assuming no temporal discounting. At the individual level, preferences were not additive, and there does not seem to be any obvious pattern. At the aggregate level, the mean direct value could be predicted from the mean values of the discrete states but this was not by means of an additive model weighted by duration, as suggested by the additivity assumption. The results were not affected by the introduction of a 5% discount rate. In general terms, the indirect values of the paths tended to be higher than the direct values, including the case where the path was not a deteriorating one.

Krabbe and Bonsel asked 104 (mostly medical) students to value 13 hypothetical health states on two separate occasions using the TTO (25). The health states lasted for 10 years. On the first occasion the respondents were given two alternatives, one of living in a fixed state (EQ5D state 21232) and the other of living for *x* years in the 'best imaginable' state followed by (10-*x*) years in the 'worst imaginable' state. On the second occasion the second alternative was changed to to live for *z* years in 'worst imaginable' state followed by (10-*z*) years in 'best imaginable' state. Under both formats, after the 10-year period, health was to return to the current level. If additive separability holds, then, with appropriate discounting, the number of years spent in the best health state in the two scenarios should coincide. This held for two-thirds of respondents when a discount rate of 5% was used for everybody. Thus, on the one hand, by allowing for individual discount rates, a higher proportion of respondents may have achieved convergence of the numbers of years. On the other hand, there is also the possibility that the discount rate that makes the numbers of years converge may not reflect the genuine temporal preference of the individual, in which case two-thirds could be an overestimate. A small proportion of the remaining wanted "best things first", while the majority wanted a "happy ending".

Mackeigan and colleagues interviewed 89 patients with type-2 diabetes (26). Nine scenarios, covering 30 years and followed by death, consisting of diet therapy, insulin use, three "mono" therapies, three "dual" therapies, and one "triple" therapy were valued using VAS and TTO. The study found that the indirect and direct values of the combination therapies were not statistically significantly different from one another. However, the agreement between the two approaches was poor, suggesting that the differences between the health states may have been too small to invoke the sequence effect. Spencer conducted interviews with 29 members of the public that tested for additive separability in two ways whilst controlling for risk attitude and time preference (27). In the first test, using the SG method, the *difference* between profiles *x-y* and *x-z* was compared to the *difference* between profiles *w-y* and *w-z*, where all profiles lasted 10 years and were followed by death. The differences were statistically significant, thus violating additive separability. The second test was first proposed by Bleichrodt (28) and consists of a choice between two gambles: one offers a 50-50 chance of the best and worst health states, and the other involves a 50-50 chance of the best-then-worst profile and the worst-then-best profile. The respondents were split roughly in half, 13 preferring the former gamble and 15 preferring the latter, while one was indifferent.

This suggests a violation of additive separability but it is not systematic and so could, in the extreme, simply represent noise in the valuation process.

4.2.2 Preference Independence

Treadwell presented 163 psychology students with pairwise choices of health profiles (8). Each combination consisted of two scenario pairs: *A* with *B* and *A′* with *B′*, all with a 30-year duration followed by death, constructed such that independence is satisfied when a respondent who prefers *A* (*B*) in the first pair also prefers *A′* (*B’*) in the second pair. The author concludes “independence was more commonly satisfied than it was violated”. Out of 42 combinations tested, the requirement was satisfied in 36. Treadwell and colleagues asked 67 outpatients with type-C hepatitis to fill out a questionnaire that asked them six pairwise choices of health profiles (29). The profiles were either both followed by “normal” health or both ended in death. About two-thirds of respondents satisfied independence. However, when respondents were asked to give reasons for their choices, explanations implying sequence effects were observed e.g. to “get [bad states] out of the way” or to have a relatively good state before death.

5. CONCLUSIONS

Let us summarise the empirical evidence relating to the two questions posed at the beginning:

1. Preferences over different health states when they are valued using different fixed durations. There have been two empirical studies addressing utility independence of SG responses from duration. The respondents in these studies did not satisfy this, although there is no clear pattern in the violations. There have been eight studies that have looked at whether constant proportional time trade-off holds for TTO responses. In general, the results suggest that the assumption holds at the aggregate level but is violated (albeit in a largely non-systematic way) at the individual level. Shorter durations typically have higher values, and longer durations are sometimes associated with a maximal endurable time, after which time death is preferred to additional survival in the state.

2. Preferences over profiles of different health states. The five studies that have addressed additive separability suggest that this requirement does not hold but we cannot really

point to any clear systematic violations. Two studies have addressed preference independence, and both found that the majority of respondents satisfy the requirement.

Thus, contrary to the assumptions of the QALY model, it would seem that an individual's preferences over health are influenced by the duration of health states and their sequence. Given that each of these are necessary conditions for the QALY model to hold, they cast serious doubt to the validity of the QALY model as a representation of individual utility with respect to their own health. Unfortunately, none of these factors appears to impact upon the QALY model in a straightforward way and so it is not possible at this stage to provide a simple algorithm to adjust the QALY model to better represent individual preferences over own health. However, there have been two developments to generalise the QALY model in order to overcome known and systematic violations. The first is the HYE (Health Years Equivalents), introduced by Mehrez and Gafni (30). Mehrez and Gafni argue that the standard QALY concept is flawed because, while the quality adjustment component of the QALY is preference-based, the life year component is not. In order to reflect this, they proposed the HYE, which is based on measuring the value of whole profiles directly, as opposed to constructing this through values of individual states. Therefore, it does not require the additive separability assumption or preference independence (31-35). However, its major practical disadvantage is that it is virtually impossible to estimate a value set for all possible profiles, given the infinite number of profiles there would be.

The second development concerns generalisations of expected utility theory. The theory has offered the main theoretical background to the QALY model, and yet the extent to which individual choice behaviour violates its axioms is well documented. The new developments base the QALY model on, for instance, rank dependent expected utility theory (36-38). This line of research consists of identifying theoretical models that satisfy both some notion of what is rational and real choice behaviour, in order to better explain the way the human mind behaves when faced with choices regarding health. However, it should also be noted that expected utility theory could remain as the theoretical basis on which to make policy choices, even if actual individual choices violate their axioms. Or, in other words, the particular notion of rationality that best fits real individual behaviour does not have to be the one that forms the basis for policy choices.

It should also be noted that, once we turn to putting the numbers to policy use (as opposed to positive uses), it is usually not the individual preferences but the aggregate (mean or median) preferences that are applied. While not all studies report whether or not aggregate preferences satisfy the assumptions of the QALY model, when they are reported, they appear to perform much better than individual preferences. Moreover, many of the violations at the individual level do not follow a systematic pattern i.e. some people violate an axiom in one direction and others violate it in another direction, which might simply represent noise in the valuation process. Ultimately, it is a matter of judgement about whether the inability of the QALY model to accurately represent all individual preferences is compensated for by the fact that it more accurately represents aggregate preferences.

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Table 1: Empirical references

Author(s)	Year	Reference no.	Design	Sample	Sample size	Country of study	Assumptions tested	Technique used
Bala et al	1999	13	SI	GP (c)	114	USA	UI	SG
Bleichrodt et al	1996	5	SQ	S	172	Sweden, the Netherlands	UI, CPT	SG, TTO
Buckingham et al	1996	18	PQ	GP (r)	1500+	UK	CPT	TTO
Cook et al	1994	14	SI	P	500+	Australia	CPT	TTO
Dolan	1996	19	SI	GP (r)	236	UK	CPT	TTO, VAS
Krabbe et al	1998	25	E	S	104	the Netherlands	AS	TTO
Kuppermannn et al	1997	24	SI	P	121	USA	AS	SG, VAS
MacKeigan et al	1999	26	SI	P	89	Canada	AS	VAS, TTO
McNeil et al	1981	12	SI	GP (c)	37	USA	CPT	SG
Miyamoto et al	1988	11	SI	P	64	USA	CPT	TTO
Pliskin et al	1980	2	SI	HP	10	USA	CPT	TTO
Richardson et al	1996	23	SI	GP (c)	63	Australia	AS	VAS, TTO, SG
Sackett et al	1978	17	SI	GP (r) P	246 29	Canada	CPT	TTO
Spencer	2000	27	SI	GP (c)	29	UK	AS	SG
Stalmeier et al	1997	16	SI	S	176	the Netherlands	CPT	RP, TTO
Stalmeier et al	1996	22	SI	S	86	the Netherlands	MET	TTO
Sutherland et al	1982	21	SI	HPA	20	Canada	MET	SG
Treadwell	1998	8	SQ	S	163	USA	PI	RP
Treadwell et al	2000	29	SQ	P	67	USA	PI	RP
Unic et al	1998	15	SI	GP (c)	54	the Netherlands	CPT	TTO

<u>**Key:**</u>

Design: PQ = postal questionnaire; SQ = self-completion questionnaire; SI = structured interview; E = experiment

Sample: GP (r) = general public (random/quota); GP (c) = general public (convenience); S = students; P = patients; HPA = health professionals or academic staff.

Assumptions tested: UI = utility independence; CPT = constant proportional time trade off; MET = maximal endurable time; PI = preference independence; AS = additive separability

Technique used: SG = standard gamble; TTO = time trade-off; VAS = visual analogue scale; RP = ranking or pairwise choice