Estudios de
Economía Aplicada

contribuciones

ESTUDIOS DE ECONOMÍA APLICADA VOL. 24-3, 2006. PÁGS. 685-696

About the robustness of theoretical foundations of QALY

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Artículo disponible en versión electrónica en la página www.revista-eea.net, ref.: e-24311.

ISSN 1697-5731 (online) – ISSN 1133-3197 (print)

1. INTRODUCTION

During the last 30 years, assessments of therapeutic strategies and health programs have been based on more and more sophisticated methodologies. After cost-benefit analyses in the 70s, the expectation to take into account medical effectiveness, assessed in the frame of its own reference systems, has suggested developing cost-effectiveness analyses. Then quality of life consideration has suggested taking into account the preferences of the decision maker (patient, physician, etc.). on "health state" alternatives and to think about methods able to aggregate in one single dimension medical effectiveness (measured for example in number of life years gained) and the quality of life of these life years.

This approach has generated "cost-utility" analyses based upon similar concept than cost-effectiveness analyses, but in which medical effectiveness has been replaced by a mono-dimensional aggregate of effectiveness and quality of life.

Considering the growing number of published cost-utility studies in the last decade and the use of these studies by public authorities to make decision, it seems important to study the effective robustness and theoretical foundations of so frequently used aggregative approaches. In this paper, we particularly focus on the technique known as "Quality Adjusted Life Years" (QALYs) because this technique is often recommended to compare results coming from various studies (league tables) in order to suggest public health program priorities. The knowledge of the assumptions underlying the validity of these comparisons is then very important.

We propose to briefly present the QALY method, then we will study the justification of this method which is the multi-attribute utility theory, after that we will propose an other way to attempt to validate this theory in one specific context.

2. KEY QUESTIONS

According to the definition, and in its simplest expression, the specification of the aggregation function proposed by the QALY approach in order to aggregate a gain of t life years in a health state which the quality is measured by the number q, is equal to the product of the duration t with the quality of life q.

Two questions need to be answered:

1) On what theoretical foundations are based methods allowing to measure the quality of a health state?
2) On what theoretical foundations is based the specification of the "multiplicative" model of the aggregation function, linking time duration and quality?

Some elements of answers of these two questions could be found in the Neumannian utility theory and in the multi-attribute utility theory.

3. NEUMANIAN UTILITY AND MULTI-ATTRIBUTE UTILITY

The concept of Neumannian utility requires that preferences of economic agents are applied on set of object endowed with a Neumannian structure [1].

We obtain a Neumannian structure on a set E by defining a family of function $(h_n)_{n\geq 2}$, where for any $n \geq 2$, h_n is an application of $E^n x\Delta(n)$[1] in E such as:

For any e_1, e_2 belonging to E, $p = (p_1, p_2)$, $q = (q_1, q_2)$ belonging to $\Delta(2)$:

$$h_2[e_1, h_2(e_1, e_2, p), q] = h_2[e_1, e_2, (p_1 + p_2q_1, p_2q_2)]$$
$$h_2[h_2(e_1, e_2, p), e_2, q] = h_2[e_1, e_2, (p_1q_1, p_2 + p_1q_2)]$$

and for any $n \geq 3$,

$$h_n(e_1,...,e_n, p_1,...,p_n) = h_{n-1}[e_1,...,e_{n-2}, h_2(e_{n-1}, e_n, \frac{p_{n-1}}{p_{n-1}+p_n}, \frac{p_n}{p_{n-1}+p_n})\ p_1,...,p_{n-2}, p_{n-1}+p_n]$$

Thus, this expression gives the recurrent definition of the functions h_3, h_4, … and, clearly $p_n \neq 0$ hence $p_{n-1}+p_n \neq 0$

We call Neumannian utility function associated with a preference relation $\succcurlyeq$ on E, all application u in E in the set of real numbers such as :

For any e_1 et e_2 belonging to E, $e_1 \succcurlyeq e_2 \Leftrightarrow u(e_1) \geq u(e_2)$

For any $e_1, …, e_n$ belonging to E, and $p = (p_1, …, p_n)$, belonging to $\Delta(n)$:

$u[h_n(e_1, …, e_n, p)] = p_1u(e_1) + … + p_nu(e_n)$

It is easy to show that if u is a Neumanian utility function associated with $\succcurlyeq$, one necessary and sufficient condition for which v is un Neumanian utility function associated to $\succcurlyeq$ is that it exist two real numbers a and b such as $v = au + b$. This result is important because it enlights the fact that Neumanian utility is measured in a reference system which we have the choice of the origin and of the unit.

If building an ordinal utility function on a set of health states is relatively easy, it is more delicate to build a cardinal or a Neumannian utility function due to the fact these constructions impose to the set of health states to have respectively either a vector space structure or a Neumannian structure. The problem is that such structures does not exist on health states sets in a relevant way.

In order to by-pass this difficulty, preferences are not anymore defined on Health states directly, but on gambles which lots are health states.

We call gamble on a set E, any random discrete variable X, having for support $S = \{e_1, …, e_m\}$ with a distribution $P(X = e_i) = \alpha_i$, $i = 1, …, m$.

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[1] $$\forall n, \Delta(n) = \left\{ \alpha \in R^n \ / \ \forall i, i = 1, ..., n \quad \alpha_i \geq 0, \ \sum_{i=1}^{n} \alpha_i = 1 \right\}$$

Any gamble with a support which only contains one element e from E is called certain gamble and is noted δ_e.

Let us denote E the set of gambles on E. Von Neumann and Morgenstern [1] have defined on E one operation named the "gamble composition".

Considering two gambles X_1 et X_2 respectively with support S_1 et S_2, and distribution $P(X_1 = x_{1i}) = \alpha_i$ i = 1, …, n, and $P(X_2 = x_{2i}) = \beta_i$ i = 1, …, m, et $p = (p_1, p_2)$ belonging to $\Delta(2)$, the gamble composition of X_1 et X_2 for the weighting system p is the gamble $Z = h_2(X_1, X_2, p)$ with support $S = S_1 \cup S_2$ and distribution :

$P(Z = x_{1i}) = p_1\alpha_i$ for any i = 1, …, n such as $(i, j) \in J(i)^c$

$P(Z = x_{1i}) = p_1\alpha_i + p_2 \sum_{j \in J(i)} \beta_j$ for any i = 1, …, n such as $(i, j) \in J(i)$

$P(Z = x_{2j}) = p_2\alpha_j$ for any j = 1, …, m such as $(i, j) \in J(i)^c$

where $\forall i$, i=1..n, $J(i) = \{(i, j) / x_{1i} = x_{2j}, i = 1, \dots, n, j = 1, \dots, m\}$, and $J(i)^c$ denote the complementary set of J(i).

It is easy to prove that the gamble composition endows E with a Neumannian structure.

Standard gamble [2] allows the experimental revelation of patient preferences on a set of gambles with health states as lots and is based on the Neumannian utility theory. This implies that Standard gamble is based on a key hypothesis: patient preferences on gambles can be represented with a Neumannian utility function. That means that the patient is risk neutral in a probabilistic way [3].

A second important consequence of this hypothesis is that measures performed with this technique are only valid in the reference system used. Generally, this reference system is set up in selecting two health states z_0 and z_1, such as $u(\delta_{z_0}) = 0$, $u(\delta_{z_1}) = 1$.

If $v(\delta_z)$ is the Neumannian utility of the certain gamble δ_z measured in an other reference system, it is obvious that $u(\delta_z)$ is different than $v(\delta_z)$. This measure $u(\delta_z)$ can be expressed in the former reference system as following:

$$u(\delta_z) = \frac{v(\delta_z) - v(\delta_{z_0})}{v(\delta_{z_1}) - v(\delta_{z_0})}$$

To be noted that if we know the utilities of certain gambles δ_z in one specific reference system, it is possible to calculate the utility of any gamble which lots are health states taken into account. If X denotes the gamble with support $S = \{z_1, \dots, z_n\}$ and distribution $P(Z = z_i) = \alpha_i$,

then:

$u(X) = u[h_n(\delta_{z_1}, \dots, \delta_{z_n}, \alpha_1, \dots, \alpha_n)] = \alpha_1 u(\delta_{z_1}) + \dots + \alpha_n u(\delta_{z_n})$

The multi-attribute utility theory proposes some partial answers of the key following question:

If the lots of the gambles of the set E are described with n attributes, what are the conditions to potentially find a relationship between the agent preferences expressed on gambles for any attribute, and his preference on gambles with lots described by the whole set of attributes?

We will clarify this issue in the particular case when lots are described with two attributes: time duration and health state. Any lot is then a couple (t, z) where t is a time duration and z a health state. For example if t = 10 years and z = "to be in good health", the meaning of the lot (t, z) corresponds to the situation "leave 10 years in good health".

In this particular case, the health state corresponding to the death is not relevant: what would be the meaning of the situation "be dead during 10 years" ?

This suggests excluding death from the set of possible health states when we refer to the multi-attribute utility theory as well as null duration time when we refer to the multi-attribute theory.

In the following, we will note T the set of time duration and Z the set of health states. We denote T and Z the set of gambles defined on T and Z respectively.

One important result [4, 5] provides a sufficient condition so that the utility measured on TxZ is equal to a multilinear form of the utilities on the gambles defined on T and Z respectively. This result is based on the concept of mutual independence in utility of T and Z [6].

Let's say that u is a Neumannian utility associated with the preference relation $\succcurlyeq$ on TxZ.

We say that T is independent in utility from Z if and only if:

- for any t belonging to T, z and z' belonging to Z, it exist a, a>0, and b independent from t such as: $u(\delta_{(t, z)}) = au(\delta_{(t, z')}) + b$

T and Z are mutually independent in utility if and only if T is independent from Z and Z independent from T.

Most of cost-utility studies use the death as the origin of utilities. Then, we can be tempted using death in the frame of multi-attribute utility theory by putting $u(\delta_{(t,death)}) = 0$, even if it is meaningless as noted before.

In this case, if T is independent in utility from Z, for any health state z, $u(\delta_{(t,z')})$ is independent of t; it is then useless to invoke the multi-attribute utility theory.

The theorem allowing expressing u as multilinear form of the utilities on the gambles defined on each attribute is the following:

Main theorem:

Given a preference relation on TxZ which can be associated to a Neumannian utility function.

Given t_0, t_1 éléments of T et z_0, z_1 éléments of Z such as:

$\delta_{(t_1,z_0)} \succ \delta_{(t_0,z_0)}$ and $\delta_{(t_0,z_1)} \succ \delta_{(t_0,z_0)}$, where $\succ$ is the strict preference relation associated to the relation $\succcurlyeq$.

We denote u the Neumannian utility function associated to $\succcurlyeq$, such as:

$u(\delta_{(t_0,z_0)}) = 0$ and $u(\delta_{(t_1,z_1)}) = 1$.

if T et Z are mutually independent in utility, then:

$u(\delta_{(t,z)}) = u(\delta_{(t,z_0)}) + u(\delta_{(t_0,z)}) + k u(\delta_{(t,z_0)})\, u(\delta_{(t_0,z)})$

$$\text{with } k = \frac{1 - u(\delta_{(t_1,z_0)}) - u(\delta_{(t_0,z_1)})}{u(\delta_{(t_1,z_0)})u(\delta_{(t_0,z_1)})}$$

or in another way:

$u(\delta_{(t,z)}) = u(\delta_{(t_0,z_1)})\, v(\delta_z) + u(\delta_{(t_1,z_0)})\, w(\delta_t) + [1 - u(\delta_{(t_0,z_1)}) - u(\delta_{(t_1,z_0)})]\, v(\delta_z)\, w(\delta_t)$

where u and v are two Neumannian utility functions associated to the preferences defined by $u(\delta_{(t_0,z)})$ and $u(\delta_{(t,z_0)})$ on T and Z respectively, and such that : $v(\delta_{z_0}) = 0$, $v(\delta_{z_1})=1$, $w(\delta_{t_0}) = 0$ and $w(\delta_{t_1}) = 1$.

Quality Adjusted Life Years referring to multi-attribute utility

Can we use the former result to justify that it exists a Neumannian utility function associated to the patient preference on the gambles with lots in TxZ can be written as a product of two Neumannian utility functions : one defined on the gambles with lots belonging to T, and the other defined on the gambles with lots belonging to Z ?

Let's assume that it exists one patient whom his preferences on the gambles with lots belonging to TxZ can be presented in the reference system defined with the gambles $\delta_{(t_0,z_0)}$ et $\delta_{(t_1,z_1)}$ in using the Neumannian utility function u.

Let's also suppose that $\delta_{(t_1,z_0)} \succ \delta_{(t_0,z_0)}$ and $\delta_{(t_0,z_1)} \succ (\delta_{t_0}, \delta_{z_0})$, and T and Z are mutually independent in utility.

If for any $\delta_{(t,z)}$, $u(\delta_{(t,z)}) = v(\delta_t)w(\delta_z)$ holds, where v and w are Neumannian utility functions respectively defined on Z and T and measured in the reference systems (δ_{z_0}, δ_{z_1}) and (δ_{t_0}, δ_{t_1}), we get:

(a) $u(\delta_{(t_0,z_0)}) = v(\delta_{z_0})\, w(\delta_{t_0}) = 0$ then either $v(\delta_{z_0}) = 0$ or $w(\delta_{t_0}) = 0$

(b) $u(\delta_{(t_0,z_1)}) = v(\delta_{z_0})\, w(\delta_{t_1}) > 0$ then $v(\delta_{z_0}) \neq 0$,

(c) $u(\delta_{t_1}, \delta_{z_0}) = v(\delta_{t_1})\, w(\delta_{z_0}) > 0$ then $w(\delta_{z_0}) \neq 0$,

which leads to a contradiction.

Then, if u is a Neumannian utility function meeting the conditions of the above main theorem, u cannot be written as the product of two Neumannian utility functions defined respectively on T and Z with reference systems using the same attributes as those defining the reference system of u.

However Pliskin JS et alii [7] used the main theorem cited above to provide sufficient conditions in order to demonstrate the existence of a Neumannian utility function on TxZ specified as the product of the time duration with a utility function defined on Z.

Two additional conditions are necessary to come up with this result.

The first condition is the risk neutrality (according to Arrow and Pratt) of an agent on the time durations.

The second condition assumes that the coefficient γ of time trade-off, between health states z_0 and z_1, attributed to the agent is independent with time.

Let suppose that u is a utility function defined on TxZ measured in the reference system defined by the gambles $\delta_{(t_0, z_0)}$ et $\delta_{(t_1, z_1)}$ and that $\delta_{(t_1, z_0)} \succ \delta_{(t_0, z_0)}$ and $\delta_{(t_0, z_1)} \succ \delta_{(t_0, z_0)}$.

T and Z being mutually independent in utility, u is expressed in this reference system as follows:

$$u(\delta_{(t, z)}) = u(\delta_{(t_0, z_1)})\, v(\delta_z) + u(\delta_{(t_1, z_0)})\, w(\delta_t) + [1 - u(\delta_{(t_0, z_1)}) - u(\delta_{(t_1, z_0)})]\, v(\delta_z)\, w(\delta_t)$$

where v et w are two Neumannian utility function associated to preferences respectively described by $u(\delta_{(t_0, z)})$ and $u(\delta_{(t, z_0)})$ on Z and T, such as : $v(\delta_{z_0}) = 0$, $v(\delta_{z_1}) = 1$, $w(\delta_{t_0}) = 0$, $w(\delta_{t_1}) = 1$.

Then, we can write:

$$\begin{aligned} u(\delta_{(\gamma t, z_1)}) &= u(\delta_{(t_0, z_1)}) + u(\delta_{(t_1, z_0)})\, w(\delta_{\gamma t}) + [1 - u(\delta_{(t_0, z_1)}) - u(\delta_{(t_1, z_0)})]\, w(\delta_{\gamma t}) \\ &= u(\delta_{(t_0, z_1)}) + [1 - u(\delta_{(t_0, z_1)})]\, w(\delta_{\gamma t}) \end{aligned}$$

$$u(\delta_{(t, z_0)}) = u(\delta_{(t_1, z_0)})\, w(\delta_t)$$

Moreover, the coefficient of time trade-off γ being independent with time duration, we have:

$$u(\delta_{(t, z_0)}) = u(\delta_{(\gamma t, z_1)})$$

and then:

$$u(\delta_{(t_1, z_0)}) w(\delta_t) = u(\delta_{(t_0, z_1)}) + [1 - u(\delta_{(t_0, z_1)})] w(\delta_{\gamma t})$$

which enables us, in assessing it for the gambles δ_{t_0} et δ_{t_1} to write:

$$u(\delta_{(t, z)}) = \frac{w(\delta_{\gamma t_0})}{w(\delta_{\gamma t_0}) - 1} v(\delta_z) + \frac{w(\delta_{\gamma t_0}) - w(\delta_{\gamma t_1})}{w(\delta_{\gamma t_0}) - 1} w(\delta_t) + \frac{w(\delta_{\gamma t_1}) - w(\delta_{\gamma t_0}) - 1}{w(\delta_{\gamma t_0}) - 1} w(\delta_t) v(\delta_z)$$

The agent being risk neutral (according to Arrow and Pratt) the utility of the gamble δ_t in the reference system δ_{t_0} and δ_{t_1} is equal to: $w(\delta_t) = \dfrac{t - t_0}{t_1 - t_0}$.

Then the utility of the gamble $\delta_{(t, z)}$ is equal to:

$$u(\delta_{(t, z)}) = \frac{1}{t_1 - \gamma t_0} \left[\gamma(t - t_0) + (1 - \gamma)\, t\, v(\delta_z)\right]$$

The function U defined on TxZ by: $U(\delta_{(t,z)}) = (t_1 - \gamma t_0)u(\delta_{(t,z)}) + \gamma t_0$ is a utility function which describes the same preferences than u in the reference system defined by the gamble $\delta_{(t^*_0, z^*_0)}$ et $\delta_{(t^*_1, z^*_1)}$ such as :

$$u(\delta_{(t^*_0, z^*_0)}) = \frac{-\gamma t_0}{t_1 - \gamma t_0} \quad \text{et} \quad u(\delta_{(t^*_1, z^*_1)}) = \frac{1 - \gamma t_0}{t_1 - \gamma t_0}$$

So, this function U is expressed as:

$$U(\delta_{(t,z)}) = [\gamma + (1 - \gamma)v(\delta_z)]\, t$$

In a similar way, the function V defined on Z by: $V(\delta_z) = \gamma + (1 - \gamma)v(\delta_z)$ is a utility function which describes the same preferences than v in the reference system defined by the gambles $\delta_{z''_0}$ et $\delta_{z''_1}$ such as :

$$V(\delta_{z''_0}) = \frac{\gamma}{\gamma - 1} = v(\delta_{z^*_0}) \quad \text{et} \quad V(\delta_{z''_1}) = \frac{1 - \gamma}{1 - \gamma} = 1 = v(\delta_{z_1})$$

and then: $U(\delta_{(t,z)}) = t\, V(\delta_z)$, with $t \neq 0$

Hence, the agent preferences on TxZ can be expressed as a Neumannian utility function equal to the time duration weighted with the Neumannian utility of the gambles with lots which are health states.

This result is often used to justify the use of QALYs from the Multi Attribute Utility Theory, but without mentioning the underlying necessary conditions. This fact leads to a non valid use of the QALY indicator when representing the agent preferences on TxZ.

Like we have explained, this writing assumes, in addition of the conditions about the agent behaviour[2], that :

- the zero time duration and the health state "death" are excluded from the set of health states,
- U and V are measured in different and precise reference systems. If the reference system, initially used, is defined by the gambles $\delta_{(t_0, z_0)}$ and $\delta_{(t_1, z_1)}$ such as $\delta_{(t_1, z_0)} \succ \delta_{(t_0, z_0)}$ et $\delta_{(t_0, z_1)} \succ \delta_{(t_0, z_0)}$ and in which preferences on TxZ are described by the function u, the reference system in which U is measured is defined by the gambles $\delta_{(t^*_0, z^*_0)}$ et $\delta_{(t^*_1, z^*_1)}$ such as:

$$u(\delta_{(t^*_0, z^*_0)}) = \frac{-\gamma t_0}{t_1 - \gamma t_0} \quad \text{et} \quad u(\delta_{(t^*_1, z^*_1)}) = \frac{1 - \gamma t_0}{t_1 - \gamma t_0} \;,$$

[2] Risk neutrality in probability on TxZ, T and Z, risk neutrality according to Arrow-Pratt on T, mutual independence on T X Z , time trade-off rate between two health states independent from time duration, conditions which the robustness has been studied in [8]

the reference system in which is measured V is characterized by the gambles:

$$\delta_{z^*_0} \text{ et } \delta_{z^*_1} \text{ such as: } v(\delta_{z^*_1}) = 1 \text{ et } v(\delta_{z^*_0}) = \frac{\gamma}{\gamma - 1}.$$

The problem is that most of studies using QALYs present QALYs as utilities referring to the multi-attribute utility theory without, any checking or even mentions of these conditions. This leads to important errors when comparing cost-utility (often presented as "cost-effectiveness") ratios coming from studies using different reference systems to calculate health states utilities.

4. QALYS AND DECISION MAKING

We have presented the difficulties to represent agent preferences on TxZ with a Neumannian utility function equal to the product of time duration with utilities on gambles defined on health states.

It is possible to reverse our approach: instead to express agent preferences by modelling as shown above, it is possible to help this agent to decide in proposing an utility function specified on TxZ as the product of a Neumannian utility function on T and a utility function on Z, which properties will guaranty rational choices.

Let us consider the utility function u on TxZ defined by:

- for any $\delta_{(t,z)}$, belonging to TxZ, $u(\delta_{(t,z)}) = v(\delta_z)\, w(\delta_t)$,
- for any gamble X with support $S = \{(t_1,z_1), \ldots, (t_n,z_n)\}$ and such as $P[X = (t_i, z_i)] = \alpha_i$, for i=1, .. , n, $u(X) = \alpha_1 u(\delta_{(t_1,z_1)}) + \ldots + \alpha_n u(\delta_{(t_n,z_n)})$

where v is a Neumannian utility function on Z such as $v(\delta_{z^*_0}) = 0$, $v(\delta_{z^*_1}) = 1$ and w is a Neumannian utility function on T such as $w(\delta_{t^*_0}) = 0$, $w(\delta_{t^*_1}) = 1$.

So it is easy to prove that u is a Neumannian function and that:

$u(\delta_{(t^*_0, z^*_0)}) = v(\delta_{z^*_0})\, w(\delta_{t^*_0}) = 0$, $u(\delta_{(t^*_1, z^*_1)}) = 1$, $u(\delta_{(t^*_0, z^*_1)}) = 0$, $u(\delta_{(t^*_1, z^*_0)}) = 0$.

Gambles $\delta_{(t^*_0, z^*_0)}$ et $\delta_{(t^*_1, z^*_1)}$ are then respectively the origin and the unit of the referencial where values of u are measured.

The only difficulty is to know in which referential $(\delta_{t^*_0}, \delta_{t^*_1})$ and $(\delta_{z^*_0}, \delta_{z^*_1})$ the utility function w and v must be respectively measured so that utilities built on TxZ are relevant.

Indeed, let's say v a Neumannian utility function on Z measured in a reference system $\delta_{z^*}{}^0, \delta_{z^*}{}^1$ and w a Neumannian utility function on T measured in the reference system $\delta_{t^*_0}, \delta_{t^*_1}$.

Suppose z, z', are two health states and t, t' two time durations, such as : $\delta_t \succ \delta_{t^*_0}$, and $\delta_z \succ \delta_{z'} \succ \delta_{z^*_0}$, then we have:

$u(\delta_{(z,t)}) = v(\delta_z)w(\delta_t)$ and $u(\delta_{(z',t')}) = v(\delta_{z'})w(\delta_{t'})$ values which are measured in the referential $\delta_{(z^*_0, t^*_0)}, \delta_{(z^*_1, t^*_1)}$.

Moreover $v(\delta_z) > v(\delta_{z'}) > 0$ et $w(\delta_t) > w(\delta_{t'}) > 0$, implies $u(\delta_{(z,t)}) > u(\delta_{(z',t')})$ and then $\delta_{(z,t)} \succ \delta_{(z',t')}$.

For any Neumannian utility function V describing the same preferences than v, it exists two real numbers, a > 0 and b such as v = aV + b.

Let's say U such as for any $\delta_{(z,t)}$, of TxZ, we have

$$U(\delta_{(z,t)}) = V(\delta_z)\, w(\delta_t) \qquad (1)$$

U is then measured in the referential $\delta_{(z^\circ_0, t^*_0)}, \delta_{(z^\circ_1, t^*_1)}$, where z°_0 and z°_1 are such as: $v(\delta_{z^\circ_0}) = b$ and $v(\delta_{z^\circ_1}) = a + b$

Now let's prove that these two particular health states z°_0 and z°_1 can be defined such that $U(\delta_{(z,t)}) < U(\delta_{(z',t')})$ and then such that:

$$[av(\delta_z) + b]w(\delta_t) < [av(\delta_{z'}) + b]w(\delta_{t'}) \qquad (2)$$

Without weakening the generalization, we can put a=1, then (2) becomes:

$[v(\delta_z) + b]w(\delta_t) < [v(\delta_{z'}) + b]w(\delta_{t'})$

$\succ$

$v(\delta_z)\, w(\delta_t) - v(\delta_{z'})\, w(\delta_{t'}) < b[w(\delta_{t'}) - w(\delta_t)]$.

It results:

$$b < \frac{v(\delta_z)w(\delta_t) - v(\delta_{z'})w(\delta_{t'})}{w(\delta_{t'}) - w(\delta_t)} \qquad (3)$$

Let b° any value of b fulfilling the condition (3) and z°_0 and z°_1 such as $v(\delta_{z^\circ_0}) = b^0$ and $v(\delta_{z^\circ_1}) = 1 + b^\circ$.

Clearly $v(\delta_{z^\circ_1}) > v(\delta_{z^\circ_0})$ and because $V(\delta_z) = v(\delta_z) - b^\circ$, we have :$V(\delta_{z^\circ_0}) = 0$ and $V(\delta_{z^\circ_1}) = 1$

The Neumannian utility function V measured in the scale $\delta_{z^\circ_0}, \delta_{z^\circ_1}$ describes exactly the same preferences than v. Then it is possible, such as above, to propose to the decision maker to use the utility function U deduced from V as given in (1) to make his decision.

For this function, we have: $U(\delta_{(z,t)}) < U(\delta_{(z',t')})$, thus: $\delta_{(z',t')} \succ (\delta_{(z,t)})$, which is the opposite result than the one obtained with the function u with no change on the decision maker preferences on TxZ!

This proves that, if we use the decision making procedure proposed above, the choice of the reference system in which are measured the utility of elements belonging to Z, impacts the ordering of TxZ elements and, "in fine" the decision maker choices!

Then it is necessary, when using this decision making approach, to justify the relevance of the reference system selection in which are measured the utilities. This justification unfortunately does not exist in most of publications using QALYs as the main outcome, leading to serious questions about the potential validity and relevance of the presented results.

5. CONCLUSION

There are two approaches which can provide strong theoretical foundations of QALY technique. The first one makes use of agent preferences and assumes that experimental methods such as Standard gamble can be used to express agent preferences on gambles with lots which are respectively time duration and health states.

This approach requires a set of conditions on the agent behaviour toward risk (risk neutrality in probabilities and risk neutrality according to Arrow and Pratt) and on its own balance between quality of life and life duration (mutual independence in utility of gambles on time durations and health states, time trade-off rate independent from time duration). This approach excludes to consider death among health states and zero time among time duration.

However, if all these conditions are met, it is possible to express a Neumannian utility function associated to agent preferences on gambles (with are time duration and health state as lots) as the product of time duration with a utility function with health states as lots.

It is very important to remind that this multiplicative formula is not valid in every reference system and it is then necessary to determine in what reference systems this formula can be used in order to measure agent preferences. This is theoretically possible, as explained, but extremely difficult to manage practically.

The second approach, which refers to decision making methods, proposes to the agent a utility function in view to express his choice on the gambles with time durations and health states as lots. It is then possible to propose as a Neumannian utility function the specification used by the QALY technique[3], under the condition one precisely defines the reference system in which this specification is relevant. As we have shown, results obtained with this specification are totally dependent on the selected reference system to assess quality of life. A simple change of the QOL scale origin could invert the assessment results expressed in QALYs !

Whatever the retained approach, reference systems of measurement must be described and validated before presenting any results expressed in QALYs. If not, any results would be considered as unfounded.

[3] In this case, it is assumed that the agent is neutral toward risk in probabilities.

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