STATISTICS IN MEDICINE, VOL. 15, 93–102 (1996)

ESTIMATION OF EXPECTED QUALITY ADJUSTED SURVIVAL BY CROSS-SECTIONAL SURVEY

JING-SHIANG HWANG

Institute of Statistical Science, Academia Sinica, Taipei 115, Taiwan

AND

JAU-YIH TSAUO AND JUNG-DER WANG

Center for Research of Environmental and Occupational Disease, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University, College of Public Health, No. 1, Sec. 1, Jen-Ai Rd, Taipei 100, Taiwan

SUMMARY

To compare both mortality and quality of life (QOL) across different illnesses, we propose an estimator to calculate the expected quality adjusted survival (QAS) by multiplying the QOL into the survival function. While the survival function can be determined by the usual life table method, the QOL data can be collected by a cross-sectional survey among patients who are currently surviving. The area under the QAS curve is thus the expected utility of health of the specific illness, which may take a common unit of quality adjusted life year ready for outcome evaluation and policy decision. A simulation is performed to demonstrate that the proposed estimator and its standard error are relatively accurate. The limitations and guidelines for using this estimator are also discussed.

1. INTRODUCTION

Although outcome evaluation has long been proposed and implemented as a necessary procedure for health service evaluation, for example, in a clinical trial, it usually focused on mortality or case fatality.[1] It is not until recently that attention has been extended to morbidity or quality of life (QOL) as measures of outcome evaluation.[2–5] While death as the common end point is the same and relatively easy to measure for all kinds of illnesses, end points for morbidity or QOL from illnesses of different organ systems are relatively difficult to set, measure or compare. Studies regarding the QOL or suffering among cancer patients of different stages or patients with different phases of cardiovascular diseases have been reported,[6–8] however, there have been relatively few, if any, studies comparing the QOL and mortality simultaneously across different kinds of illnesses. In 1981, the Ghana Health Assessment Project Team proposed the DHLL (days of healthy life lost) as an indicator for comparison of the overall impact of different illnesses and priority setting of health policy.[9] The model has not received much attention, probably because it assumed a long term stable condition for all kinds of permanent disability and did not take into account the survival probability. This limited its use in acute diseases or injuries and was not suitable for chronic diseases. In 1990, Glasziou *et al.* proposed another model which considered the survival probability and QOL together.[10] However, their model treated the

CCC 0277–6715/96/010093–10

Received September 1994
Revised January 1995

progression of illness as several discrete states, which may be applicable for cancer patients but still cannot be universally applicable or comparable across different illnesses with too many states to be conceptualized and quantified as QOL. It appears to us that there is still a need to develop alternative methodology to solve this problem.

In this paper, we first briefly review the conceptual quantification method of QOL, as suggested by Torrance and Glasziou *et al.*, then propose an estimation method for quality-adjusted survival time by simply multiplying the QOL into the survival function. To keep our concept simple, we shall limit our discussion of QOL only to the health-related quality of life (HRQL).[3]

2. CONCEPTUAL DEVELOPMENT

Torrance's utility approach to measuring HRQL is to combine QOL and survival to give quality adjusted life years (QALYs).[2] This places states of health on a utility scale with reference points from 0 to 1; perfect health is assigned a weight of 1, and a state equivalent to being dead a weight of 0 (negative weights are also possible).[10] A patient's QOL can be treated as a stochastic process $q(t|T, x)$, $t \in [0, T]$, where T is the survival time and x is a covariate vector. The quality adjusted survival (QAS) time of the patient, measured in QALYs, is

$$\text{QAS} = \int_0^T q(t|T, x)\,\mathrm{d}t. \tag{1}$$

According to Glasziou *et al.*, patients are assumed to experience k health states which differ in their QOL.[10] The QAS is given as

$$\text{QAS} = \sum_{i=1}^{k} q_i s_i,$$

where $q_1, \ldots, q_k$ is the utility assigned to each of k health states and $s_1, \ldots, s_k$ is the time (years) spent in each state. The model makes a strong assumption on the independence of health state and survival; that is, the utility scales for QOL are specified independently of the survival period. Also, to avoid the assumption of risk neutrality, Glasziou *et al.* proposed a more general utility model which replaces s_i with a monotonic function of time in health state i during the survival period to enable the discounting of future gains compared with more immediate benefits.[10]

To estimate the mean QAS, Glasziou *et al.* proposed a methodology, partitioned survival analysis, in which they first estimate times spent in each state, then recombine these to form the QALY estimates.[10] The partitioned survival analysis avoids the bias of forming QALYs from a direct use of an individual's comprehensive history from onset of diseases to death. However, several limitations of the approach had been pointed out by Glasziou *et al.*, such as the need to use a progression of discrete states, the lack of methods for examining the effect of covariates and the need for an upper time limit for the analysis of censored data. In addition, the method has limited application as it only applies to the studies in which patient's whole QOL histories have been well recorded, which is rarely the case.

As well as current life tables published annually in the national vital statistics, there are some cohort life table data of different kinds of diseases with covariates such as treatments, sex and age.[11-13] To estimate the expected QAS, we propose combining the survival data with a QOL sample obtained from a cross-sectional survey designed to assess the most recent QOL among patients who are current surviving.

3. METHOD OF ESTIMATION

Our approach to estimate the expected QAS is first to assume that the QOL values of patients who are surviving at time t have a common distribution. The mean of the distribution at time t is denoted as $E[q(t|x)]$. Let $f(t|x)$ be the density function of the survival time T and $S(t|x)$ be the survival function. Then, a simple approximation to the expected QAS could be derived as follows.

$$\begin{aligned}
E[\mathrm{QAS}|x] &= E\left[\int_0^T q(u|T,x)\,\mathrm{d}u\right] \\
&= E\left[E\left[\int_0^T q(u|T,x)\,\mathrm{d}u\right]\middle| T=t\right] \\
&\approx E\left[\int_0^t E[q(u|x)]\,\mathrm{d}u\right] \\
&= \int_0^\infty \int_0^t E[q(u|x)]\,\mathrm{d}u f(t|x)\,\mathrm{d}t \\
&= \left\{\int_0^t E[q(u|x)]\,du(1-S(t|x))\right\}\Big|_0^\infty - \int_0^\infty E[q(t|x)](1-S(t|x))\,\mathrm{d}t \\
&= \int_0^\infty E[q(t|x)]S(t|x)\,\mathrm{d}t. \qquad (2)
\end{aligned}$$

Thus, the expected quality adjusted survival time is the area under a *quality adjusted survival curve*, denoted by $\mathrm{qasc}(t|x) = E[q(t|x)]S(t|x)$, which could be approximated locally by a linear function. Hence, we propose an estimator of the expected quality adjusted survival time as

$$\begin{aligned}
\widehat{\mathrm{QAS}} &= \sum_{k=0}^{J} \widehat{\mathrm{qasc}}(t_k|x)(t_{k+1}-t_k) \\
&= \sum_{k=0}^{J}\left[\frac{\hat{q}(t_k|x)+\hat{q}(t_{k+1}|x)}{2}\,\frac{\hat{S}(t_k|x)+\hat{S}(t_{k+1}|x)}{2}\right](t_{k+1}-t_k), \qquad (3)
\end{aligned}$$

where $0 = t_0 < t_1 < \cdots < t_J < t_{J+1} = \infty$ are times chosen for estimating survival function, denoted by $\hat{S}(t|x)$, and mean QOL, denoted by $\hat{q}(t|x)$.

Another interpretation of the quality adjusted survival curve is to write

$$\widehat{\mathrm{qasc}}(t_k|x) = \frac{\hat{q}(t_k|x)+\hat{q}(t_{k+1}|x)}{2}\,\frac{\hat{S}(t_k|x)-\hat{S}(t_{k+1}|x)}{2} + \frac{\hat{q}(t_k|x)+\hat{q}(t_{k+1}|x)}{2}\,\hat{S}(t_{k+1}|x). \qquad (4)$$

The first term of (4) corresponds to the quality adjusted survival portion contributed by the patients who die in $[t_k, t_{k+1})$, and the second term is the part from the patients who still survive at t_{k+1}.

If we want to consider an annual discount rate r for the later years, as proposed by Barnum,[14] Landefeld and Seskin,[15] then the $\widehat{\mathrm{qasc}}(t_k|x)$ term in (3) can be modified as

$$\widehat{\mathrm{qasc}}(t_k|x) = \left[\frac{\hat{q}(t_k|x)+\hat{q}(t_{k+1}|x)}{2}\,\frac{\hat{S}(t_k|x)+\hat{S}(t_{k+1}|x)}{2}\right]\left(\frac{1}{1+r}\right)^{Y_k}, \qquad (5)$$

where Y_k is the number of years from onset of the disease to time t_k.

The survival function could be estimated from available survival data of size N using standard methods such as the life table method, product limit estimator or by parametric models. The mean QOL at time t_k will be estimated using QOL values of a sample of patients who are surviving at times around t_k.

To estimate the mean QOL at the chosen times, we suggest conducting a simple survey that randomly chooses n patients who are still surviving. Namely, samples are randomly drawn from a steady-state patient pool, of which there is no other unusual or catastrophic mortality or morbidity. Let τ_i be the ith patient's assessing time and $q_i(\tau_i|x)$ be the QOL value of the patient at that time. For simplicity, a kernel-type smoother is applied to the sample $\{\tau_i, q_i(\tau_i|x)\}_{i=1}^n$ to estimate the mean QOL at times $t_0, t_1, \ldots, t_J$. A kernel-type smoother is a generalization of local average type smoothing.[16] The smoothed values $\hat{q}(t_0|x), \hat{q}(t_1|x), \ldots, \hat{q}(t_J|x)$ thus produced by a kernel smoother are given by

$$\hat{q}(t_k|x) = \frac{\sum_{j=1}^n K(\frac{\tau_j - t_k}{b})\, q_j(\tau_j|x)}{\sum_{j=1}^n K(\frac{\tau_j - t_k}{b})}, \quad k = 0, 1, \ldots, J. \tag{6}$$

Here b is the bandwidth parameter and K is a simple kernel function defined as $K(w) = 1$ if $|w| \leqslant 1, 0$ otherwise.

The intuitive sense of the kernel estimate $\hat{q}(t_k|x)$ is as follows. Only values of $q_j(\tau_j|x)$ such that τ_j is close to t_k are used. The bandwidth b controls the size of the region around t_k for which $q_j(\tau_j|x)$ is to be included. When the sampled $\{\tau_i\}_{i=1}^n$ is not uniformly distributed, it is not easy to find a suitable bandwidth. Since the sampled $\{\tau_i\}_{i=1}^n$ are strongly related to the survival times and are usually not uniformly distributed, we propose a modification to replace the kernel in (6) with

$$K\left(\frac{F_n(\tau_j) - F_n(t_k)}{b}\right),$$

where $F_n(u) =$ Number of $\tau_j \leqslant u/n$ is the empirical distribution of $\{\tau_i\}_{i=1}^n$. The bandwidth b is the proportion of time points to be used for smoothing. That is, $[bn]$, the largest integer less than or equal to bn, points from the left and $[bn]$ points from the right of t_k to be used for computing $\hat{q}(t_k|x)$. The procedure is as follows.

First, let $\tau_{(1)} \leqslant \tau_{(2)} \leqslant \cdots \leqslant \tau_{(n)}$ be the ordered time points of $\{\tau_i\}_{i=1}^n$ and the corresponding QOL values are $q_{(1)}(\tau_{(1)}|x), \ldots, q_{(n)}(\tau_{(n)}|x)$. Then, find out where t_k falls, say $\tau_{(h)} \leqslant t_k \leqslant \tau_{(h+1)}$. The estimated mean QOL at time t_k will be

$$\hat{q}(t_k|x) = \frac{\sum_{j=\max(1,\, h-[bn]+1)}^{\min(h+[bn],\, n)} q_{(j)}(\tau_{(j)}|x)}{\min(h + [bn], n) - \max(1, h - [bn] + 1) + 1}. \tag{7}$$

The standard error of $\widehat{\text{QAS}}$, denoted by $\text{SE}(\widehat{\text{QAS}})$, is mathematically complicated in the calculations of the autocovariances of $\hat{q}(t_k|x)\,\hat{S}(t_k)$. Therefore we may use a bootstrap method to obtain a rough estimate of $\text{SE}(\widehat{\text{QAS}})$.[17] The bootstrap is implemented by repeatedly sampling, with replacement, from the n pairs of patients' QOL values and assessing times to obtain a new sample of size n for constructing new $\hat{q}(t_k|x)$. At the same time, we do the same for the survival data to obtain a new sample of size N to produce new $\hat{S}(t_k)$. Then we combine these two to obtain a new $\widehat{\text{QAS}}$. This process is repeated B times to estimate $\text{SE}(\widehat{\text{QAS}})$ by the empirical standard derivation of the replications. Often, $B = 50$ is sufficient to give a good estimate of standard error of an estimator.[17] The result is called the bootstrap estimate of standard error, denoted by $\widehat{\text{SE}}(\widehat{\text{QAS}})$

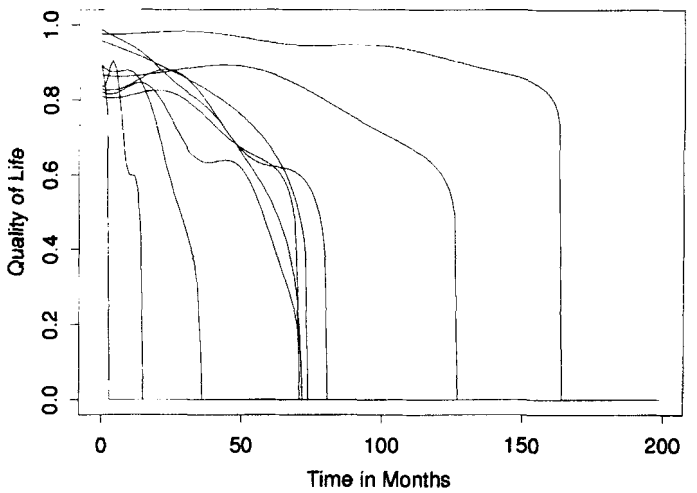

Figure 1. Hypothetical quality of life curves generated from equation (8) with $(p_1, p_2) = (0{\cdot}8, 1), (a_1, a_2) = (0{\cdot}01, 0{\cdot}5), c = 4$ and $d = 1$

4. SIMULATIONS

The hypothetical population consists of 50,000 patients whose survival times are generated from an exponential distribution with a mean of 72 months. Each patient's QOL through his/her survival time T_i is determined by

$$q_i(t \mid p, \alpha, \gamma, \delta) = p(1 - t/T_i)^{\alpha} + \delta(1 - p)\sin^2(\gamma t\pi/T_i), \tag{8}$$

where p, α, γ and δ are uniformly distributed in (p_1, p_2), (a_1, a_2), $(0, c)$ and $(0, d)$, respectively.

The first term of $q_i(t|p, \alpha, \gamma, \delta)$ describes that a patient's QOL gets worse with time through a parameter α used to reflect the speed of worsening. The second term is designed to add γ periods with small amplitudes to describe possible improvements of QOL during the survival. Several simulated QOL functions over time are given in Figure 1.

The ith patient's QALY is given by

$$\int_0^{T_i} q_i(t|p, \alpha, \gamma, \delta)\,\mathrm{d}t = \frac{pT_i}{1+\alpha} + \frac{\delta(1-p)T_i}{2}\left(1 - \frac{\sin 2\gamma\pi}{2\gamma\pi}\right).$$

Hence, the true mean QAS, denoted by E(QAS), is the average of the 50,000 QALYs in the simulation.

A survival time sample of size N is randomly chosen from the population. About 10 per cent of the sample survival times are multiplied by random numbers from a uniform (0·1, 0·9) distribution and treated as censored observations.

Another n patients are randomly selected from the population. For each patient, an assessing time is generated from 0 to his/her survival time uniformly. To allow sampling error, a QOL value of the patient at a time drawn uniformly between three months before and after that selected time is recorded as the sampled QOL value at that sampled assessing time. These n pairs are then used for estimating the mean QOL function at chosen times. In this simulation, the chosen times are $0, 12, 24, \ldots, 492$ months.

Table I. Some simulation results. $E(\text{QAS})$ is the true mean QAS; ave($\widehat{\text{QAS}}$) and SE($\widehat{\text{QAS}}$) are the average and standard deviation of the 1000 $\widehat{\text{QAS}}$ replications; $\widehat{\text{SE}}(\widehat{\text{QAS}})$ is the average of the 1000 bootstrap standard error estimates; RB is the relative bias

N	n	a_1	a_2	E(QAS)	ave($\widehat{\text{QAS}}$)	RB	SE($\widehat{\text{QAS}}$)	$\widehat{\text{SE}}(\widehat{\text{QAS}})$
100	50	0·01	0·25	59·19	60·36	0·02	6·39	6·11
100	50	0·01	0·50	53·92	53·73	0·00	5·91	5·66
100	50	0·01	0·75	49·75	48·58	0·02	5·60	5·37
100	200	0·01	0·25	59·19	59·90	0·01	5·89	5·84
100	200	0·01	0·50	53·92	53·15	− 0·01	5·17	5·13
100	200	0·01	0·75	49·75	47·93	− 0·04	4·65	4·62
400	50	0·01	0·25	59·19	60·44	0·02	3·26	3·42
400	50	0·01	0·50	53·92	53·75	0·00	3·52	3·57
400	50	0·01	0·75	49·75	48·56	− 0·02	3·75	3·73
400	200	0·01	0·25	59·19	60·07	0·01	2·96	3·08
400	200	0·01	0·50	53·92	53·23	− 0·01	2·75	2·84
400	200	0·01	0·75	49·75	47·96	− 0·04	2·61	2·70

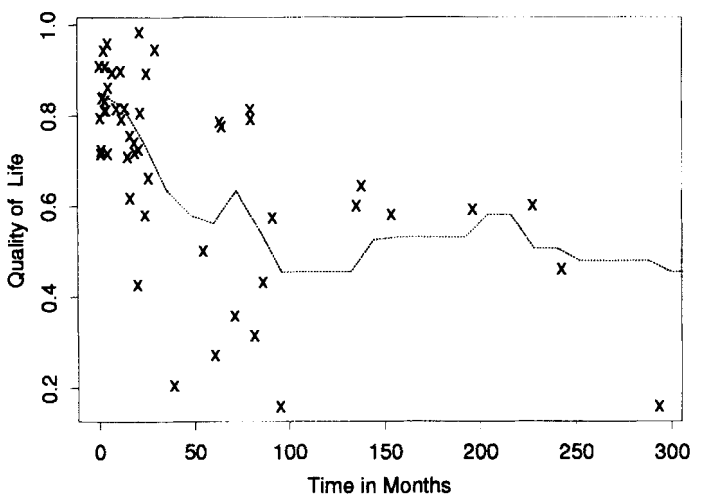

Figure 2. Quality of life: cross-sectional samples and kernel-type smoothed mean

The life table method is used to estimate the survival at the chosen times. The kernel-type smoother (7) with bandwidth 0·05 is used to estimate the mean QOL at those time points in the simulation.

The purpose of this simulation is to see how much effect bias of the estimator $\widehat{\text{QAS}}$ may have in estimating the true mean QAS and how good the bootstrap estimate of $\widehat{\text{SE}}(\widehat{\text{QAS}})$ may be used in estimating SE($\widehat{\text{QAS}}$). The main parameters that may affect the bias and SE($\widehat{\text{QAS}}$) are the sample sizes N, n and the interval (a_1, a_2). For demonstration, we let (p_1, p_2, c, d) be fixed at $(0{\cdot}8, 1, 4, 1)$ and consider several combinations of N, n, a_1, a_2, shown in Table I.

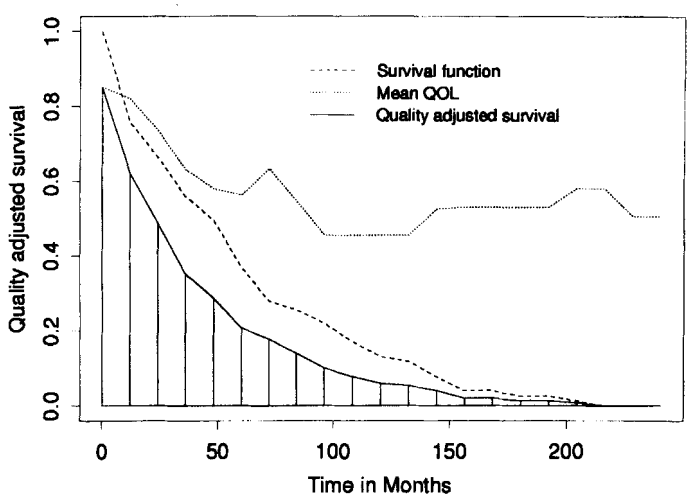

Figure 3. Estimated survival function, mean QOL and quality adjusted survival curve; the area under the qasc is the expected quality adjusted survival time

For each set-up, we repeated sampling survival times of size N and QOL values of size n 1000 times to calculate 1000 $\widehat{\text{QAS}}$s. For each repetition 50 bootstrap estimates of $\widehat{\text{QAS}}$ were calculated to obtain a bootstrap estimate of standard error. That is, we have 1000 pairs of $\widehat{\text{QAS}}$ and $\widehat{\text{SE}}(\widehat{\text{QAS}})$ for each interval (a_1, a_2) and sample sizes N and n.

Figure 2 gives a sample of QOL assessed at $n = 50$ time points and the estimated mean QOL curve. The estimated survival curve, mean QOL curve and $\widehat{\text{QAS}}$ obtained from a sample of survival times and QOL values are plotted in Figure 3. The sample means and standard deviations of the 1000 estimated $\widehat{\text{QAS}}$s, denoted by ave($\widehat{\text{QAS}}$) and SE($\widehat{\text{QAS}}$), are listed in Table I. The relative biases, $RB = (\text{ave}(\widehat{\text{QAS}}) - E(\text{QAS}))/E(\text{QAS})$, are all within 5 per cent. The average of the 1000 $\widehat{\text{SE}}(\widehat{\text{QAS}})$s, denoted by $\overline{\widehat{\text{SE}}(\widehat{\text{QAS}})}$, is seen very close to the standard error of $\widehat{\text{QAS}}$.

The simulation results in Table I have shown that the estimator $\widehat{\text{QAS}}$ and the bootstrap standard error estimate of $\widehat{\text{QAS}}$ are relatively accurate under these hypothetical set-ups of survival and quality of life functions. We believe that our estimator may not work well under some other hypothetical populations, but in the real world, when the quality of life processes of patients with a specific disease behave like those in Figure 1, then our estimator could be applied to estimate the expected quality adjusted survival time.

5. DISCUSSION

Although QAS can thus be theoretically estimated from a *combinational* use of a survival function plus a sample of QOL assessment from currently surviving patients, we need to clarify the logistics of how to implement such a study in reality. For any cohort or data set of which the survival function or a life table is readily available or estimatable, we can simply perform a cross-sectional survey among currently surviving patients to obtain the QOL data from different survival time, and put these numbers into equation (3) to estimate the QAS. To avoid any sampling bias or misrepresentation, we recommend that such a sample be taken actively and randomly, and particular attention be paid to investigating the causes of non-response to see whether they are associated with the QOL. If there is any reason to believe that patients who

regularly come back for follow-up are more likely to have a higher or lower QOL, then adjustment or supplementary statement should be made at the inference. For any disease for which no cohort or life table data have been collected so far, we recommend simultaneously collecting both survival and QOL data for the estimation of QAS in the future. To increase the sample size, we propose following as many patients as possible, perhaps from many centres or clinics, with a standardized protocol which includes both the utility assessment of QOL and the survival condition. Different health profiles[3, 5, 18, 19] can also be simultaneously collected to further validate the utility measurements.

One of the major concerns of the application of QAS and QALY for health outcome evaluation or policy decision is the ethical controversy of age discrimination and the legitimacy of trade-off between the quantity and quality of life.[20–24] However, there is an increasing trend to accept such an approach for the planning and allocation of the limited health resources because of the growing demand for cost containment and equitable distribution.[25] Hence, we suggest using the calculation of QALY within a certain age stratum, for example., less than 10–15 years for cost-effectiveness evaluation, but simultaneously consider mortality as the primary indicator if comparison is needed across a wider range of age.[26]

A second limitation of our model is how accurately we can measure the QOL or severity of illness or the extent of disability to obtain QALY itself. We are measuring people's utility function, which essentially assumes that human beings are logical and that such a preference follows the transitive law,[27, 28] but in reality it may change with time, place, types of illness and culture and the variation may be quite large. As the illness becomes more severe, or if the patient suffers from a psychiatric disease and is not in a clinically stable condition, his consciousness and/or judgement may be affected and this will certainly impede us in quantifying the patient's utility function. To deal with this problem, we propose that both patients who suffer from a specific illness and medical professionals who directly take care of such patients should be periodically asked for the measurement of such losses, and that such utility functions should at least be measured separately for populations of different cultures. The different figures can be put in the model for a sensitivity analysis.

In addition to the above limitations, one might also raise the question of whether an annual discount rate be applied to the QALY's gained in the later years of life.[14, 24, 29] Since an individual may contract diseases or injuries before future days are realized, a healthy day of life at present generally has a greater intrinsic value and is preferable to him/her now than a day in the future. From an economic point of view, the marginal value of the first additional one or two years of survival are usually larger than those of the same duration added one or two decades later. Furthermore, if we want to calculate the potential working years of life and the salary lost,[30] namely, estimate the potential value of monetary loss, the adjustment of annual discount is necessary. Thus, it is no surprising that such an adjustment is frequently applied in spite of constant debate,[24, 25] and we have prepared equation (5) ready for such use. However, the QAS we propose here have already taken the survival probability into account. Moreover, the cross-sectional survey will collect a random sample of QOL data from currently surviving patients with different duration- to-dates of the illness of interest, which represent the actual utility values. So, we suggest that QAS be estimated both with and without different annual discount rates for comparison and sensitivity analysis, which then leaves the final decision to public choice.[22, 24, 26, 29]

Given all the above limitations, the QALY calculated from our model is still a common unit that can be used for outcome evaluation. It has the potential for us to compare the overall impact from both mortality and morbidity of different health-related events. A

detailed model of cost-utility analysis is also proposed in another manuscript to show its use.[31]

ACKNOWLEDGEMENTS

The authors wish to acknowledge gratefully the helpful comments and suggestions of Dr. Markku Nurminen and two anonymous referees. This study was supported by Contract NSC-84-2621-P-002-006 from the National Science Council of ROC, Taiwan.

REFERENCES

1. Weinstein, M. C. and Stason, W. B. 'Foundations of cost-effectiveness analysis for health and medical practices', *New England Journal of Medicine*, **296**, 716–721 (1977).
2. Torrance, G. W. 'Measurement of health state utilities for economic appraisal: A review', *Journal of Health Economics*, **5**, 1–30 (1986).
3. Patrick, D. L. and Erickson, P. *Health Status nad Health Policy: Quality of Life in Health Care Evaluation and Resource Allocation*, Oxford University Press, Oxford, 1993.
4. Katz, S. 'The science of quality of life', *Journal of Chronic Diseases*, **40**, 459–463 (1987).
5. Spizer, W. O. 'State of science 1986: Quality of life and functional status as target variables for research', *Journal of Chronic Diseases*, **40**, 465–471 (1987).
6. Mor, V. 'Cancer patients' quality of life over the disease course: Lessons from the real world', *Journal of Chronic Diseases*, **40**, 535–544 (1987).
7. Morris, J. N. and Sherwood, S. 'Quality of life of cancer patients at different stages in the disease trajectory', *Journal of Chronic Diseases*, **40**, 545–553 (1987).
8. Fletcher, A. E., Hunt, B. M. and Bulpitt, C. J. 'Evaluation of quality of life in clinical trials of cardiovascular disease', *Journal of Chronic Diseases*, **40**, 557–566 (1987).
9. Ghana Health Assessment Project Team. 'A quantitative method of assessing the health impact of different diseases in less developed countries', *International Journal of Epidemiology*, **10**, 73–80 (1981).
10. Glasziou, P. P., Simes, R. J. and Gelber, R. D. 'Quality adjusted survival analysis', *Statistics in Medicine*, **9**, 1259–1276 (1990).
11. National Center for Health Statistics. *U.S. Life Tables*, DHHS Publication No. (PHS) 85-1150-1, 1985.
12. Department of Health, Executive Yuan (R.O.C.) *Vital Statistics 1950–1991*, Department of Health, Executive Yuan, Taipei, Taiwan, 1991.
13. Lee, E. T. *Statistical methods for Survivial Data Analysis*, 2nd edn., Wiley, New York, 1992, pp. 19–103.
14. Barnum, H. 'Evaluating healthy days of life gained from health projects', *Social Science and Medicine*, **10**, 833–841 (1987).
15. Landefeld, J. S. and Seskin, E. P. 'The economic value of life: Linking theory to practice', *American Journal of Public Health*, **72**, 555–566 (1982).
16. Watson, G. S. 'Smooth regression analysis', *Sankha, Series A*, **26**, 359–378 (1966).
17. Efron, B. and Tibshirani, R. J. *An Introduction to the Bootstrap*, Chapman and Hall, New York, London, 1993.
18. Ware J. E, Jun. 'Standards for validating health measures: definition and content', *Jounral of Chronic Diseases*, **40**, 473–480 (1987).
19. Guyatt, G. H., Feeney, D. H. and Patrick, D. L. 'Measuring health-related quality of life', *Annals of Internal Medicine*, **118**, 622–629 (1993).
20. Beauchamp, T. L. and Childress, J. F. *Principles of Biomedical Ethics*, 4th edn., Oxford University Press, Oxford, 1994, 308–313 and 368–372.
21. LaPuma, J. and Lawlor, E. F. 'Quality-adjusted life-years: ethical implications for physicians and policy-makers', *Journal of the American Medical Association*, **263**, 2917–2921 (1990).
22. Carr-Hill, R. 'Assumption of the QALY procedure', *Social Science and Medicine*, **29**, 469–477 (1989).
23. Barry, P. P. 'Age-based rationing of medical care', *Geriatrics*, **47**, 64–67 (1992).
24. Spiegelhalter, D. J., Gore, S. M., Fitzpatrick, R., Fletcher, A. E., Jones, D. R. and Cox, D. R. 'Quality of life measures in health care. III: resource allocation', *British Medical Journal*, **305**, 1205–1209 (1992).
25. The World Bank. *World Development Report 1993: Investing in Health*, Oxford University Press, Oxford, 1993.
26. American Geriatrics Society Public Committee. 'Equitable distribution of limited medical resources', *Journal of the American Geriatrics Society*, **37**, 1063–1064 (1989).

27. Savage, L. J. *Foundation of Statistics*, Dover Publications, New York, 1972, pp. 69–104.
28. French, S. *Readings in Decision Analysis*, 1st edn., Chapman and Hall, London, 1993, pp. 21–62.
29. Robinson, R. 'Cost-utility analysis', *British Medical Journal*, **307**, 859–862 (1993).
30. Chang, Y. C. and Wang, J. D. 'Cumulative injury rate and potential work days and salary lost', *Scandinavian Journal of Work, Environment and Health*, **21**, (1995).
31. Wang, J. D., Tsauo, J. Y. and Hwang, J. S. 'Estimation of utility gained or lost of an individual or a population by quality adjusted survival time', submitted to *American Journal of Epidemiology*(1995).