Special Article

Handling Uncertainty of the Economic Evaluation Result: Sensitivity Analysis

Supon Limwattananon MPHM, PhD*

** Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen*

An economic evaluation of health technology and interventions often comes with uncertainty in the parameters that were used in the model. To determine sensitivity of the result obtained from a reference case analysis, researchers can employ deterministic and probabilistic approaches. This methodological guideline summarizes the principles underlying the sensitivity analysis and recommends that the probabilistic sensitivity analysis is the best method to handle the parameter uncertainty.

Keywords: *Acceptability curve, Monte Carlo simulation, Sensitivity analysis, Tornado diagram*

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The result obtained from an economic evaluation of health technology and interventions can vary upon and be very sensitive to the assumptions and certain parameters specified in a reference (or base) case analysis. In addition, transferring the analysis result from one setting to another may introduce additional uncertainty due to differences in economic and health care contexts. A methodological approach to the parameter uncertainty is called sensitivity analysis (SA) and will be the focus of the present article.

Types of sensitivity analysis

Briggs classified methods of handling uncertainty due to parameters in the economic evaluation model into three types[1]. The first approach is called a deterministic sensitivity analysis (DSA). This DSA is conducted by varying the value of each parameter, given that the remaining parameters are constant. The second approach is an extreme scenario analysis, in which several important parameters are set under two extreme scenarios (the best-case vs. the worst-case) for the intervention of interest. The last approach is a probabilistic sensitivity analysis (PSA) which assumes that a variation in each of the parameters follows a defined pattern of data distribution. The next subsection sheds light on a detailed analysis approach for common SA.

Correspondence to: Limwattananon S. Faculty of Pharmaceutical Sciences, Khon Kaen University, Amphoe Muang, Khon Kaen 40002, Thailand. Phone: 043-362-090, Fax: 043-362-090, E-mail: supon@kku.ac.th

Deterministic sensitivity analysis

The most common type of DSA is the oneway sensitivity analysis, which is found in more than 70% of publications[2]. In this simplest SA, one parameter is set to vary over a reasonable range (for example, minimum-maximum, standard deviation, 95% confidence interval), one at a time. Then, the resulting cost, effectiveness, and cost-effectiveness ratio (CER) are determined accordingly. The sensitivity of the results can be easily detected through a line graph depicting the relationship between the varying cost- or effectiveness-related parameters and the cost and effectiveness outcomes (Fig. 1 and 2).

The above one-way SA shows a variation in the CER of tissue plasminogen activator (t-PA) when compared with streptokinase due to varying clinical efficacy (in terms of an increase in patient survival) and treatment cost of t-PA[3]. Noticeably, a reduction in CER of t-PA, due to an increase in t-PA efficacy, is not linear and is very sensitive to the first 2-5 years of increased survival (Fig. 1), whereas the result is proportional to the whole range of treatment cost increment (Fig. 2).

Tornado diagram

An alternative presentation of one-way SA is

a tornado diagram. In the diagram, sensitivity of the study result is reflected through the length (maximum-minimum values) of a horizontal bar that represents variation in the cost and effectiveness outcomes for each parameter. The very influential parameters appear at the cloud level or at the top of the tornado, whereas the less influential parameters are at the base of the tornado. The reference case result is a vertical straight line stretching through the tornado touchdown point.

Fig. 3 illustrates a tornado diagram of the referent CER for paclitaxel used additionally to anthracyclines as an adjuvant in early stage breast cancer[4]. The relative efficacy (in terms of hazard ratio, HR) of paclitaxel can affect the study result a lot more than variations in adverse drug events, treatment of recurrence, and terminal care cost.

A major limitation of one-way SA is that it cannot accommodate all parameter uncertainties, whereas the extreme scenario analysis tends to exaggerate true uncertainty. Manning et al. argued that probabilistic sensitivity analysis (PSA) would capture the uncertainty to within a fraction of the actual uncertainty[5]. This will be elaborated in the next subsection.

Probabilistic sensitivity analysis

Recent papers have proposed innovative

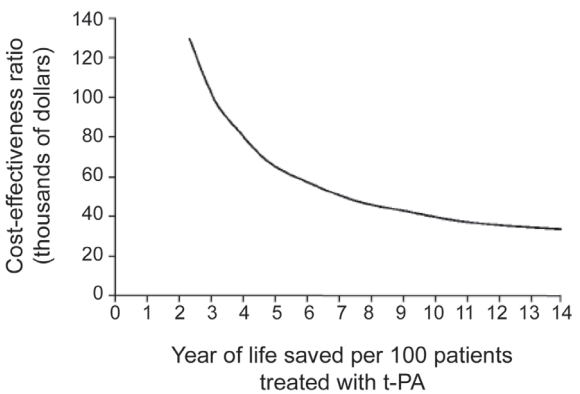
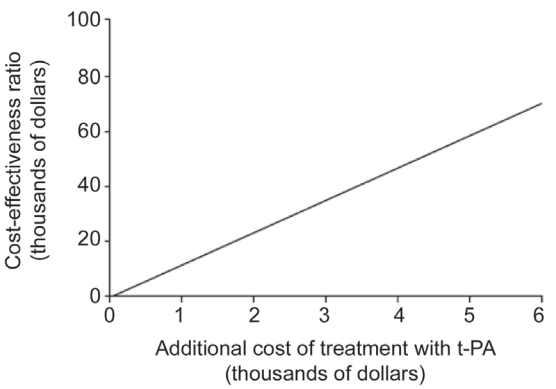
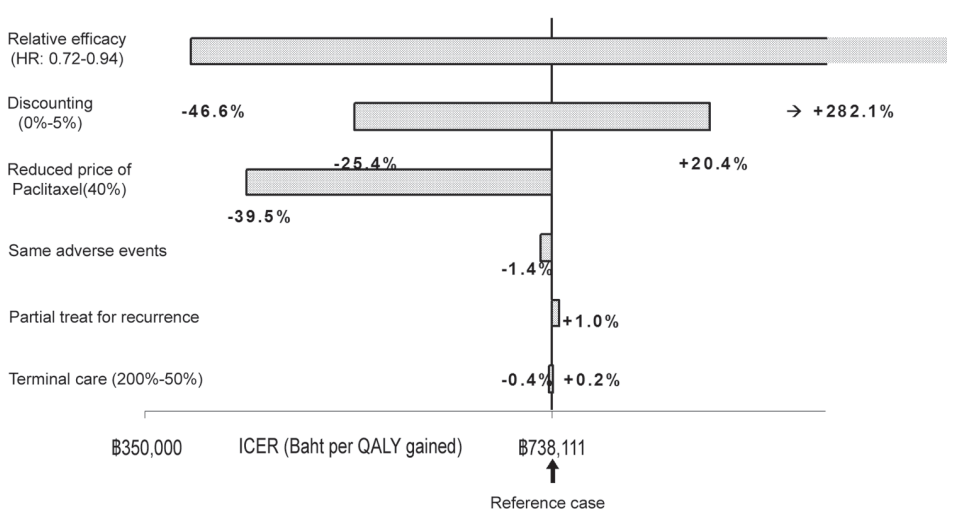


Fig. 1 One-way SA due to a change in patient survival from t-PA as compared with streptokinase



Source: Mark et al (1995)

Fig. 2 One-way SA due to the treatment cost difference between t-PA and streptokinase



Source: Limwattananon et al (2006)

Fig. 3 Sensitivity of CER for paclitaxel due to various model parameters

methods in handling the uncertainty due to parameters derived from the secondary data and individual-level information[6-8]. Probabilistic sensitivity analysis (PSA) is a more powerful approach in dealing with the uncertainty stemming from several parameters. Performing PSA is facilitated by a computer-based Monte Carlo simulation. This is done through feeding a randomly selected set of parameters into the analysis model repeatedly several hundred or even several thousand times. How the values of each parameter will be selected depends upon the defined data distribution. Table 1 presents data distribution patterns commonly used for cost- and effectiveness-related parameters.

It should be noted that a normal distribution as assumed for conventional parametric statistics plays a limited role in PSA since most real-world economic and health data do not behave well. In Table 1, the parameters on probability and utility follow a beta distribution, in which the minimum and maximum values are restricted to zero and one. The relative efficacy (or relative risk) of an intervention tends to be distributed normally after the parameters are transformed by a logarithmic function. For the cost parameter, several economists have stated that its variance is not constant and can be approximated as a square of the mean and this fits a gamma distribution[9-12].

Fig. 4 illustrates the PSA of an economic evaluation of anastrozole as an adjuvant for early-stage breast cancer, using a cost-effectiveness (CE) plane[13]. The horizontal axis represents the incremental effectiveness of the drug of interest as compared with the standard tamoxifen therapy in terms of quality-adjusted life years (QALYs). The vertical axis captures the cost difference in Baht between the two interventions. Uncertainty in the effectiveness and cost is reflected by the distribution of 1,000 dots generated by running the Monte Carlo simulation 1,000 times for the important cost and effectiveness-related parameters and assuming various data distributions as shown in Table 1.

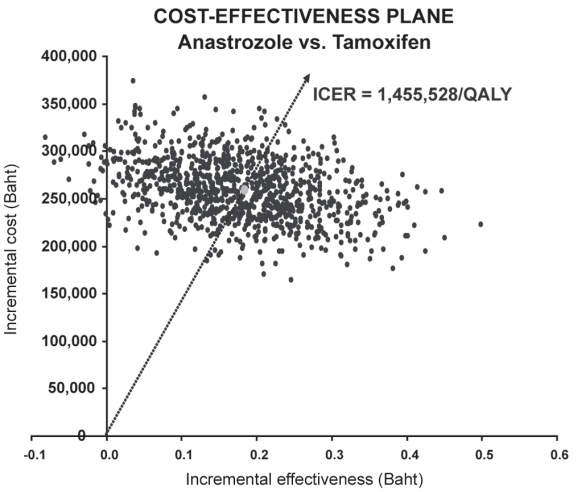
The result from the reference case analysis is the dot located in the middle of the 1,000 uncertainty dots. The incremental cost-effectiveness ratio (ICER) of anastrozole (as compared with tamoxifen) is equal to the slope of the straight line drawn from the origin to the reference case dot. This is equal to 1,455,528 Baht/QALY. Notably, the reference case ICER divides the cost-effectiveness uncertainty cluster into two groups. Approximately half of the uncertainty dots are located in the left-hand side of the reference ICER and have the ICERs greater than 1,455,528 Baht/QALY whereas the second half, to the right, encompasses a relatively lower ICER when compared with the reference case. This means that if one set the cost-effectiveness threshold at 1,455,528 Baht/QALY, anastrozole would have an approximately 50% chance (or probability = 0.5) of becoming cost-effective. Hence, the probability that an intervention will become cost-effective can be derived from the proportion of the uncertainty dots lying below the ICER line. The PSA depicted by this uncertainty plot on the CE plane can be used to determine how likely it is that an intervention of interest will be accepted as a cost-effective intervention with respect to varying ICER thresholds. This will be explained through the decision criteria in the next subsection.

Net benefit approach

Probabilistic sensitivity analysis is helpful in overcoming the limitation due to the use of a single CER threshold as the decision rule for cost-effective interventions. The fact that both the cost numerator and the effectiveness denominator are unavoidably uncertain in some degrees will make the derived ratio (i.e., ICER) even more complicated in its uncertainty. In addition, if the point estimate of the ICER result was negative, the authors would not know exactly if the numerator or denominator is negative (in other words, the intervention of interest was either less expensive or less effective than the comparator). An alternative approach is to vary the predetermined ICER threshold, then see how likely the intervention of interest will produce its ICER below such a threshold. This decision criterion is called a 'net benefit approach (NBA)'.

Table 1. Data distribution for cost and effectiveness parameters

Parameter	Family of distribution	Nature of data	Possible range
Probability	Beta distribution	Proportion	0-1
Utility	Beta distribution	Integer	0-1 (0 = death, 1 = full health)
Relative efficacy or relative risk	Log-normal distribution	Ratio	0-11 – Positive numbers
Cost	Gamma distribution	Very skew	Positive numbers



Source: Limwattananon et al (2005a)

Fig. 4 Uncertainty of the incremental cost and effectiveness of anastrozole

The principle of NBA can be explained through the following formulations:

Given that:

C_A is the total cost incurred by an intervention of interest 'A'

C_B is the total cost incurred by an appropriate comparator 'B'

E_A is the effectiveness outcome of 'A'

E_B is the effectiveness outcome of 'B'

IC is the incremental cost of 'A' when compared with 'B'

IB is the incremental effectiveness of 'A' when compared with 'B'

$ICER_{A\ vs.\ B}$ is the incremental cost-effectiveness ratio of 'A' when compared with 'B' and is equal to the ratio between IC and IE

$$ICER_{A\ vs.\ B} = IC/IE = (C_A - C_B) / (E_A - E_B)$$

Willingness to pay (WTP) is a monetary threshold (or ceiling ratio) to be traded off for an effectiveness unit of A relative to that of B. Hence, the intervention A is deemed 'cost-effective' as long as the $ICER_{A\ vs.\ B}$ is less than the set WTP threshold.

Based on the Monte Carlo simulation, which results in a cluster of the ICER uncertainty dots, an initiation of NBA is used to define a monetary threshold (i.e., economic cost) that societies, payers, or patients (depending on whose perspective) are willing to pay for a unit of effectiveness (e.g., year of life, QALY) gained by the intervention of interest relative to a comparator. In the CE plane, the number of uncertainty dots below such a threshold proportional to all dots was counted as the % acceptance of cost-effectiveness.

Fig. 5 illustrates the PSA of the addition of trastuzumab to a conventional chemotherapy (paclitaxel) for treating metastatic breast cancer[14].

The authors can see that trastuzumab is unlikely to be cost-effective if the society's WTP is not beyond 1 million Baht per QALY gained. Even though the society is willing to pay as much as 2 million Baht per QALY for the effectiveness of trastuzumab, the chance that the drug will be accepted as a cost-effective intervention is less than 20%.

The NBA for a cost-effectiveness decision can be operationalized through the measures of net health benefit –NHB[15] and net monetary benefit –NMB[7,16].

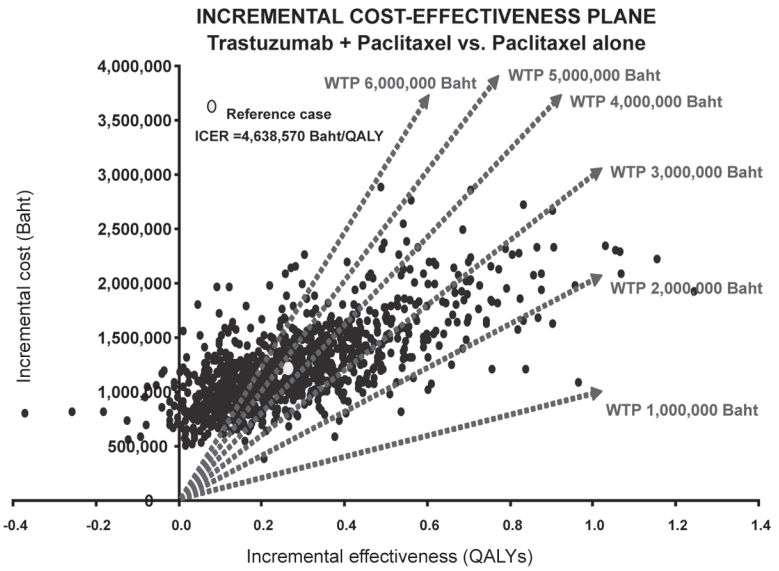
The NHB is a measure in an effectiveness scale which is a magnitude of the difference between the incremental effectiveness (IE) and the ratio of the incremental cost (IC) divided by the WTP threshold. Similarly, the NMB is a measure in a cost scale which is equal to the difference between the product of IE multiplied by WTP and minus the IC.

$$NHB = (E_A - E_B) - [(C_A - C_B) / WTP]$$
$$NMB = [(E_A - E_B)WTP] - (C_A - C_B)$$

Acceptability curve

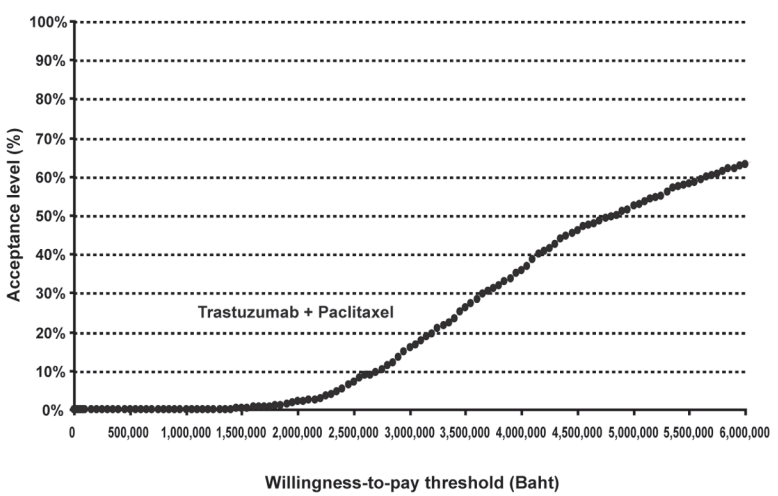
If the NHB or NMB is positive (or greater than zero), the intervention 'A' is considered a cost-effective intervention. This means that intervention 'A' yields, in the NHB sense, an increase in effectiveness at a greater extent than the effectiveness that could be expected from the set WTP threshold or, in the NMB sense, an increase in cost at a lower extent than the cost expected from the set threshold. When the WTP threshold is raised, the likelihood that intervention 'A' becomes cost-effective will increase accordingly. This process will be performed repeatedly with respect to an increasing WTP until the cost-effectiveness acceptance for intervention 'A' approaches 100%. The relationship between varying WTP thresholds and the likelihood (%) of cost-effectiveness can be depicted by an acceptability curve[8,17] (Fig. 6).

The acceptability curve for trastuzumab (Fig. 6) crosses the horizontal axis at approximately 1.1 million Baht of the WTP threshold[14]. This means that if the society is willing to pay for a one-year increase in the patient's life at the amount of 1 million Baht, trastuzumab will not be cost-effective at all. The drug will, however, have more than a 50% chance of becoming



Source: Limwattananon et al (2005b)

Fig. 5 Uncertainty of the incremental cost-effectiveness of trastuzumab



Source: Limwattananon et al (2005b)

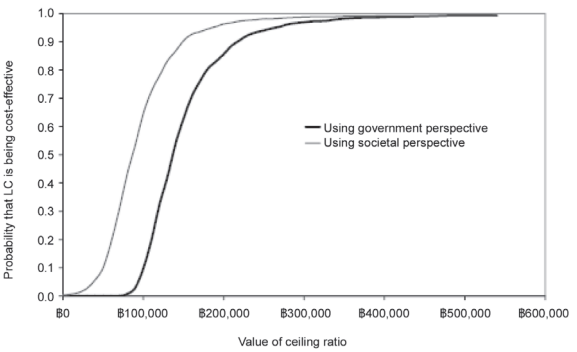
Fig. 6 Acceptability curve of trastuzumab for metastatic breast cancer

cost-effective if the WTP of the society is more than 5 million Baht per QALY.

With this same acceptability curve, the 95% CI for ICER of trastuzumab can be determined by the 2.5% and 97.5% acceptance levels. In this case, the lower limit of 95% CI for ICER is equal to 2.1 million Baht per QALY, whereas the upper limit is beyond the limits depicted by this curve.

The acceptability curve can be used to demonstrate the cost-effectiveness likelihood for varying scenarios used in CEA. Fig. 7 illustrates the CEA results from two perspectives, the government's and societal[18].

If there were no resources intended to be devoted to the incremental effectiveness delivered by an innovative health interventions (i.e., zero WTP), the



Source: Teerawattananon et al (2005)

Fig. 7 Cost-effectiveness acceptability curve for laparoscopic cholecystectomy

conventional open cholecystectomy (OC) would be more cost-effective for managing gallbladder-stone disease in Thailand than laparoscopic cholecystectomy (LC). Not until the WTP reaches 90,000 Baht based on the societal perspective (or 140,000 Baht based on the government's perspective) per one QALY gained that LC would be more likely to be cost-effective than OC. The likelihood of LC dominating OC would not be greater than 95% unless the WTP was greater than 190,000 and 270,000 Baht per QALY based on the societal and government's perspectives, respectively.

Recommendations

The best SA of the economic evaluation result due to parameter uncertainty is PSA. The PSA can be achieved if the mean (or proportion) values and the standard error (SE) of input parameters used in the CEA model are known. This is usually the case if the individual level observations are readily available. Otherwise, the mean (or proportion) and SE need to be reported. The assumed data distribution appropriate for the components related to cost and effectiveness will determine the variations in cost and effectiveness of the compared interventions facilitated by the iterative process of the Monte Carlo simulation. The WTP threshold set by society (in the case of using the societal perspective for an analysis) per unit gain in effectiveness will determine the likelihood that an intervention of interest would be deemed cost-effective. The NBA approach is the fundamental of this decision rule, which is reflected through a cost-effectiveness acceptability curve.

If the individual-level data is not available or there is no reported mean (or proportion) or SE, sensitivity of the CEA result can be analyzed using a conventional deterministic SA. The easiest approach is a one-way SA where uncertain parameters are set to vary one at a time, holding other parameters constant. A tornado diagram can help identify the most influential parameter on sensitivity of the CEA result.

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การจัดการกับความไม่แน่นอนของผลลัพธ์จากการประเมินความคุ้มค่าทางการแพทย์ภาวิเคราะห์ความไว

สุพล ลิมวัฒนานนท์

การประเมินความคุ้มค่าทางการแพทย์ของเทคโนโลยีและมาตรการด้านสุขภาพมักประสบกับความไม่แน่นอนของข้อมูลจากตัวแปรที่ใช้วิเคราะห์ในแบบจำลอง เพื่อแสดงให้เห็นถึงความไวของผลลัพธ์ซึ่งได้จากการวิเคราะห์ที่ค่าอ้างอิง นักวิจัยสามารถใช้วิธีทั้งแบบที่อาศัยและไม่อาศัยความน่าจะเป็น บทความนี้จะสรุปหลักการของการวิเคราะห์ความไวและเสนอแนะว่าการวิเคราะห์ความไวแบบอาศัยความน่าจะเป็นเป็นวิธีที่ดีที่สุดในการจัดการกับความไม่แน่นอนที่เกิดจากตัวแปรต่าง ๆ