Sensitivity Analysis for Handling Uncertainty in an Economic Evaluation

Supon Limwattananon MPHM, PhD*

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

To meet updated international standards, this paper revises the previous Thai guidelines for conducting sensitivity analyses as part of the decision analysis model for health technology assessment. It recommends both deterministic and probabilistic sensitivity analyses to handle uncertainty of the model parameters, which are best represented graphically. Two new methodological issues are introduced-a threshold analysis of medicines' unit prices for fulfilling the National Lists of Essential Medicines' requirements and the expected value of information for delaying decision-making in contexts where there are high levels of uncertainty. Further research is recommended where parameter uncertainty is significant and where the cost of conducting the research is not prohibitive.

Keywords: *Acceptability curve, Expected value of information, Sensitivity analysis, Threshold analysis, Tornado diagram*

J Med Assoc Thai 2014; 97 (Suppl. 5): S59-64
Full text. e-Journal: *http://www.jmatonline.com*

This paper gives an overview of the key methods used to conduct sensitivity analyses (SA) in economic evaluations of health technologies and therapeutic interventions. It revises previous recommendations, published in 2008[1], by addressing and updating several methodological issues that have been highlighted since then by the National Institute for Health and Clinical Excellence (NICE) Guide to the Methods of Technology Appraisal[2], the International Society for Pharmaco-economics and Outcomes Research (ISPOR), and the Society for Medical Decision Making (SMDM) Good Research Practices in Modelling[3].

This paper focuses on approaches to handling parameter uncertainty, a second-order uncertainty in decision analysis models. Issues arising from first-order uncertainty due to random error and structural or model uncertainty due to assumptions are not covered. This article provides a number of recommendations, with concrete examples on the appropriate graphical presentation of results from deterministic[4] and probabilistic sensitivity analyses[5,6]. Additionally, a threshold analysis of medicines' unit prices is recommended as a way to fulfill the cost-effectiveness criteria set by the committee on National Lists of Essential Medicines (NLEM). Lastly, the concept of expected value of information is introduced as a way to determine whether delaying decision-making at the expense of further research to avoid the parameter uncertainty is a valid decision.

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

Deterministic sensitivity analysis (DSA)

The primary objective of conducting a deterministic sensitivity analysis (DSA) is to examine the direction and magnitude of any possible changes in the study result over a reasonable fixed range, such as range, standard deviation, and 95% confidence interval of the model parameters. The simplest approach is to use a one-way SA, which determines the sensitivity of the result by examining variation between parameters, one by one[7]. Tornado diagrams (Fig. 1) are a very useful tool for illustrating the degree of the result sensitivity with respect to uncertainty in each parameter.

In Fig. 1, the vertical line represents the point estimate (606,000 Baht/quality-adjusted life year, QALY) of the incremental cost-effectiveness ratio (ICER) obtained from a reference (or base case) analysis when adding a monoclonal antibody (rituximab) to the conventional chemotherapy (CHOP) for non-Hodgkin lymphoma[8]. The length of each horizontal bar reflects the extent to which the study result would vary in accordance with a change in the model parameter on the vertical axis, given all other things being constant (as in the reference case). The most influential parameter stays at the top most (i.e. relative efficacy of rituximab on clinical response), whereas the least influential

parameter (i.e. relative risk for cancer relapse) stays at the bottom.

Threshold analysis

Threshold analysis is an approach that is used to determine the threshold value of a given parameter that would result in one treatment option being more cost-effective than the other. The analysis result can be described using a narrative text, for example 'The ICER of …(option A)… is less than … Baht/QALY as long as …(parameter X)… is higher than …'; or '… (option A)… is more cost-effective than …(option B)… as long as …(parameter X)… is higher than …'.

It is not uncommon to find that a medicine's unit price (or acquisition cost) can significantly influence the sensitivity of the analysis result. The cost-effectiveness of the treatment of interest can be analysed against the willingness to pay (WTP) threshold of societies[9]. In this paper, the threshold of 120,000 Baht/QALY, the NLEM-recommended level at the time the paper was written, is used[10]. In late 2013, the NLEM committee recommended raising the GNI to 160,000 Baht/QALY)[11]. The Thai Office of the National Economic and Social Development Board reported that the average national income was 153,952 Baht in 2010, according to data garnered using chain volume measures[12]. In July 2011, Thailand was reclassified as an upper, middle-income country, as the per capita GNI, calculated according to the World Bank's Atlas method, increased to USD 4,210[13]. Therefore, in cases where the reference case ICER is above the national threshold, a threshold analysis is recommended to determine the reduced unit price of medicines.

A multi-way SA is undertaken when two or more parameters need to be taken into consideration at the same time. A graphical approach is very useful when presenting the results of a multi-way SA. Fig. 2 depicts the threshold plot using a two-way SA with three treatment options, A, B, and C. Contour lines represent the combined threshold values of two model parameters (horizontal axis for X and vertical axis for Y) that would clarify which one of the three options was most cost-effective at a certain WTP level.

Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis (PSA) is increasingly becoming regarded as an indispensable tool in models where parameters are derived from research findings and individual databases, which are prone to uncertainty[14-16]. An analysis of the economic evaluation model results can be repeated using random sampling of the model parameters based on appropriate assumptions of the data distribution.

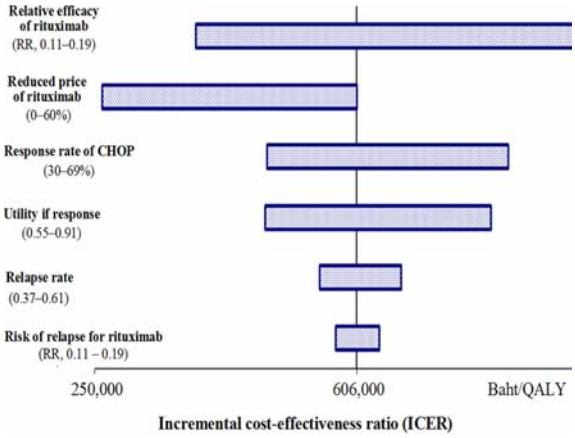

Fig. 1 Sensitivity of ICER for rituximab in non-Hodgkin lymphoma with respect to variations in drug efficacy, price and utility[8].

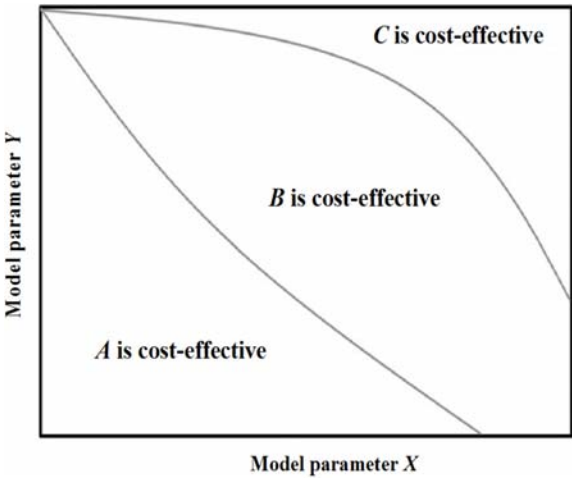

Fig. 2 Two-way threshold plot for three treatment options (A, B and C) Source: adapted from[3].

Cost-effectiveness (CE) plane

Results from PSAs are usually presented initially using a CE plane, a two-dimensional diagram with four quadrants that gives an estimate of incremental cost (vertical axis) and incremental effectiveness (horizontal axis). Results of the PSAs are plotted on the diagram so that incremental cost and incremental effectiveness of the treatment of interest can be compared with a comparator, which is set at the 0-0 coordinate (origin). The slope of the straight line that connects the comparator at the origin and the treatment in quadrant 1 gives the ICER. This ICER value should

not be presented as valid if its value is less than zero, because while numerically valid, the implications for drawing conclusions from a negative ICER are likely to be vague or misleading. When results from the treatment of interest are located in either quadrant 2 (i.e. more effective and less costly) or quadrant 4 (less effective and more costly), this in itself is a clear indication of the treatment of interest's superiority or inferiority[17,18].

Fig. 3 shows the results of an economic evaluation of gefitinib as compared with docetaxel in treating non-small cell lung cancer. The analysis comprised 1,000 repetitions of PSA[19], and the scatter of dots around the point estimate of the reference case reflect parameter uncertainty.

The vertical and horizontal dash lines in Fig. 3 that pass through the origin indicate that the total effectiveness (measured in QALYs) and total cost (measured in thousands of baht) of gefitinib are the same as those of docetaxel, the comparator. The result representing a reference case in quadrant 1 indicates that gefitinib is more effective and is more costly than docetaxel by approximately 0.06 QALY and 88.5 thousand baht, respectively, yielding an ICER of approximately 1.5 million baht/QALY[18].

The PSA that resulted in 1,000 dots in quadrants 1 and 2 suggests that gefitinib is always more effective than docetaxel. However, some PSA repetitions show gefitinib to be less costly (falling in quadrant 2) and some show it to be more costly (falling in quadrant 1) than docetaxel.

When the WTP threshold is greater than zero, the proportion of the dots below the level that indicates that gefitinib is cost-saving increases. For a given WTP threshold, the probability that a treatment is found to be cost-saving can be calculated using a net benefit calculation that takes into account both net monetary benefit[15,20] and net health benefit[21].

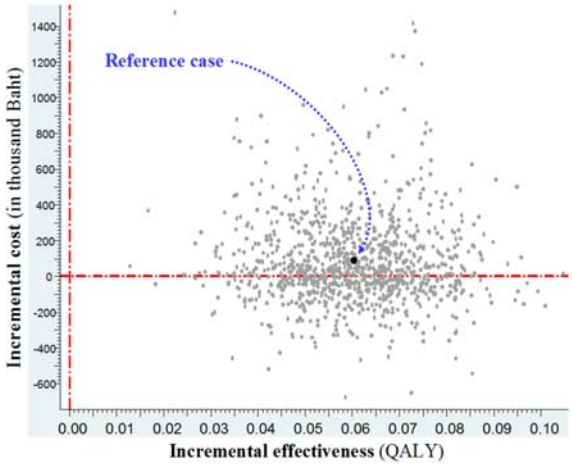

Fig. 3 CE plane of the incremental cost and effectiveness of gefitinib as compared with docetaxel from 1,000 repetitions of PSA[19].

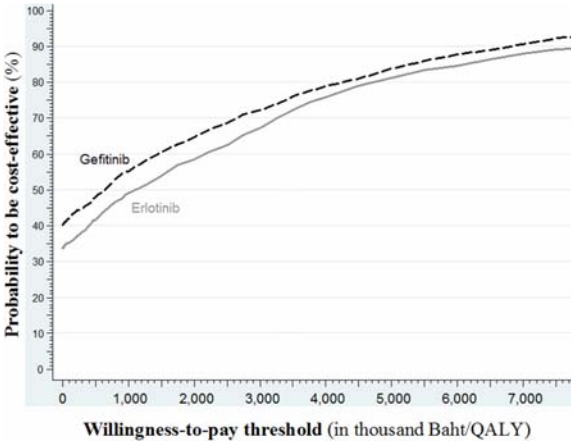

Fig. 4 Acceptability curves of gefitinib and erlotinib for treatment of non-small cell lung cancer[19].

Acceptability curve

The cost-effectiveness acceptability curve represents how change in the probability of a treatment being cost-effective relates to change in the WTP threshold (Fig. 4)[16,22].

The acceptability curve in Fig. 4 shows that there is a 40% probability that gefitinib is more effective and less costly than (or economically dominant over) docetaxel. The probability of gefitinib being found to be cost-effective increases gradually when the WTP increases. For instance, at WTP thresholds of 100,000; 300,000; 500,000, and 1,000,000 baht/QALY, the probability of gefitinib being found to be cost effective is 42%, 45%, 48% and 55% respectively. The fact that the acceptability curve for erlotinib is lower than that for gefitinib indicates that erlotinib is less cost-effective than gefitinib at the same WTP threshold.

Expected value of information

Where model parameters are uncertain, immediate decisions about whether a treatment should be regarded as optimal should be delayed while an assessment of the viability of further research to clarify the parameters is conducted. Uncertain parameters may lead to incorrect findings, which may contribute to a consequential loss. This kind of opportunity cost can

be calculated in terms of expected value of information[23], an approach that is widely used in decision analyses[24]. An overall loss resulting from a wrong decision due to all-parameter uncertainty is called the "expected value of perfect information" (EVPI). This is equal to the difference between the best payoff (namely, expected value with perfect information or EVwPI) and the expected value (EV) of making a decision when all the parameters are uncertain. Table 1 presents a calculation for the EVPI of three alternatives (A, B, and C), which result in outcomes X, Y, and Z.

A decision analysis conducted on the uncertainty of outcomes X, Y, and Z shows that option A is optimal, because it yields the maximum EV of 68,000 baht (EV_A = 200,000x0.3 + 40,000x0.5 - 60,000x0.2). Option B would yield a relatively lower EV of 42,000 baht (EV_B = 70,000x0.3 + 50,000x0.5 - 20,000x0.2), while Option C (for example, doing nothing) would yield the EV of 0 (zero).

If the probability for an outcome X, Y, and Z of 0.3, 0.5, and 0.2, respectively was known exactly, the maximum payoff among the three options for each outcome, which is equal to 200,000; 50,000, and 0 baht, respectively would yield the best payoff under this perfect information (EVwPI) of 85,000 baht (EVwPI = 200,000x0.3 + 50,000x0.5 + 0x0.2).

The EVPI is thus an opportunity cost incurred as a result of making the wrong decision under the current situation of data uncertainty, which is equal to the difference between the EVwPI and the EV_A (in this case, 85,000 - 68,000 = 17,000 baht). The EVPI suggests that the decision should be delayed until further study results can be obtained. If in this case, the cost of conducting further research is higher than the EVPI of 17,000 baht, option A should be chosen immediately.

Because EVPI is derived using a net benefit approach, it should be presented in the same way as an acceptability curve. Fig. 5 illustrates the relationship between the EVPI and various degrees of the WTP threshold.

As Fig. 5 shows, if societies place a monetary value of 40,000 baht on an additional gain of one QALY, the potential loss resulting from a wrong decision under the current parameter uncertainty would be 800,000 baht, the maximum. In this case, the decision should be delayed until further research can be conducted, as long as that research costs less than 800,000 baht.

If however, the WTP threshold per QALY is less than 30,000 baht or more than 60,000 baht (as is the case in the current threshold suggested by the NLEM subcommittee), the opportunity cost of making the wrong decision will be very low.

Table 1. EVwPI and EVPI under uncertainty of outcomes X, Y and Z

	Possible outcomes		
	X	Y	Z
Probability	0.3	0.5	0.2
Payoff (in baht)			
Option A	200,000	40,000	-60,000
Option B	70,000	50,000	-20,000
Option C	0	0	0

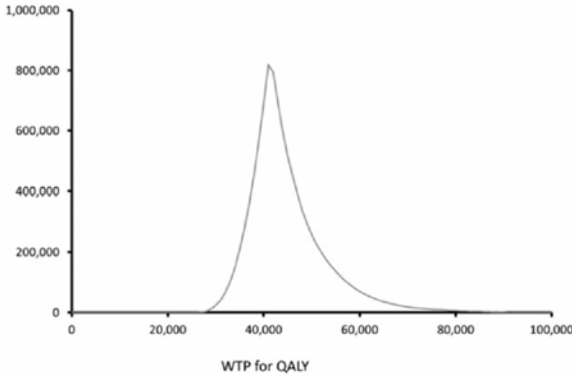

Fig. 5 EVPI (in baht) and WTP threshold (in baht/QALY)[3].

The potential loss due to uncertainty resulting from any given set of parameters can be expressed in terms of expected value of partial perfect information' (EVPPI). In practice, these parameters should be analysed as one common set if they are correlated[25,26]. If the EVPPI is found to be very high, further research on that particular set of parameters should be conducted.

Guidelines for Health Technology Assessment in Thailand (second edition): Recommendations for handling uncertainty in economic evaluations

In any economic evaluation that is based on a decision analysis model, SA should be reported alongside the reference case analysis. The simplest method for this is DSA, which can be part of either a one-way or multi-way SA. While a one-way SA, presented in the form of a tornado diagram, identifies each parameter that influences the analysis result, a threshold plot from the multi-way SA will help identify an appropriate decision threshold, where there are high

levels of uncertainty in the parameters.

When uncertainty arises from several parameters simultaneously, PSA should be conducted. At any given WTP threshold, the probability of a cost-effective treatment being cost-effective can be detected using an acceptability curve. To delay a decision under the uncertainty while pursuing further research to obtain better data (where economically appropriate), an estimation of the expected value of information is helpful.

Acknowledgement

The development of these guidelines would not have been possible without the technical support, challenging criticism and encouragement of many colleagues and institutions. As author, I wish to acknowledge all individuals and related organizations that contributed throughout the process for guideline development. In addition, I would like to give particular thanks to the funding support through the Health Intervention and Technology Assessment Program (HITAP) from National Health Security Office, the Thailand Research Fund under the Senior Research Scholar on Health Technology Assessment (RTA5580010) and Thai Health Global Link Initiative Program (TGLIP), supported by Thai Health Promotion Foundation.

Potential conflicts of interest

None.

References

1. Limwattananon S. Handling uncertainty of the economic evaluation result: sensitivity analysis. J Med Assoc Thai 2008; 91 (Suppl 2): S59-65.
2. National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. London: NICE; 2008.
3. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—6. Value Health 2012; 15: 835-42.
4. Walker D, Fox-Rushby J. Allowing for uncertainty in economic evaluations: qualitative sensitivity analysis. Health Policy Plan 2001; 16: 435-43.
5. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. New York: Oxford University Press; 2006.
6. Claxton K. Exploring uncertainty in cost-effectiveness analysis. Pharmacoeconomics 2008; 26: 781-98.
7. Briggs AH, Gray AM. Handling uncertainty in economic evaluations of healthcare interventions. BMJ 1999; 319: 635-8.
8. Limwattananon C, Chansung K, Ratanachotpanich T, Waleekhachonlert O, Kijvithi P, Motanates S, et al. Cost-effectiveness of rituximab for diffused large B-cell lymphoma and follicular lymphoma. Research report for Pharmaco-economics Taskforce under Subcommittee on Development of National Lists of Essential Medicines. Khon Kaen: Khon Kaen University; 2012.
9. Gyrd-Hansen D. Willingness to pay for a QALY: theoretical and methodological issues. Pharmacoeconomics 2005; 23: 423-32.
10. Subcommittee on Development of National Lists of Essential Medicines. Appropriate threshold for Thailand. Meeting minutes, 9/2550. Nonthaburi: Food and Drug Administration; 2007.
11. Thavorncharoensap M, Leelahavarong P, Doungthipsirkul S, Sompitak S, Teerawattananon Y. Assessing a societal value for a ceiling threshold in Thailand. Nonthaburi: Health Intervention and Technology Assessment Program (HITAP), Ministry of Public Health; 2013.
12. Office of the National Economic and Social Development Board (ONESDB). National income of Thailand, chain volume measures: 1990-2010 edition. Bangkok: ONESDB; 2012.
13. World Bank. Thailand now an upper middle income economy [Internet]. Press Release, August 2, 2011 [cited 2012 Nov 6]. Available from: http://www.worldbank.org/en/news/2011/08/02/thailand-now-upper-middle-income-economy
14. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. Health Econ 1996; 5: 513-24.
15. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999; 18: 341-64.
16. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health 2002; 23: 377-401.
17. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ 1998; 7: 723-40.
18. Stinnett AA, Mullahy J. The negative side of cost-effectiveness analysis. JAMA 1997; 277: 1931-2.
19. Limwattananon S, Sukprasert U, Waleekhachonlert

O, Ratanachotpanich T, Kijvithi P, Motanates S, et al. Cost-effectiveness analysis and budget impact of erlotinib and gefitinib for non-small cell lung cancer after failure from first-line chemotherapy. Research report for Pharmaco-economics Taskforce under Subcommittee on Development of National Lists of Essential Medicines. Khon Kaen: Khon Kaen University; 2012.
20. Tambour M, Zethraeus N, Johannesson M. A note on confidence intervals in cost-effectiveness analysis. Int J Technol Assess Health Care 1998; 14: 467-71.
21. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998; 18: S68-S80.
22. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001; 10: 779-87.
23. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). Lancet 2002; 360: 711-5.
24. Raiffa H. Decision analysis: introductory lectures on choices under uncertainty. Reading, MA: Addison-Wesley; 1967.
25. Brennan A, Kharroubi S, O'hagan A, Chilcott J. Calculating partial expected value of perfect information via Monte Carlo sampling algorithms. Med Decis Making 2007; 27: 448-70.
26. Groot KB, Myriam Hunink MG, Stijnen T, Weinstein MC. Identifying key parameters in cost-effectiveness analysis using value of information: a comparison of methods. Health Econ 2006; 15: 383-92.

การวิเคราะห์ความไวสำหรับจัดการกับความไม่แน่นอนในการประเมินความคุ้มค่าทางสาธารณสุข

สุพล ลิมวัฒนานนท์

บทความนี้ให้ข้อเสนอแนะด้านการวิเคราะห์ความไวโดยปรับปรุงเนื้อหาเดิมที่ปรากฏ ในคู่มือประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทยฉบับล่าสุดเพื่อให้เป็นไปตามมาตรฐานสากลในปัจจุบัน บทความนี้ได้แนะนำวิธีวิเคราะห์ความไวทั้งแบบที่อาศัยและที่ไม่อาศัยความน่าจะเป็นในการจัดการกับความไม่แน่นอนของตัวแปร ในรูปแบบจำลองและเสนอแนะเพิ่มเติมอีก 2 ประเด็น ได้แก่ การหาราคาต่อหน่วยของยาที่จะทำให้เกิดความคุ้มค่าตามที่กำหนดในการคัดเลือกยาในบัญชียาหลักแห่งชาติและการประมาณค่าเสียโอกาส หากต้องการชะลอการตัดสินใจเพื่อให้ได้ข้อมูลที่มีความแน่นอนยิ่งขึ้น