Special Article

Measurement of Clinical Effects

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The measurement and valuation of clinical effects is a significant component of economic evaluation. Decision makers are commonly interested in how a particular health intervention works in everyday practice; therefore, the resulting outcome under this circumstance is called the effectiveness. Clinical effects usually measure final intended effects of a proposed health technology in terms of the ultimate change in health state brought about by the technology. The systematic review and meta-analysis of high quality RCTs is the most favorable method to synthesize evidence because they are disciplined and transparent methods. The present chapter focuses on how to make a valid measure of clinical effects for use in cost-effectiveness analysis and how clinical effect is to be appropriately defined and measured.

Keywords: *Clinical effects, Clinical evidence, Measure, Effectiveness*

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The measurement and valuation of clinical effects is a significant component of economic evaluation because economic evaluation seeks to inform decision makers about the net change in costs and clinical benefits arising from alternative approaches to providing a particular sort of care. However, it is always difficult to identify all the benefits and disadvantages of an intervention. Traditionally, health benefit has been measured using mortality parameters such as 'number of deaths averted' or 'life-years saved'. Since health is more than just being alive, its effects on morbidity are increasingly being taken into consideration[1].

When the benefits of alternative interventions are identical, or at least very similar, the cost-effectiveness analysis is equivalent to the cost-minimization approach. Under these circumstances, there is no need to measure the clinical benefits as the intervention with the least cost is the most cost-effective. Unfortunately, this situation seldom arises, in part because of the uncertainty that usually exists around the estimates of benefits that require a full investigation of the uncertainty[2].

Where the benefit of competing interventions can be measured along a single dimension, cost-effectiveness analysis can be used to rank interventions in terms of their ratios of cost per unit of effect. Some economic evaluation studies include 'surrogate measures', for example, a reduction in left ventricular size, a reduction in mmHg of blood pressure or improvements in bone mineral density, however, these surrogate measures should be avoided. The use of surrogate measures could limit the full application of economic evaluation studies, since these studies aim to inform decision makers about the trade-off between health investment and its outputs that contributes to overall welfare (welfarists) or health itself (extra-welfarist), not on said surrogate indicators. As a result, the clinical effects used in economic evaluation studies are usually measured in terms of 'life-years saved' for treatments, or 'number of cases detected' for screening programs[3].

The advantages of cost-effectiveness analysis are that the benefits or outcomes of health care programs are explicitly measured and the units of measurement are easy to understand and readily

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accepted by both the public and medical professionals. However, one of its disadvantages is that a single physical measure (such as life-years saved) is unlikely to capture all the dimensions of the benefits of interventions. Some interventions may not save many lives but may reduce pain or otherwise increase the quality of life. Another problem arises because units of measurement vary from program to program; it is difficult to compare the relative effectiveness of programs with different outcomes. As a consequence, there now exists a number of approaches which combine morbidity and mortality dimensions into a composite measure, namely Quality Adjusted Life Year (QALY) or Disability Adjusted Life Year (DALY). This in turn leads to the development of cost-utility analysis.

The present article focuses on how to make a valid measure of clinical effects for use in cost-effectiveness analysis while another article examines the more specific issues of valuing health consequences, health state preference scores and utility weights. Specifically, this chapter addresses a number of important questions; namely, how clinical effects are to be defined and measured.

Efficacy vs. effectiveness

The British pioneer clinical epidemiologist Archie Cochrane defined "efficacy" as the extent to which an intervention does more good than harm under ideal circumstances ("Can it work?"), and "effectiveness" as the extent to which an intervention does more good than harm when provided under the usual circumstances of healthcare practice ("Does it work in practice?")[4]. For instance, in randomized controlled clinical studies, researchers seek to test the effects of health technology under standardized conditions by reducing the systematic effects of other factors which can influence the outcome of the technology. These effects are usually gauged as efficacy. In clinical practice, however, there will often be a number of factors which contribute to an outcome which differs from that from testing done in random clinical studies. The resulting outcome under this circumstance is called effectiveness.

Decision makers are commonly interested in how a particular intervention works in everyday practice. Economic evaluation should, therefore, measure the effectiveness found in a clinical everyday setting rather than the efficacy achieved in a well-controlled experimental setting[5-8].

During the past ten years, one of the growing trends in this evaluation has been the incorporation of economic evaluations alongside randomized controlled trials of healthcare interventions. Frequently, these assessments are incorporated into the drug development process; phase III, during which a drug's efficacy is evaluated prior to regulatory approval, and phase IV, which occurs after the drug is marketed[9]. This poses big challenges to researchers, for example, whether any adjustments should be made on clinical effects and costs to increase the relevance of economic evaluation studies that are comparable to real-life clinical practices. Some researchers suggested the use of modeling approaches such as decision trees or Markov models to estimate the consequences and costs of the health technology as they would appear in general practice. If this is the case, the conditions, assumptions and data used to create the basis for the models must be clearly presented in such a manner as to make them relevant, understandable and re-examinable. The data basis used must be as relevant as possible with regard to the indication and treatment context of the drug in clinical practice.

Intermediate vs. final outcomes

Although there are no limits to the types of measures of clinical effects included in economic evaluation studies, the surrogate outcome indicators[1], such as a reduction in left ventricular size or a reduction in blood pressure, may themselves sometimes have some value or clinical meaning. It is widely accepted that economic evaluation should use a final outcome as its effectiveness measure[10,11]. Researchers should consider the final intended effects of the proposed health technology in terms of the ultimate change in health state brought about by the technology because this information will provide meaningful guidance to policy makers in making broad resource allocation decisions. For instance, the ultimate aim of lowering moderately elevated blood pressure is to prevent death and impaired quality of life from a stroke or possibly a myocardial infarction. The ultimate aim of treating a patient with severe asthma is to prevent death, to prevent hospitalization and to return the patient to a normal level of functioning.

However, results on health improvement are obtained from experimental studies that usually report short-term or surrogate clinical outcomes since only a few clinical trials are large enough to measure changes in final outcomes. In this case, if relationships have been established, or have been proposed, between surrogate and final outcome indicators, the use of decision modeling may be necessary for the extrapolation

of short-term or surrogate clinical outcomes to long-term or final health benefits. The form of the relationships, which have been established between the surrogate and final outcomes may vary according to whether the data was derived from longitudinal studies or randomized trials. Examples include blood pressure and blood cholesterol and incidence of acute coronary syndrome; level of prostate-specific antigen and survival from prostate cancer; and serological liver function tests and the cure of viral hepatitis.

Quality of evidence

The process of obtaining efficacy or effectiveness data can present its challenges. In practice, the preferred source of data is dependent on the complexity of the question being investigated. Researchers must think carefully about the economic question at hand and the most appropriate sources of data for that question. Generally, there are different ways of gathering the effectiveness of a health intervention in economic evaluation[5]. These include:

- incorporating economic evaluation within a randomized controlled trial (RCT);
- using information from RCT, observational cohort or case-control studies;
- combining or modeling data from a variety of studies

As there are a growing number of RCT-based economic studies, the International Society for Pharmacoeconomics and Outcome Research (ISPOR) has recently developed a guidance document for the design, conduct, and reporting of cost-effectiveness analyses conducted as a part of clinical trials[12]. An advantage of incorporating economic evaluation within RCT is that the method allows for the prospective collection of cost and effectiveness data from a single source.

If well-designed and properly executed, RCTs are believed to provide the best evidence on the outcome of health care interventions. However, results from an RCT usually represent the efficacy of an intervention but not necessarily its effectiveness[6]. There are some exceptions where effectiveness studies use pragmatic designs in normal health care settings. In addition, the patient inclusion and exclusion criteria of the trial may limit the generalizability of the results; fully correcting these biases in economic evaluation is problematic[5]. However, RCTs have drawbacks too. Besides the issues of external validity, another limitation is that an RCT cannot be used in some instances such as intentional exposure to harmful substances[13]. In addition, an RCT conducted for social intervention or policy intervention is quite limited, when compared to medical intervention, in terms of the number of studies that can be conducted. In contrast to RCTs, data from observational studies is more prone to being confounded[5].

Synthesis methods are generally recommended as an alternative where there is insufficient data from any one source[5,6,8,14]. Combining data from a variety of studies can also increase the power to detect true effects, improve the precision of the estimate of effect size and also increase generalizability for applying results across settings[6]. Meta-analysis is a process of combining study results in such a way as to be able to draw conclusions about the efficacy/effectiveness of health technology. It can also highlight advantages and disadvantages of the proposed health technology and its comparators which are too small to be detected accurately in individual trials. However, it has been argued that there is potential for bias if the study is not based on the best available effectiveness data.

Table 1. Levels of clinical evidence

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case control or cohort studies. High-quality case control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+	Well-conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3	Non-analytic studies: for example, case reports, case series.
4	Expert opinion.

Source: Based on Sackett and others (Canadian Task Force on the Periodic Health Examination)[17]

Even though several measures, namely Relative Risk (RR), Odd ratio (OR) and Absolute risk reduction (ARR) have been widely used to measure clinical outcomes for economic evaluation, the use of Number-Needed-To-Treat (NNT) is not recommended[15]. NNT, the reciprocal of the ARR, expresses the number of patients that need to be treated for a period of time for one less adverse event to be observed at a specific point in time. Although the economic evaluation based on NNT can be conducted so as to calculate the cost per avoided treatment by multiplying the treatment cost per patient by NNT, the results of this analysis may yield biased, misleading information, and are better avoided[15]. The major limitation of using NNT in economic evaluation stems from that fact that an effect measure with one dimension (survival probability) cannot capture an effect with two dimensions such as time and survival probability. These limitations, therefore, affect the chance of correctly accounting for all costs and benefits and their timing, and hence reduce the ability for such evaluations to serve as a useful tool in the decision making processes[15].

Recommendations for Thai Health Technology Assessment (HTA) Guidelines

This guideline recommends that clinical effectiveness should be used in economic evaluation studies rather than clinical efficacy, derived under highly controlled circumstances. Outcome measures should include the final intended effects of the proposed health technology in terms of the ultimate change in health state brought about by the technology while the use of surrogate indicators and NNT should be avoided.

The efficacy or effectiveness data should be obtained in a systematic and transparent way. Researchers must make the presentation of the data transparent and explain the rationale for the source of the data used in the study. The inclusion of grey literature, such as research reports, master dissertations or Ph.D. theses is also considered to be very important in the Thai context.

The systematic review and meta-analysis of high quality RCTs is the most favorable method to synthesize evidence. The advantages of using systematic reviews of clinical effects are twofold[16]. First, a more precise estimate can be attained from combining the outcome data from a number of studies. Second, by using the results from studies carried out in a range of settings, assuming that these studies are sufficiently homogenous to be comparable, the estimate can then be applied to a more general patient population with different baseline risks, rather than specifically for a population group selected for an individual trial.

Where the meta-analysis of RCT is impossible for particular reasons, then evidence available in a higher hierarchy should be selected, based on the Table 1, which presents the broad agreement on the level of clinical evidence.

Moreover, the use of modeling in economic evaluation is acceptable. As recommended in various guidelines, the use of modeling methods should be considered where: (i) trial samples are not consistent with the typical patients likely to use the intervention within the context of the economic evaluation; (ii) the extrapolation of a short term clinical trial to ultimate health effects is needed; and (iii) relevant comparators have not been used or the trial did not include evidence on the relevant subgroups[5,14,18,19]. It is noteworthy that the model should be used in a transparent way but not as a replacement for scientific evidence. Transparency of selection and a clear statement describing the choice of input parameters in a model is very important. The conditions, assumptions and data creating the basis for the economic models must be clearly presented in such a manner as to make them relevant, understandable and re-examinable.

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การวัดผลได้ทางคลินิก

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การวัดและการประเมินผลได้ทางคลินิก เป็นส่วนประกอบสำคัญของการประเมินความคุ้มค่าทางการแพทย์ โดยทั่วไปผู้ตัดสินใจมักสนใจว่ามาตรการทางสุขภาพนั้นๆ สามารถนำมาใช้ในเวชปฏิบัติประจำวันได้อย่างไร ดังนั้น ผลลัพธ์ที่เกิดขึ้นภายใต้สภาวการณ์เช่นนี้ จึงเรียกว่าการวัดประสิทธิผลทางคลินิก ผลลัพธ์ทางคลินิกควรวัดผลลัพธ์สุดท้ายที่เกิดจากการใช้เทคโนโลยีด้านสุขภาพนั้น ๆ โดยวัดจากผลการเปลี่ยนแปลงสุดท้ายของสภาวะทางสุขภาพอันเนื่องมาจากเทคโนโลยีด้านสุขภาพ การทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) และการวิเคราะห์อภิมาน (meta-analysis) ของการศึกษาแบบสุ่มทางคลินิก (RCT) ที่มีคุณภาพ เป็นวิธีการที่ดีที่สุดในการสังเคราะห์หลักฐานทางคลินิก เนื่องจากเป็นวิธีการที่มีระเบียบแบบแผนและมีความโปร่งใส บทความนี้จะกล่าวถึงผลลัพธ์ทางคลินิกที่มีความน่าเชื่อถือสำหรับวิเคราะห์ต้นทุนประสิทธิผลรวมถึงการระบุและวัดผลลัพธ์ทางคลินิกอย่างเหมาะสม