Guidelines of Methodological Standards for Pharmacoeconomic Evaluations in Taiwan

(Version 1.0)

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I. Brief Introduction

The economic evaluation of an intervention should describe, analyze, and compare costs and consequence of the alternative interventions. If the economic evaluation examines medications and medical devices, then the term "pharmacoeconomic evaluation" should be used, even if the comparator is no treatment at all, or non-pharmacological treatment. But the economic evaluation can also be applied to interventions of other health technologies, including diagnostics or medical/surgical treatments, etc.

A pharmacoeconomic evaluation can identify whether a medication possesses additional value—that is, if the medication, compared to a current treatment, can increase monetary benefits and/or effectiveness. Therefore, evidence must be provided to justify the health insurance organization reimbursing a new medication or revising current reimbursement guidance. An important idea is that a cost-effective medication may increase both health benefits and health care costs, or provide the same health effects for a lower cost. Therefore, increases in the cost-effectiveness of health technologies may or may not decrease medical expenditures, but will in subsequence increase health effects per dollar spent. The purpose of pharmacoeconomic evaluations is to provide data as reference for the decision makers, so that they can make decisions based on more credible and valid information, and therefore decide the most efficient allocation of medical resources.

"Guidelines of Methodological Standards for Pharmacoeconomic Evaluations" has been developed to provide a methodological standard for conducting pharmacoeconomic evaluations. By adhering to the guidelines, results of pharmacoeconomic evaluations will be considered reliable by the health insurance organization. For example, when a pharmaceutical manufacturer has a new product and intends to carry out an economic evaluation based on the settings in Taiwan, it is recommended that the evaluation be carried out by following the guidelines and is reported according to the suggested report format.

The guidelines of methodological standards can be applied to the following situations: designing and conducting an economic evaluation of a new health technology, reviewing the result of the evaluation, and applying the result to the real clinical practice setting. Therefore, researchers, reviewers, and users of clinical personnel must all be familiar with the standard methodologies of pharmacoeconomic evaluations. Every suggestion in the methodological standards guidelines offers some specific evaluation methods to choose from, so that the comparability of the evaluation results can be maximized, and the possibility of misinterpreting the results can be minimized. But these methodological

standards are not intended to limit the creativity of researchers, nor are a complete conformability with these methodological standards demanded. The guidelines are not intended to prevent innovation in methodologies from producing, or to limit the freedom of scientific research.

Although literature on the subject has established some consensus in methodological standards for economic evaluations, there are many controversial issues in this field. Partly this is because the field is new and developing, methodologies of cost measurement and quality-of-life measurement are still in development. So it is worthwhile to reach consensus on methodological standards in order to thereby reduce the possibility of controversy.

Many nations with established pharmacoeconomic evaluation methodological standards guidelines use such guidelines as principles and guidance for conducting such studies, but not as administrative laws to stipulate how to carry out the evaluations. Therefore, the principles may not be complete, and nor are they compulsory. Adopting other methods can be acceptable as long as proper explanations are provided, and the authenticity can be verified by evidence. The established "Guidelines of Methodological Standards for Pharmacoeconomic Evaluations" are an excellent standard for conducting evaluations. The guidelines are expected to be extensively applied to different medical institutions, diseases, and health technologies, including medicines, biological products, medical devices, diagnostic technology or medical treatment, etc.

In addition to pharmacoeconomic evaluations, the health insurance organization may also need to know in depth the extent of the financial impact if a new medicine is listed in the formulary. The budget impact analysis is listed in Guideline 22. But this is not a part of pharmacoeconomic evaluations and this analysis can become an independent guideline of methodological standards.

II. Guidelines for Pharmacoeconomic Evaluation

The guidelines for pharmacoeconomic evaluation consist of 22 principles altogether, which present the methods extensively used at present. Researchers, reviewers and users of clinical personnel should all refer to them. The description under each guideline provides adequate explanation and points out which field of health care policy the guideline applies to.

Guideline 1. Target Audience

The target audience of pharmacoeconomic evaluations must be identified, likely including the health insurance organization, the patient, the prescribing physician, the hospital, or the researcher.

Description:

In Taiwan, the pharmaceutical group, which the Bureau of National Health Insurance (BNHI) has established, is responsible for evaluating pharmaceutical products and putting forward the suggestion whether or not the product is reimbursed by the health insurance program. The suggestion is provided to the general manager of the BNHI, who decides whether the pharmaceutical product is to be listed in the positive listing of the formulary. When a doctor uses a pharmaceutical product listed in the positive listing, he can get payment from the BNHI. Pharmacoeconomic evaluations can provide in-depth assessment of costs and effectiveness/benefit of medications. The information and data of the analyses can be referred to for other audiences to decide whether to adopt the cost-effective medication. As the costs taken into consideration by different target audiences may be different, any plan of pharmacoeconomic evaluations must first identify a target audience, and measure costs relevant to the target audience.

Guideline 2. The Perspective

Pharmacoeconomic evaluations are recommended to be conducted and reported from the societal perspective; then analyses for different target audiences are presented separately.

Description:

The societal perspective means that evaluations must include all the costs and benefits, no matter who actually bears the cost or gets the benefit. This means that all costs and benefits outside the health insurance payment system must also be considered. Any direct or indirect cost outside the health insurance payment system must be presented and calculated separately. Therefore, there are three categories of analysis results to be

displayed: (1) direct costs in the health insurance payment system (the perspective of the BNHI); (2) costs in (1) plus direct costs not paid for by the health insurance payment system (the perspective of healthcare system); and (3) costs in (2) plus indirect costs outside the health insurance payment system (the societal perspective).

Guideline 3. Timing of Studies

Pharmacoeconomic evaluations can be conducted in any phase of a clinical trial for a new medicine (usually in phase II, phase III or phase IV).

Description:

The timing over which economic evaluations are conducted depends on a user's needs. In early phases of the research and development of a new drug, a pharmaceutical manufacturer may conduct evaluations to decide the clinical research in phase III or phase IV and draw up marketing strategies. Economic evaluations that are conducted during phase III clinical trials can be of importance to help determine whether to list a drug and its price in the early stages of a life cycle of the drug. Economic evaluations conducted in Phase IV, the post-marketing phase, can provide the latest information on effectiveness, utilization patterns, and incidences of side effects of a drug after it is used in real-world settings. Sometimes, phase IV research is initiated by a medical institution or a research institution to develop better clinical treatment guidelines, to help determine the formulary for certain disease, or to assist in deciding the formulary for certain medications or for specific patient groups.

Guideline 4. Disclosure of Relationships

Pharmacoeconomic evaluations can be conducted by any qualified researchers. However, all companies who conduct such research and the relationship between them and the consignor (usually the pharmaceutical manufacturer of the product) must be made public and transparent.

Description:

In principle, pharmacoeconomic evaluations can be carried out by industry, academics, consulting companies, independent specialists, or any combination of these. A qualified researcher is one who possesses the training and experience in research, is familiar with the research background and requirements, and conforms to the excellent moral standards of the specialty. The research plan must conform to the professional moral standards of the specialty and the requirements of the guidelines.

The relationship between those who provide funding and those who write the report, between sponsors and each researcher making evaluations, must be described clearly in a contract. If more than one research team works on any part of a report, then what they contribute and their relationship with other researchers must be made explicit. Therefore, in a cooperation contract, the following must be described clearly for reference: financial affairs, copyright on publications, other conditions and letters of consent, etc. Researchers of the evaluations must think independently in the methodologies for every phase of the research and must have the copyright in the journal they choose. Disclosure of the relationships can be reached by providing a copy of the (standard) contract.

Guideline 5. Evaluation Techniques

If a new drug has higher therapeutic value as compared with conventional treatment(s), cost-effectiveness analysis (CEA) and/or cost utility analysis (CUA) are recommended, depending on the expected outcomes of the drug, and the disease.

Description:

In general, information required for an economic evaluation can be collected through the adoption of one of four different research designs: (1) "Piggyback" evaluations: data on costs and quality of life required for an economic evaluation are collected alongside a clinical trial which typically examines efficacy and safety. (2) Naturalistic trials: the economic evaluations are conducted in real-world practice and settings. (3) Integrated research: the research aims to integrate the data of many study results (meta-analysis) or data which is obtained by analyzing a large database. (4) Research carried out by using mathematical or statistical models.

For a new medicine, a clinical trial aims to verify the safety and efficacy of the medicine. If a drug has higher therapeutic value compared with other medications, economic evaluations can be conducted to identify costs relevant to the drug, and the relationship between the costs and the additional therapeutic value. The evaluations take into account all aspects of the treatment, including its side effects and the treatment costs of the side effects. In pharmacoeconomic evaluations, an incremental analysis is necessary to examine the additional costs and additional effects when treatment A is replaced by treatment B.

Pharmacoeconomic evaluations have several analytical methods to be adopted as follows: cost-consequences analysis (CCA), cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) or cost-benefit analysis (CBA).

Cost-consequences Analysis (CCA)

Cost-consequences analysis is an analytical method which does not integrate different treatment effect indicators into one common indicator. This method displays information on various effects of a drug therapy or a health care intervention. This is the simplest analysis in concept. In general, because CCA reports the effects of a new therapy in a most complete and transparent way, decision makers can choose the most favorable effect indicator for their needs. CCA can give them assurance that their decisions on medical resource allocation are supported by the credible data.

Cost-minimization Analysis (CMA)

If clinical effectiveness of a new drug is similar or equivalent to that of its comparator, then consider using cost-minimization analysis. This method compares the costs of the two treatments.

Cost-effectiveness Analysis (CEA)

In the analytical method, the clinical outcomes are measured in appropriate physical units, and outcomes and costs of two treatments are compared. There are a variety of measurement units for effectiveness, such as reduction in blood pressure, deaths averted, and additional life-years gained, etc. In cost-effectiveness analysis, it would be better to link intermediate outcomes such as blood pressure to final outcomes such as life-years gained.

Cost-utility Analysis (CUA)

In fact, cost-utility analysis (CUA) is a metamorphosis from cost-effectiveness analysis. In CUA, the measurement unit of effect is quality-adjusted life-years (QALYs). QALYs incorporate changes in life years and quality of life (mortality rate and incidence) into a single measure. In principle, QALYs are independent of types of health care interventions and disease progression. The measurement of the quality of life requires instruments to measure utility values. The utility values need to reflect preferences of society—that is, to value life years and quality of life from the societal perspective.

Cost-benefit Analysis (CBA)

In cost-benefit analysis, both costs and benefits are measured in monetary values. Therefore, different interventions can be comprehensively compared by the same unit.

Because only new drugs with additional therapeutic values are worth conducting economic evaluations, cost-minimization analysis is seldom used for new drugs. However, it is likely used to assess market competition for off-patent drugs. In cost-benefit analysis, willingness-to-pay (WTP) is thought as the best method at present to calculate the monetary value of the effect. But the method is still in development, and currently there is no consensus with respect to the most appropriate method of measurement. Therefore, it is considered insufficient to conduct cost-benefit analysis only. For economic evaluations of new drugs, it is suggested that results be reported based on cost-effectiveness analysis or

cost-utility analysis.

Guideline 6. Indications and Population under Evaluation

Pharmacoeconomic evaluations usually aim to assess approved main indications of drugs of interest, and the target patient groups must be explicitly indicated in the contents of the evaluations. Moreover, if subgroup analysis will be conducted, specify patient groupings, different disease patterns, disease severity, and comorbidities, etc. Economic evaluations have to be carried out for the entire patient group of the study, and for the subgroups specified by the study. The subgroups can be selected according to possible differences in clinical effect, costs, or other controversial issues.

Description:

In the research plan of pharmacoeconomic evaluations, it is necessary to specify the covered indication(s) of the plan: all approved indications, a part of the indications, or subgroups of certain indications.

The group selected for pharmacoeconomic evaluation or modeling must be representative of the population who will receive the drug in real-world clinical practice in the future. To be completely transparent, describe explicitly the target population, including the prevalence of the indication, diagnostic techniques, severity of the disease, and distribution of the age and sex of the patients. Other relevant factors are included as follows: mortality rate, whether there is any comorbidity, concurrent treatments, disease distribution in different regions, and distribution of socioeconomic groups. Estimate how many will receive the medicine in Taiwan, including the prevalence and incidence.

If the drug is considered more cost-effective when used in a specific subgroup of the patient population than in the entire patient population, define the subgroup in the study plan – for example, men or women of different age levels, different severities of the disease, and different degrees of risk. There should be results of clinical trials conducted in the subgroup available, along with different effects and safety profiles.

The purpose of pharmacoeconomic evaluation is to identify in which patient groups or in which indication(s) the use of the drug is cost-effective. The evaluation aims to confirm cost-effectiveness of the use of the drug, rather than that of the drug itself. From that perspective, the result will likely recommend to limit the use of the drug to a smaller range of certain approved indications.

Guideline 7. Choice of Comparative Treatment

Pharmacoeconomic evaluations should involve a comparison of treatment options. In

principle, the comparator can be what is most likely to be replaced by the drug in clinical practice. It can be another drug, a surgery, or no treatment.

Description:

The economic evaluation of a medicine is always built upon comparison with other treatments. The result of the economic evaluation is significantly influenced by the choice of comparative treatments. Therefore, choosing the correct comparative group is important not only for economic evaluation, but also for evaluating the therapeutic value of the medicine. It is recommended to choose the comparative treatment by following the guidelines and evaluation procedures. However, explain clearly the reason for the choice of comparative treatment. A precondition is: the comparative treatment and the new medicine must have the same patient population and indication.

In Taiwan, as to choosing a comparative treatment, proceed according to the following principles. If a new medicine belongs to an existing category of medicines, the most frequently prescribed medicine in this category should be chosen as the comparator. If a new medicine belongs to a new category of medicines, and there are medicines of other categories used for the same indication, then the most frequently prescribed medicine among them should be chosen as the comparator.

Other comparative treatments that can be taken into consideration include: the medicine of first choice in clinical practice (its efficacy has been verified), or the most effective medicine. The comparator may not be a medicine—for example, a surgical practice, or even no treatment (using a placebo).

The dosage, usage, duration, efficacy, and side-effect profile of the chosen comparator must be in the range of approved indication, and can reflect the use of the medicine in clinical practice. Further explanation is required if they deviate from the common usage of the comparator in clinical practice.

It is possible to encounter some questions during the application of this guideline. The physician's prescribing behavior and the therapeutic value of a medicine may change over time, which means that the most appropriate comparative treatment may not be the same at different time points. The most appropriate comparative treatment in a phase III randomized controlled trial may not be the most suitable comparator when the trial is over, or when the medicine is approved for market. In addition, it is equally important that the clinical trial of a new medicine has characteristics that reflect international clinical practices. While choosing a comparative treatment, a pharmaceutical manufacturer cannot consider viewpoints of various countries or every possible situation. Therefore, the chosen comparator may not be an appropriate or the best treatment choice in Taiwan. If the results of pharmacoeconomic evaluations should be applied to the settings in Taiwan, the choice of comparative treatment must satisfy the circumstances in Taiwan.

The report of a pharmacoeconomic evaluation must include a section discussing how the comparative treatment is chosen, and should bring up the description or evidence to show that the choice of comparative treatment is appropriate.

Guideline 8. Incremental and Total Analysis

Present the cost and effect in the form of incremental value, which means the differences in cost and effect between two treatments. The evaluation must also provide all details and total values for the costs and effects of the two treatments.

Description:

All pharmacoeconomic evaluations should be comparative and use incremental terms to present results—that is, if intervention "B" replaces intervention "A", what is the extent of the differences in cost and effect. Based on incremental analysis, we can observe not only the differences in cost and effect but also the ratio of the differences after the conventional treatment is replaced by the new medicine.

In addition to incremental analysis, it is very useful to report the total cost and total effect of every treatment. By total values, a user can understand clearly the quantities involved, which cannot be found out from the differences and the ratio of the differences. The total values will also increase comparability between the research result and other study results reported in the future. Therefore a future user can update the information while comparing newer treatment, or comparing the research of different regions or practice settings.

Guideline 9. Time Horizon

The time horizon of an evaluation must be long enough to present all relevant costs and effects, so that a reliable conclusion can be reached. If a model is adopted to meet the requirements, both the structure and theoretical basis of the model need to be described clearly. When such an evaluation is conducted, the analytical model should be supported by strong scientific evidence.

Description:

The time horizon represents a time range from the beginning to the end of the observation period of an economic evaluation. Costs and effects of a therapy within the time range must be measured. The time range must be long enough to reveal all relevant health outcomes and use of resources for all treatments. The expected time range is determined by treatment objectives, i.e., expected treatment effects.

Because lengths of follow-up of clinical trials are sometimes too short to show long-term treatment effects, an economic model is necessary to predict the long-term treatment outcomes. To assure that users of the study results can confirm the consistency and analyze the reliability of the results, both the methodology adopted and assumptions made for analyses in the model must be explained explicitly. Sometimes a study may analyze the available information based on more than one time horizon – for example, a short-term analysis based on data from a clinical trial, and a long-term analysis based on modeled data.

Guideline 10. Efficacy versus Effectiveness

Ideally, pharmacoeconomic evaluations are to show the effectiveness rather than the efficacy of a medicine. Do the best to collect information of morbidity and mortality in the real-world practice settings. If there is no effectiveness data, use adequate modeling techniques to transform efficacy data from clinical trials to effectiveness data expected in the real-world practice settings. All assumptions used in the model must be described in detail, and sensitivity analyses must be conducted.

Description:

Efficacy and effectiveness are two different concepts. Efficacy is the outcome of a medicine used in a highly controlled condition. Highly motivated research-oriented clinical personnel are responsible for drug administration and outcomes monitoring according to a written protocol with a strict study design. Subjects are patients who are carefully selected through strict inclusion and exclusion criteria, and agree to participate and cooperate in the trial. Effectiveness is the outcome of a medicine used in real-world practice settings. Patients with different severity levels and characteristics receive medications according to their clinical needs from physicians of different specialties. They have little knowledge of, and low compliance with the medications. Besides, the treatment outcomes may be interfered by comorbidities or concurrent use of other medications. These situations do not exist in a randomized controlled trial.

A pharmacoeconomic research faces a very important problem: when a medicine is just introduced into a market, there is only efficacy data available in medical literature. In any research conducted during this period, the effectiveness of the medication inevitably has to be inferred from the efficacy data of clinical trials. Economic models can be adopted to solve this problem. But for such research, the model adopted and all assumptions used in the model must be described in detail, and sensitivity analyses must be conducted.

Effectiveness research usually measures the final outcome of a treatment. Final outcomes are changes in health status – for example, an increased incidence of

well-controlled symptoms, a decreased incidence of a disease, increased incidences of some complications (problems with movement, cardiovascular events, hysterectomies, adverse drug reactions), a decreased crude mortality rate or mortality rate of a specific disease, increased life-years (increased survival rate or life-years), increased life years without disease or disability, or increased quality-adjusted life-years (QALYs). It is recommended that increased life-years and increased quality-adjusted life-years be used as outcome measurements, because they reflect overall improvement in health. It is not suggested that measurements such as the number of deaths avoided and number of lives saved should be adopted, especially when the survival rate is unknown, and quality of life in the future is expected to be low.

When a medicine is introduced to the market, health policy decision makers hope to obtain its effectiveness data, even though in practice this is usually impossible. Even though the results of Phase III clinical trials are required for pre-marketing registration and review, they are efficacy and safety data that are not ideal for pharmacoeconomic evaluations. After all, the environment of a clinical trial is different from that of real-world practice. If the time period from a medicine's being approved to its being listed in the BNHI formulary is too short, there will be no effectiveness research results. Another question is that in a clinical trial, the outcome measurements are usually intermediate endpoints (for example, the blood pressure dropping 5 mmHg) rather than final outcomes such as reduced mortality rate and morbidity rate that are required for pharmacoeconomic evaluations.

In order to state the effectiveness of a medicine, data from clinical trials can be applied to economic models using real and clear assumptions. All assumptions must be scientifically reviewed and explained in detail. The reliability and validity of important variables in the models must be examined.

Economic evaluations must be based on complete data for effectiveness and side effects, which are obtained from reviewing and organizing the existing data of all treatments for a specific indication. Conducting a systematic literature review using a relevant database will be necessary. List clearly the conditions used for literature searches, including the database used, key words used for the inquiry, and inclusion and exclusion criteria of literature. Moreover, unpublished reports that examine treatments of indications can also be presented.

It is recommended to make a summary table for all selected literature, if possible. Meta-analysis can increase the accuracy of estimating the difference between the medicine and its comparator. Meta-analysis can also find some characteristics of the medicine that are of clinical importance but cannot be observed in randomized clinical trials. When conducting a meta-analysis, it is required to clearly describe the literature selection process and the statistical methods adopted. Conducting a systematic literature review and

meth-analysis must follow existing and acceptable guidelines such as the methods developed by the Cochrane Library, which will be discussed later.

Sources of effectiveness data can be from experimental research or observational research. If no such research is available, expert opinion is acceptable. However, the evidence of lower value data can be adopted in an economic evaluation only when the evidence of higher value data does not exist. Expert opinion cannot replace results from scientific research. The methods of choosing experts and collecting their opinions must be described in detail in the evaluation reports. Expert opinion is meaningful in the following conditions:

- to define the scenario of a pharmacoeconomic evaluation (that is, to define the treatment role of a medicine, such as its main indication and its main comparative treatment);
- to revise the data on resource use (the data which is from clinical trials conducted in other countries or other circumstances);
- to infer and estimate the quantities of resources need to be used to attain the outcomes of randomized clinical trials.

The values of clinical data can be ordered as follow:

Experimental studies

I Randomized controlled clinical trials

II-1a Controlled clinical trial with pseudo-randomization

II-1b Controlled clinical trial without randomization

Observational studies

II-2a Cohort prospective studies with parallel control

II-2b Cohort prosp. studies with historical control

II-2c Cohort retrospective study with parallel control

II-3 Epidemiological case - controlled studies retrospective

III Studies of a "before and after" type

IV Expert opinion (Delphi Methodology, committee letter report and descriptive studies)

Another classification method of the authenticity for treatment outcomes is decided by the following classifications arranged from highest to lowest:

-- evidence from systematic review;
-- evidence from prospective randomized studies;
-- evidence from large-scale prospective comparative nonrandomized studies;
-- evidence from large-scale retrospective comparative studies;
-- evidence from noncomparative studies of a limited group of patients;
-- evidence from occasional observations;
-- data from formalized expert opinion.

Guideline 11. Health-Related Quality of Life, HRQoL

Health-related quality of life is a measurement of effect, and can be measured by using generic questionnaires, disease-specific questionnaires, or preference-based measures. These instruments are recommended to evaluate the effect if a medicine is better than its comparators not only in clinical outcomes but also in health-related quality of life.

Description:

If health-related quality of life is to be included in the study design, this variable must be measured by highly reliable measures. There must be a discussion to support whether or not the variable is included in the study. There are three types of questionnaires: generic questionnaires, disease-specific questionnaires and utilities measures.

Generic questionnaires

The questionnaires contain different concepts of quality of life, which constitute different dimensions of the questionnaires. Therefore, they can be used in patient groups of any disease or any characteristics. The scores can be compared with those of other groups or healthy individuals. Because the questions of the questionnaires are for extensive and overall health conditions, the scores of the questionnaires, compared with those of disease-specific questionnaires, are less sensitive to symptom improvement of a disease. To measure overall quality of life, it is suggested to use Medical Outcomes Study 36 – item Short Form (SF-36) and WHO Quality of Life Questionnaire (WHOQOL).

Disease-specific questionnaires

The questionnaires are developed for every concept of health-related quality of life, and are influenced by diseases, age, or changes in functioning. Therefore, disease-specific questionnaires are sensitive to the variation of health-related quality of life. Owing to the specificity (being specific to a disease or a characteristic) of the questionnaires, it is impossible to use them to compare quality of life among different diseases.

Utilities measures

Preference-based measures offer a single summarized value, utility, which reflects the valuation of health-related quality of life. Like generic questionnaires, the measures can be applied to different diseases and individuals with high inference. However, they are the least responsive among the three types of questionnaires. The advantage of the preference-based measures is that they can reflect the value of HRQoL from 0 to 1, and can be applied to cost-utility analysis (CUA).There are various methods to measure the utility of a health condition. The direct method is to use questioning techniques such as “standard gamble” and “time trade-off.” In addition, there are some methods which use standard questionnaires to measure the valuation of health states as follows: the Quality of

Well-Being scale, EQ-5D, and the Health Utility Index.

The utilities of health states can be determined by patients themselves or the general population. If utilities are determined by the general population, the evaluations based on them are considered as "from the societal perspective." Economic evaluations of health care are recommended to be conducted and reported from the societal perspective.

Guideline 12. Outcomes for Cost-Utility Analysis, CUA

In Cost-Utility Analysis, both life years (the survival years) and health-related quality of life (HRQoL) must be presented. How these two measures are combined also needs to be described clearly. Quality-adjusted life-years (QALYs) are recommended to be used to combine survival years and HRQoL. While calculating QALYs, use the utilities as the weighted value of quality of life. The measurement of QALYs must be a continuous interval scale, in which 0 stands for death and 1 stands for a completely healthy state.

Description:

In a cost-utility analysis, health-related quality of life must be evaluated by utility measures. When the analysis is conducted from the societal perspective, the most adequate data source of utilities of quality of life is those measured based on a randomly selected sample which is representative of the society. Explain and describe clearly why a specific measure is chosen. Pharmacoeconomic studies can be compared to one another when the same outcome, that is, QALY, is chosen. QALY is currently the most widely used and recommended outcome measure. For pharmaceutical manufacturers, it is recommended that QALY be used in the main analysis and other effects be used in the secondary analysis. For example, the World Bank suggested adopting disability-adjusted life-years (DALY) as an alternative to QALY.

Guideline 13. Cost Identification

From the societal perspective, direct medical costs, direct non-medical costs, and indirect costs should all be included in cost analysis. Direct medical costs due to disease irrelevant to the health intervention of interest should be excluded. If indirect costs are included in the analysis, explain explicitly the importance of the costs and how they are estimated. In general, it is recommended that a human capital approach be used to estimate indirect costs. There are three categories of costs that should be reported: (1) direct medical costs; (2) direct non-medical costs; (3) indirect costs.

Description:

To estimate treatment costs, all relevant resource use of each treatment must be listed. A decision tree needs to be developed to identify probabilities of all possible events, and all resources relevant to each treatment.

Medications used during the treatment and their daily dosage must be described, and the number of repetitions of the treatment needs to be estimated. Medication adherence also should be taken into account. Concurrent use of other medications or treatments should be recorded. Describe and explain clearly if a treatment is expected to reduce use of other medications or treatments.

Adverse drug reactions may be a key factor when choosing a treatment option, and even influence treatment costs. If there are adverse drug reactions, describe how they are handled.

There are three categories of costs in a pharmacoeconomic evaluation: (1) direct costs; (2) indirect costs; (3) intangible costs. The direct costs indicate resources consumed directly related to the medical treatment or disease management, including medical costs (within the healthcare system, and paid for by the insurer) and non-medical costs (outside the healthcare system, and paid for by the patient). The indirect costs refer to money losses due to the medical treatment or disease management, and are usually demonstrated by reduction of productivity. The intangible costs indicate personal feelings and perceptions due to the treatment such as anxiety, sorrow, and pain, which cannot be measured in monetary value. The intangible costs are usually not included in a pharmacoeconomic evaluation.

If a pharmacoeconomic evaluation is conducted from the societal perspective, the relevant costs are the overall cost (direct medical costs, direct non-medical cost and indirect costs); in other words, the cost is shared by every member of the society. In this case, transfer of incomes (such as being ill or unemployment compensation) should not be regarded as some individuals' profits or loss, but a redistribution of incomes without consuming any resource. If an evaluation is conducted from other perspective, all costs relevant to the perspective must be listed.

The defined categories of costs are as follows:

Direct costs within the healthcare system

Costs directly related to disease treatment are direct medical costs, which are usually paid for by the health insurance organization, and only account for a part of the treatment cost. For example, costs of diagnosis, treatment, rehabilitation, preventive medical services, technical services (including home care), medications, caregivers for hospitalized patients, lab tests, management of adverse drug reactions etc. Co-payment is included in the direct medical costs.

Direct costs outside the healthcare system:

Direct costs outside the healthcare system are direct non-medical costs, including

expenses for services provided at the patient's home (not paid for by insurance organizations); out-of-pocket expenses of the patient such as the expense of a special diet, caregivers, transportation fares, and accommodation (if not in the patient's own home); the maintenance expenses of the patient's residence can sometimes be included too, based on the patient's health status.

Indirect costs outside the healthcare system:

From the societal perspective, direct costs within or outside the healthcare system, and indirect costs are all key points of the evaluation. Indirect costs indicate the productivity losses or loss of salary by the patients or their family members due to being absent from work and taking care of the patients – for example, temporary inability to work due to the illness, permanent damage of functioning, and premature death.

There are two methods to calculate indirect costs: (1) the human capital approach (HCA); (2) the friction cost method. An HCA estimates possible income loss (however, real productivity loss may be lower than the estimation). Productivity loss is measured by market wage, that is, the market wage rate is multiplied by work hours lost. The human capital approach may overestimate the cost, because the potential loss of productivity (in theory, it is estimated by its maximum value) is estimated by summing up income loss from the onset of the illness to retire or die. The friction cost method estimates the loss of productivity due to a person's disease based on the time period needed to restore the initial production level, for example, the time from the beginning of absence from work to a replacement found. Because it is challenging to collect data for the friction cost method, it is recommended to adopt HCA.

Indirect costs within the healthcare system:

The costs refer to medical costs consumed due to prolonged life-years after the treatment. More and more people recommend if the cost obviously is related to the intervention of interest, it should be included in the evaluation which is conducted from the societal perspective. Costs irrelevant to the intervention of interest should be excluded from the analysis.

In an economic evaluation, the rationality of including indirect costs must be explained explicitly by reporting loss of productivity due to the illness or the treatment. The variations during the treatment must be reported respectively, and sensitivity analyses must be conducted to reflect the impact of the variations on the research results.

Note: The aim of cost estimation is to compare alternative treatments. Therefore, if same costs are incurred by different treatments, they can be excluded from the evaluation. Only different costs, or costs of the same resources that are used in different quantities should be included in the analysis.

Guideline 14. Cost Measurements (Resources Used)

The medical resources used during the treatment period must be shown in their natural units (non-monetary) at the beginning—for example: the hours, number of working days, number of nursing days, dosages of medications, and number of pills used. If the data of resource use comes from international studies, make sure that they can be applied to the evaluation in Taiwan.

Description:

Cost measurement aims to calculate quantities of resources consumed in the treatment. The natural units should be expressed as clearly as possible – for example: medications used every day or every regimen; number of laboratory tests; number of nursing hours during the treatment; average hospital days etc. The natural units must be identified according to clinical experience in Taiwan.

It is easier to transfer research results to other countries or environments when personnel and resource use are recorded by their natural units. If the data of the resource use come from international research reports, the information must be reassessed. Only costs relevant to regular medical practices should be taken into account. However, be careful to avoid double-counting. This can happen if the costs of a disease and the benefits of a treatment are not clearly differentiated.

Guideline 15. Cost Valuation (Unit Prices)

Unit prices of resources used must be based on the evidence. Ideally, unanimous unit prices should be able to be applied to some categories of costs in order to improve the comparability and extrapolatability of different study results.

Description:

The total cost is quantities of resources used multiplied by their unit prices. From the perspective of economic evaluations, cost valuation should be based on the economic definition of the cost, instead of the accounting definition of it. It is important to differentiate between expenses and costs, and pay attention to the perspective of the evaluation. The basis of valuation is usually the average unit cost. Ideally, it is better to use costs instead of expenses to do cost valuation. Only if it is impossible to calculate costs can expenses be used, and proper explanations should be provided. In the process of cost valuation, there are principles should be followed:

1. The unit prices of the medical resources can adopt the BNHI's reimbursed prices.
2. Market prices can be used to show out-of-pocket expenses.
3. Loss of productivity can be estimated by the human capital approach (HCA).

4. It is better to use standard cost values to estimate resources consumed, so that the application of the study results will be more general, and it will be easy to compare different studies.
5. Real unit prices are collected during the process of conducting economic evaluations. When reporting the numbers, analysts should explain explicitly whether mean or median values are used, and show why the central tendency is chosen.
6. Be sure to use up-to-date unit prices and provide sources for the data and the references.
7. Both estimated consumption of resources and their unit prices must reflect real-world settings in Taiwan.

Cost analysis of economic evaluations must all follow the four steps below:

1. Cost identification: List medical resources that are consumed, including diagnostic and treatment techniques, prescriptions, time of physicians or other professional personnel, hospitalization days, etc.
2. Cost measurement: Resources used are presented by the number of their physical units. For example, hospitalization days, number of physician visits or professional consultations, number of laboratory tests, number of nursing care, dosage and pill number of medicines.
3. Cost valuation: The unit prices of resources used, such as the unit price of each hospitalization, the unit price of personnel, the unit price of a laboratory test, and the unit price of medicine.
4. After quantities of resources used are multiplied by their unit prices, sum them up. The costs should be adjusted by taking into account uncertain factors, and be discounted.

Guideline 16. Modeling

The modeling techniques are usually adopted in pharmacoeconomic evaluations. The modeling of data is used in two situations: (1) the effectiveness data are obtained from the efficacy data; (2) data are from reports of other countries or other healthcare systems. The second situation is particularly important when reports of multiple countries are used. When developing a model, be very prudent and provide rational explanation of the choices made.

Description:

Many research reports of other countries are adopted in Taiwan. However, before an international research report can be applied to reflect the real-world settings of Taiwan, it needs to be revised by taking into account differences in demographic and epidemiological

characteristics, medical rules, practice patterns due to different financial incentives, and relative prices.

To improve the external validity of a clinical trial (the differences between a clinical trial and clinical practice must be adjusted in Taiwan), or to apply clinical trials conducted in other countries to Taiwan, developing models can be an option. Modeling can incorporate the following information: (1) efficacy data, obtained from international randomized clinical trials; (2) practice patterns, costs, and characteristics of patient groups in Taiwan.

To develop models, the structure and the theoretical framework of the models should be explained explicitly, and they should be presented through diagrams (for example, decision trees, Markov models). The aim of developing models is not to replace the "real" data. Pharmacoeconomic evaluations conducted by using decision models are acceptable if the models are used in the proper situation and applied suitably.

Developing models is to reach the following objectives:

1. Treatment outcomes can be inferred from efficacy data of randomized or nonrandomized clinical trials.
2. Intermediate results (surrogate results) of clinical trials can be linked to end results.
3. Data from clinical trials can be applied to real-world settings, or be adopted by other countries.
4. If proper reports are unavailable, modeling can provide integrated and direct comparison results.
5. If reliable data is not available, modeling offers primary data for evaluation.
6. Modeling can be used to evaluate completeness of a study in its initial stage.

Once developing models are considered the most suitable method, following requirements need to be met:

1. A model should be as simple as possible, and easily understood by all users.
2. The conditions, assumptions, and data of a model must all be stated clearly so that it can be easily understood and reexamined.
3. The study results must be explained clearly, so that end users can distinguish between the data of reliable sources and the data of lower scientific evidence levels. In addition, the results should be repeatable and reproducible.
4. The aim of the development of a model is to clarify contradictions of arguments, and confirm study results. This is the reason why the sensitivity analysis must be conducted to confirm the power of the study result.
5. Every model should be evaluated in order to judge its accuracy, and whether it accords with other models or studies of similar study topics. If there is new data available, every model should be investigated and verified.

When choosing relevant clinical trial data that are to be included in the models, be sure to choose literature of similar characteristics. To meet the requirement of consistency, factors such as patient groups, inclusion and exclusion criteria, problems encountered during trials, and treatment durations need to be taken into consideration. When conducting pharmacoeconomic evaluations by using decision models, treatment costs used in the models must reflect the real situation in Taiwan. Therefore, costs, quantities, and unit prices are from data of Taiwan. If Taiwanese data such as clinical efficacy and probabilities are not available, the efficacy data of international clinical trials can be adopted, while the data from meta-analyses conducted after doing a systemic review is preferred. Sensitivity analyses are required for all uncertain data, and their processes must be described clearly. An explanation is necessary for results without any sensitivity analysis carried out. Because the results of decision models usually bear uncertainty to some extent, it is important to interpret them cautiously, and to conduct sensitivity analyses.

Guideline 17. Discounting for Future Outcomes and Costs

Future outcomes and costs should be discounted to their present values by the same discount rate. The discount rate must be included in sensitivity analyses. If using different discount rates, an explanation must be provided.

Description:

The discount rate is used to adjust both costs and outcomes to their values at a specific time point. The treatment outcomes and costs of a medication and those of its comparator must be compared by their values at the same time point. If the treatment outcomes and costs are occurred at different time points, they must be discounted to their value at the designated time point. It is one of the basic characteristics of economic evaluations that both future costs and benefits are discounted to their present values. To the majority of people, however, the value of a cost is higher than that of the same cost occurred in the future; similarly, the immediate benefits are more valuable than future benefits. If the treatment of a disease lasts more than one year, discounting becomes very important.

The necessity of cost discounting is unquestionable, but the discounting of health outcomes may be controversial. If we want to assess the effects of receiving alternative therapies for several years, discounting health outcomes means that the value of life years will decrease gradually along with time. Without discounting, there will be biases, because the analysis results will favor alternative therapies with long-term effects at the expense of those with short-term effects. In this case, not discounting the health outcomes can be considered. Generally, it is recommended that all three kinds of analyses be conducted:

discounting costs only, discounting both costs and health outcomes, and no discounting. Then the differences in results of the analyses should be compared.

The perfect market can provide the most complete information, in which the discount rate is equivalent not only to the risk-adjusted market rate of interest (cost of long-term capital), but also to the rate of time preference. By contrast, there are a variety of interest rates in the imperfect market, which reflects that people have different expectations for the rate of returns of different economic fields, time preference, and uncertainty. Because the discount rate is very subjective, it cannot be calculated based on experience. Even so, we can estimate the discount rate according to the long-term market interest rate, which is approximately 4-5 % in Taiwan. Therefore, we assume a discounting rate of 5%. The range of the discount rate used in the sensitivity analysis is recommended to be between 0 and 10%.

Examples

For a three-year research plan, the cost of each year is 200(NTD), 300(NTD) and 400(NTD), respectively. The discount rate is 5%. Suppose that the cost is announced at the beginning of the year. The present value of the cost for the research plan is as follows:

$NT\$ 200 + 300/(1+0.05)^1 + 400/(1+0.05)^2 = NT\$ 848.5$

Contrast with this formula as follows:

NT$ 200 + 300 + 400 = NT$ 900

Or suppose that the cost is announced at the end of the year, and another kind of algorithm can be used. The discount rate is 5%. The present value of the cost for the research plan turns out into:

$NT\$ 200/(1+0.05)^1 + 300/(1+0.05)^2 + 400/(1+0.05)^3 = NT\$ 808$

Guideline 18. Sensitivity Analysis

While interpreting the results of sensitivity analyses, list all possible assumptions and explain them explicitly. If there are any important restrictions regarding the assumptions, state them also. Sensitivity analysis must be used to demonstrate the relationship between the study results and the assumptions. The basic method is the univariate sensitivity analysis. If it cannot meet the study needs, use multivariate techniques. Explain clearly the choices of parameters, the ranges of the parameters, and the method used.

Description:

Sensitivity analysis is conducted to examine the impact of changing values of key assumptions on evaluation results. If the costs, effects or probabilities are obtained from population sample (for example: the data are obtained from a large database), the confidence interval (the upper limit and the lower limit of each uncertain parameter; these represent the range of uncertainty) can be used as the basis for conducting the sensitivity analyses. After adopting different numbers, observe how study results are changed.

If there is any doubt about the accuracy of parameter data (for example: different studies report different incidences of side effects and relative effectiveness, or disparities of treatment costs in different hospitals), the variation intervals (for example: threshold analysis, 95% confidence interval) of the doubtful parameters should be included in the sensitivity analyses, or specific values must be determined for the intervals.

To define reliable variation intervals of parameters, refer to the reliable means suggested by suitable scientific literature and experts as the basis. After changing the value of a parameter, we can examine the changes in the costs, cost-effectiveness ratio, or the final decision. If there is only the value of one parameter changed in each sensitivity analysis, the method is called "univariate sensitivity analysis."

"Multivariate sensitivity analysis" takes into account the relationships among a lot of parameters, and examines how the study results will be affected after the values of different parameters are changed simultaneously. The latest technique is to determine the probability distribution of each parameter. Next, the expected costs, benefits, and cost-effective ratio will be estimated repeatedly, so that whether the study results will be changed can be observed. The risk distribution of the study results should be described.

If conducting univariate sensitivity analysis is considered inappropriate, do multivariate sensitivity analysis. Once the result of the sensitivity analysis is adopted, a decision maker can appraise the value and credibility of the economic evaluation, for example, degree of reliability of the study results.

Guideline 19. Equity

If the purpose of an evaluation is to be used for resource allocation, then any equity assumption, implicit or explicit must be emphasized. While stating the study results, use the same weights for lives, life-years and quality-adjusted life-years (QALYs). Explain the weights clearly so that the decision maker can replace them with different weights. Once the research plans begin to be carried out, the analytical method adopted should be able to distinguish which group is the main beneficiary.

Description:

In any economic evaluations used for allocating resources, the equity is an important

factor. The equity assumption of the basic case in economic evaluations means that all patients, in clinical trials and economic evaluations, have a fair participation opportunity and obtain the expected treatment outcomes.

Equity means that an intervention affects values of all lives, life years, or QALYs equally, regardless of age, gender, or socioeconomic status of individuals in a target group, or the population. One point is very important: Researchers must state clearly the equity assumption in the study, especially when economic evaluations and the clinical trials are conducted simultaneously. The equity assumption has been included in every model and analytical method of economic evaluations. It is of great importance to understand and point out these assumptions in an analysis. For example, in the cost-effectiveness analysis (CEA), the cost per life saved or life-years gained is based on the assumption that all lives are equal, regardless of their age, comorbidities, or other states. The equity assumption of cost utility analysis (CUA) is as follows: everyone's increase in "Quality-adjusted life-years" is of the same value, no matter who the person is. In other words, an additional QALY of a 30-year-old man and that of an 80-year-old man are equally preferable. Analysts must emphasize that the weights used in their evaluations are the same.

Guideline 20. Presentation of Results of Pharmacoeconomic Evaluation

All results must be reported separately and explained carefully, and then the aggregated result be explained. The content of the report must be in accordance with the standard form.

Description:

The reports of the economic evaluations must be detailed, clear, and transparent. For example, the main categories of costs and health outcomes include direct costs, indirect costs, life years gained, and improved quality of life. Before these categories are added as a single value or a single rate, the values of their sub-categories should be presented first. In addition, the total cost and health outcome must be presented separately, so that the total cost and health outcome after a treatment can be observed. The reports with disaggregated data are helpful for readers to clearly estimate and understand the details and appropriateness of the evaluations.

The method for reporting a study result depends on the analytic method adopted in the study. For cost-effectiveness analysis (CEA) and cost utility analysis (CUA), total cost, total effectiveness or utilities, cost-effectiveness or cost-utility ratio, and incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR) must be presented in the report. The study result of cost-benefit analysis (CBA) must be reported using the net benefit.

The content of the result must include the discussions of the data, analytical method and results. While quoting results of clinical trials carried out in other countries, be sure to discuss the transferability and portability of the results — that is, whether the data of clinical efficacy and effectiveness are applicable to the real practice settings in Taiwan. If there is any other published or unpublished report of pharmacoeconomic evaluation, the disparities between the result of that report and of this report, or any questioning issues must be included in the discussion. If data are obtained from a systematic literature review, the method of the review must be stated in the report. A description is necessary if the analytical method adopted is different from the methods used in published studies. In the discussion, be sure to state whether or not the assumptions or uncertain parameters of the study have already been tested in the sensitivity analysis. In addition, the potential impact of the introduction of the new treatment on the society in Taiwan also needs to be assessed. In the end of the research report, list the references and the assumptions of the analytical methods. If patient-level data are used in the study, pay attention to the privacy of personal information, and confidentiality of clinical research files. The format of the reports of pharmacoeconomic evaluations must comply with the standard form, which is presented in the section three.

Guideline 21. Portability of Economic Evaluations

The portability of economic evaluations needs consideration as follows: whether the study results can be applicable to other settings; the validity of transferring an evaluation result (costs, clinical outcome, and quality of life) in one country to other countries or other healthcare systems. This guideline is particularly important if the study result is applied to the settings of multinational or multicenter trials.

Description:

There are two aspects involved in the portability of economic evaluations: (1) the degree of applicability: the extent to which the efficacy data from the original study setting or study group can be applied to another real practice setting or population; (2) the validity of transferring an evaluation result in one country or healthcare system to other countries or healthcare systems. When planning a study, or interpreting and discussing results of economic evaluations, analysts must emphasize these two aspects. Decision makers also need to examine these two issues – degree of applicability and the validity of transferring – before making any resource allocation decision based on the study result.

The degree of applicability of economic evaluations involves distinguishing the efficacy data and the effectiveness data, which has been discussed in guideline 10. As to the validity of transference, if the results of economic evaluations conducted in other countries

will be introduced into Taiwan, three aspects of results – costs, clinical outcomes, quality of life – must be taken into consideration. Adopting the results of cost evaluations from other countries will be influenced by important economic factors: the relative unit prices of resources in different countries or areas will not be the same, and the medical resources used may be different as well. The most important clinical factors influencing the validity of transference include: whether or not the patient characteristics and disease epidemiology of the country where the study was conducted are similar to those of Taiwan; the disparities in clinical practice patterns, which are a determinant of quantities of medical resources consumed; the differences in incentives to use medical resources or regulations for medical personnel. Both analysts and users of the study results can not conclude that the results assessed under specific assumptions of economic valuations will remain unchanged in different countries or cultures. Therefore, the cross-cultural adaptation and validation is important for instruments of quality of life measurement, and is important for effectiveness research.

Guideline 22. Budget Impact Analysis

The budget impact analysis is not part of pharmacoeconomic evaluations. But for a decision maker, whether or not to adopt a medicine recommended by the health insurance system depends not only on the cost-effectiveness of the medicine, but also on its budget impact, which contributes to understanding the influence of the decision on finances.

Description:

One of the purposes of conducting pharmacoeconomic evaluations is to determine whether it is worth to reimburse the new medicines: the evaluation results will indicate whether or not the new medicines are cost-effective, and whether it can substitute for current treatments. For health policy decision-makers, it is of great importance to know what impact on overall healthcare cost or medication costs listing a new medicine in the formulary will have. Therefore, a budget impact analysis is necessary. To conduct the budget impact analysis, be sure to follow the appropriate set of guidelines.

There are differences in concepts and applications between pharmacoeconomic evaluations and budget impact analysis:

1. From the perspective of budget impact analysis, only costs of resource items reimbursed by the health insurance system should be included in the analysis; costs occurred outside the system (which are important from the societal perspective) are excluded.
2. In pharmacoeconomic evaluations, the unit of evaluation is the individual (namely, the costs and effects are measured from the individual's perspective). The budget impact

analysis, however, is conducted from an overall perspective.

3. The results of the budget impact analysis are presented in the form of financial impact per member per month (PMPM). Those of pharmacoeconomic evaluations are reported as the additional cost for an additional effect.

III. Report Format of Standardization for Pharmacoeconomic Evaluations

1. EXECUTIVE SUMMARY

- According to the principle of the report format, the study brief and the bottom line result can be written in summary format.
- State the reasons of choosing an alternative therapy, and factors of analysis limitations.
- Offer suggestions, if proper

2. INTRODUCTION

2.1 General comments on the disease or condition

- Pathology / condition
- Epidemiology data
- Current clinical practices
- Impact on the economy

2.2 Product Description

- Therapeutic classification, brand-name or generic name, dose, route of administration
- Approved indication(s)
- The indication considered in the economic evaluation. Describe the pathology, epidemiology, and current treatments of the indication, and the specific patient group included in the analysis.

2.3 Objective of the study

2.4 Disclosure of relationship

- The relation between funders and the person who writes the report, and the arrangements in the contract
- The researcher's autonomy and the rights for publishing the report

3. METHODS

3.1 Type of economic analyses

- Prospective, retrospective, modeling, or mixed methods
- Analytic skill used, the reasons, and important assumptions (for instance: cost-minimization analysis, cost-consequences analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis)
- Study design and procedure adopted, statistical method, and validation method

3.2 Target audience

- The main audience likely to consult this study result (for example: decision makers of formulary, medical insurance organization, or prescribers)

3.3 Viewpoint of analysis

- Choice and reason of the perspective of analysis (for example, the perspective of the society, the perspective of the Department of Health)

3.4 Treatment comparator

- Choice of the comparator and the reason for this choice (for instance: medicine, surgery, or no treatment)
- Method used to analyze clinical effects of the comparator (for instance: head-to-head comparison in randomized clinical trials, or meta-analysis of different trials)

3.5 Time horizon

3.6 Related studies/background

- Systematically search existing economic evaluation literature of similar situation or treatment

3.7 Outcome measurement

- Outcome parameters
- Outcome of clinical effects (method used, source of information, assumptions made)
- Clinical data collected
- Parameters of clinic outcomes included and measured (for instance: side effects, disability rate, mortality rate)
- Instruments of health-related quality of life measurement (e.g. disease-specific measures, general health profiles measures, and health index measures)
- Other outcome parameters considered but rejected (with explanation)

3.8 Cost measurement and valuation

- Categories of costs included and measured (e.g. direct costs, costs of time lost, costs of others sectors, costs of other individuals)
- How unit prices were determined (For instance: whether the standard cost is used or not)
- Source of data or data of resource use collected
- Assumptions made

- Discounting for costs and outcomes

3.9 Variable uncertainty

- Has comprehensive sensitivity analysis been carried out? What are the variation intervals of the parameters? Are they reasonable?
- List sources of uncertainty – sampling error, or the range resulting from assumptions made.
- Outline the results of statistical methods (confidence intervals) or sensitivity analysis.

3.10 Sub-group analyses

- If outcomes are different for pre-identified subgroups (e.g. subgroups of effectiveness, subgroups of preference, subgroups of costs, subgroups of cost-effectiveness)?

3.11 List of assumptions

- Identify major assumptions and limitations (both economic and clinical) in the analysis, and explain how they might affect the results

4. RESULTS

4.1 Analysis and results

- Present analysis procedures step by step so readers can replicate the calculations if interested
- Clearly display models used and assumptions made
- First, present detailed categories of results (e.g., study population, sociodemographic data, clinical data, data of resource utilization, etc.). Then, display the aggregated result, and the result of the value judgment (e.g. degree of preference)
- Consider all possible alternative therapies, and then interpret the final result
- The confidence intervals and sensitivity analyses
- Outline important limitations of the analysis in a transparent manner (i.e. what issues limit the results, and their applicability to other groups)
- Comments on whether or not the practice patterns of the medical institutes will influence the study result.

4.2 Sensitivity analysis results

4.3 Subgroup analysis results

4.4 Equity

- Equity assumption (e.g. a QALY, a quality-adjusted life-year, is equal for all persons).
- Consideration of distribution (e.g. who gets, and who loses)

5. DISCUSSION

- Be sure to discuss the limitations of the study, robustness of the results (how the results are changed by sensitivity analyses), the bottom line used to judge if the medicine is cost-effective, methodological issues, and the applicability of the results to other situations or countries.
- What is the "bottom line?" There should be quantified results. There are following ways to express the results: (1) compared to another product, this product costs $X, or the range from $Y to $Z, for an additional quality-adjusted life-year (QALY); (2) compared to the alternative therapy, this product increases cost by $X (the marginal cost), but reduces Y major side effects and Z other side effects.

6. CONCLUSION

- Following topics should be concluded in the report: bottom line result, equity assumptions, aggregate impact, and confidence in results.

7. REFERENCES

8. APPENDICES

- Detailed tables of data
- Details of analyses step by step
- Intermediate results
- Copies of forms, questionnaires, instruments, etc. use for data collection

IV. Focal Points of Review for Pharmacoeconomic Evaluations Report

This chapter puts forward some questions according to Report Format of Standardization in chapter three. The focal points are what a reviewer of research reports usually pays attention to while examining economic evaluations. These questions can be regarded as a reminder for study report writers so they can recognize what should be clearly emphasized in a report. They also remind users of the reports to consider these issues while reviewing the reports.

1. EXECUTIVE SUMMARY

Q1. What is "bottom line"? There should be quantified results. There are following ways to express the results: (1) compared to another product, this product costs $X, or the range from $Y to $Z, for an additional quality-adjusted life-year (QALY); (2) compared to the alternative therapy, this product increases cost by $X (the marginal cost), but reduces Y major side effects and Z other side effects.

2. INTRODUCTION

2.1 General comments on the disease or condition
2.2 Product Description
2.3 Objective of the study
2.4 To distinguish the relation between the researcher and supporter (Disclosure of relationship)

Q2. Who finished this analysis? Do several authors of the research paper sign a letter of consent, to show that everybody agrees to all contents in the report? Does the report point out that the author has the autonomy and the initiative right to select the analytical methods, and has the right to issue this result, no matter how the result is?

3. METHODS

3.1 Type of economic analyses (Type of analyses)

Q3. What is the question of this analysis? Is this economic question relevant? What method of economic analysis is adopted to answer this question? (i.e. Cost comparison, CMA, CCA, CEA, CUA, CBA)

Q4. Is an incremental analysis adopted?

3.2 Target audience

3.3 From whose view and position an analysis is done (Viewpoint)

Q5. Is the view of the analysis explained clearly? State a reason for the choice. Is this analysis from the societal perspective or the patient's perspective, or from the view of a medical insurance company? Does this analysis demonstrate the results of different views separately?

3.4 Treatment comparator

Q6. Does the research aim at the patients of the same situation, and compare the treatment group with comparative group? Are various kinds of alternative therapies described clearly? Is the comparative group chosen proper and reasonable?

3.5 The length of time for treatment (Time horizon)

3.6 Related studies/background

3.7 Outcome measurement

Q7. Is the evidence of the efficacy of the medicine from a randomized clinical trial? Is the evidence of the efficacy supported by the evidence from the main patient's group or from the secondary patient's group? Does the evidence of effect come from the records of the real clinical practices? Are the differences of all relevant and apparent effects, in different subgroups, confirmed and reported?

Q8. Is the analytical method used in the study demonstrated in a clear and transparent way? Are all categories of costs and effects presented clearly? Is the clinical result presented by its natural unit first, and then changed into another kind of unit, such as the units of benefit and utility?

Q9. Are all important and relevant costs and results (including the side effects of each treatment) recognized and explained explicitly?

Q10. How is health-related quality of life measured?

Q11. Is the measurement of health-related quality of life an important effect in this economic analysis? Is the conclusion of the cost-utility analysis sensitive to the change of

health-related quality of life?

3.8 Cost measurement and valuation

Q12. Are the data of costs and consequences (in a decision tree) derived from a variety of literatures or estimated directly from (a) specific patient population(s)?

Q13. Are direct medical costs and indirect medical costs included as well as overhead cost (equipment depreciation; water and electricity)? How are they measured?

Q14. How have indirect costs (i.e. productivity costs, cost of lost time) been identified and estimated?

3.9 Variable uncertainty
3.10 Sub-group analyses
3.11 List of assumptions

4. RESULTS

4.1 Analysis and results

Q15. For variables which are difficult to measure, what method is used to handle this difficulty? Does this method favor any treatment and therefore bias the result?

Q16. How applicable are these results for the target patients? Comment on the external validity of results and on the validity of the data. Comment on any international or regional differences in the following parameters: epidemiology of the disease, practice patterns of physicians, clinical effects, and costs. If differences exist, how likely is it that each factor would affect the results? In which direction would each factor change the results? While all variables are considered altogether, how would they impact the results and of what extent the impact is? When these potential differences exist, how would the conclusions likely change in the current setting? How to quantify this?

4.2 Sensitivity analysis results
4.3 Subgroup analysis results
4.4 Equity

Q17. What equity assumptions have been made in the analysis? For example: should

QALYs (quality-adjusted life-years) gained by any individual be considered equal?

Q18. Do you estimate the incremental cost-effectiveness ratio for a specific clinical indication? Does the estimate represent the ratio of all indications of the medicine for which the BNHI will pay? Are there other indications which involve using a large amount of the medicine for which the ratio may be very different?

Q19. Is there an estimate to report the aggregated incremental expenditure? (How much more the Bureau of National Health Insurance will pay?) What are the aggregated incremental costs? (When this medicine is used but not other medicine, how much will the overall cost increase?) Does this estimate cover all indications for the product?

5. DISCUSSION
6. CONCLUSION
7. REFERENCES
8. APPENDICES

V. GLOSSARY OF TERMS

Acquisition cost: The purchase cost of a drug to a medical institution, agency (hospital) or person.

Analytic perspective: The viewpoint chosen for the analysis (e.g. societal, government, health care system, payer).

Average cost: Total costs of a treatment or program divided by total quantity of treatment units provided (see also marginal cost).

Consequences: The outcome(s) associated with a disease and/or intervention (e.g. stroke, death, side effects, and avoided morbidity).

Contingent valuation (Hypothetical Marketing Evaluation): A method for evaluation of benefit or value to individuals of therapy that uses survey methods to establish willingness to pay. (For example: How much is the individual willing to expend to acquire an advantage?)

Cost: A product of the quantities of resources (Q) and the unit prices (P).

Cost measurement: The process of determining the quantity of resources (Q) used as part of an intervention.

Cost of lost time: See indirect cost.

Incremental cost per QALY (quality-adjusted life-year) gained: An indicative method of curative effects which are used in CUA (cost utility analysis) to show more monetary cost per unit of QALY, to compare every medicine. The incremental ratio of cost and result for every medicine is the incremental value.

Cost-benefit analysis (CBA): Type of analysis that measures costs and benefits in pecuniary units and computes a net monetary gain/loss (i.e. as net cost or net benefit) or a cost/benefit ratio.

Cost-consequence analysis (CCA): Type of analysis that makes no attempt to aggregate across different kinds of consequences (e.g. incidence rate of strokes, deaths, side effects),

but describe and display individually. Any weighting or aggregation is left to the user of the study.

Cost-effectiveness analysis (CEA): Type of analysis that compares the cost expense among treatments, having a common health outcome (e.g. reduction of blood pressure; life-years saved). It is expressed usually according to incremental cost-effectiveness ratio (ICER).

Cost-minimization analysis (CMA): Type of analysis that finds the least costly program among those shown or assumed to be of equal benefit.

Cost-utility analysis (CUA): Type of analysis that shows its curative effect in utility units or quality-adjusted life-years (QALYs); usually to appear in ratio of a cost to QALY.

Decision analysis: An explicit quantitative approach for helping to decide what intervention to choose; under conditions of uncertainty.

Decision tree: A tree diagram framework for representing the results of every kind of treatment methods in decision analysis.

Delphi panel method: A structured method of eliciting expert judgment, for obtaining data regarding effectiveness estimation.

Direct medical cost: Fixed and variable costs associated directly with a health care intervention (e.g. expense in hospital and physician salaries).

Direct non-medical cost: A non-medical cost associated with provision of medical services (e.g. transportation of a patient to a hospital, and the fee for asking someone to look after).

Discount rate: Rate of discount used to convert future costs and benefits into equivalent present values; typically 2 to 6% per annum for costs, and 0 to 6% for benefits. [It is, however, recommended in these Guidelines that the standard be 5% for both costs and benefits, and that variations on this rate, including 0% and 3%, be tested by sensitivity analyses.]

Dominance: A comparison of the costs and effectiveness of each treatment. The effectual one with low costs has Dominance and is the most proper choice.

Effectiveness (of a drug): The therapeutic outcome in a real world patient population (it usually differs from efficacy determined in controlled clinical trials).

Efficacy: The therapeutic outcome determined in a randomized controlled clinical trial.

Equity: the fairness while distributing treatment method or resources, to different individuals or the group.

Formulary: A list of drugs reimbursable under a health insurance plan or under a managed medical institution. Various kinds of medicine information are compiled into the list.

Friction cost method: A method of estimating the productivity costs by calculating the value of production losses during the friction period (i.e. between start of absence from work and replacement).

Future health care costs: Costs which result from the additional consumption of medical resources (via longer life span, etc.) due to a given intervention.

Health-related quality of life (HRQOL): QOL measures which are likely to be influenced by health interventions.

Healthy Years Equivalent: The hypothetical number of years spent in perfect health which could be considered equivalent to the actual number of years spent in a defined imperfect state of health.

Human capital method: A means of calculating the indirect cost of medical illness, based on the remaining lifetime economic value to society of a healthy individual of that age, measured by potential market earnings.

Incremental cost: Difference between the cost of a program (treatment) and the cost of the comparison program.

Indirect cost: The cost of lower productivity resulted because of the disease or treatment (it can be assessed by losses of the salary or other methods). It is called as the cost of losing the work time and productivity cost.

Intangible cost: The cost of pain and suffering occurring as a result of illness or treatment

(it can't be calculated).
Marginal cost (see also average cost): The extra cost of one extra unit of product or service delivered (usually differs from average cost).

Markov model: A statistical algorithm which repeats simulation for events by computer software, and is used usually in analysis of making policy.

Meta-analysis: A systematic process for finding, evaluating and combining the results of sets of data from different scientific studies.

Net benefit: Benefit (in pecuniary units) minus total cost (in pecuniary units). It is a basic decision criterion in CBA.

Opportunity cost: It is a concept of economics and regards the benefit, which an investment produces on the next best alternative use, as the best investment item at present.

Preference: Preference is a subjective attitude and a concept that refers to the desirability of a health outcome. Both utility and value are special cases of the concept of preference. Utility is a kind of judgment of describing individual's health degree to the disease state, and Value means how much a person is willing to expend for health state expected.

Quality of life (QOL): Physical, social and emotional aspects of a patient's well-being that are relevant and important to the patient.

Quality-adjusted life year (gained) [QALY]: A common measure of health improvement used in CUA: It combines survival year and the health quality obtained (outcome of a curative effect is totally health years in which the number of saved life years is adjusted for quality).

Revealed preference: Preferences revealed by the choices that individuals make. The choices may be those made by individuals in natural settings or responses to choices in questions posed by an investigator.
Sensitivity analysis: A process through which the robustness of an economic model is assessed by examining the changes in results of the analysis when key variables are varied over a specified range.

Standard gamble (SG): A method of directly measuring utility, founded directly on expected utility theory of the fundamental von Neumann-Morgenstern axioms. Standard

gamble is to consider making the decision under the unknown environment. Two states will be offered for the persons who answer to choose: Choose (1) is to live in some special health state (i) (There are certainly chronic disease states); choose (2) offer a kind of new dangerous treatment method, and in the choose there is some probability (p) to get back to the complete health state, (under unknown situation, it needs the gambling or concludes the business) but some probability (1- p) to die at once. The patient can choose (1) which represents to maintain the health state (i), or choose (2) which represents to be willing to accept the gambling and carry on the new treatment method. The researcher continues to change p probability value to observe the decision of the persons who answer, until the persons who answer are unable to make decision finally to choose (1) or (2); because he thinks there is no indifference point. If the persons who answer are unable to determine the choice again while p = 0.65, this represents that the utility value of health state (i) is 0.65.

Its shortcoming is that if there is no state of chosen (2) in disease treatment described, especially the chronic disease, this method can't be used to measure; such as the arthritis, there is no curing method and there is no treatment to cause death of patient at once. In addition, the persons who answer must be very earnest and think clearly.

Subgroup analysis: The process of analyzing data from subpopulations of patients which have been defined based on explicitly outlined parameters prior to the study.

Time trade-off (TTO): A method of measuring utility value. The patient has two choose too: (1) The patient lives for a span (t) in health state (i) of certain chronic disease and then dies, or (2) lives a shorter span (x) in complete health state and then dies. The researcher continues to change x time all the way, until respondent is unable to distinguish the difference between choice (1) and (2). At this moment, the preference value or utility of health state (i) from personal judgment of this patient is x / t. For example: One answers that he must walk with the walking stick two years and it is equivalent to the complete health state one year in, and then 1/2 = 0.5. So the utility value of health state of walking with the walking stick is 0.5. This method can reflect the concept of QALY the most in theory.

Transfer payment: A payment (transfer of money) from one group to another without consumption of any physical resource; not recognized as a cost to society (e.g. sick benefit payment, unemployment insurance benefits or social welfare benefits).

Unrelated costs: Costs that are not specifically attributable to the therapeutic pathway and its consequences.

Utility: In Decision Science, utility is a measure value in common use. It is usually under the unknown state (under uncertainty) to measure the preference degree or intensity expecting to obtain, to a kind of particular health state or effect result. Utility and the preference degree, the two nouns, often can be interchanged in economics analysis, and its focal point lies in uncertain (unknown) environment.

Value: A cardinal measure of the preference for, or desirability of, a specific level of health status or a specific health outcome, measured under certainty.

Willingness to pay (WTP): The maximum amount that a person is willing to pay: (i) to achieve a particular good health state or outcome, or to increase its probability of occurrence; or (ii) to avoid particular bad health state or outcome, or to decrease its probability.

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