Guidelines for pharmaco-economic research, updated version

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1. Introduction

Guidelines from 1999

In 1999 the Health Care Insurance Board (College voor zorgverzekeringen, CVZ) published the ‘Dutch guidelines for pharmacoeconomic research’. These Guidelines were recently updated and published in the report ‘Guidelines for pharmacoeconomic research; evaluation and actualisation’ which was sent to the Minister of Health, Welfare and Sport on the 27th of October 2005. The report elaborates on the background and method for updating the guidelines. For convenience the text of the updated guidelines is also published separately via this booklet.

Aim

The guidelines are intended for designing, conducting and reporting pharmacoeconomic research, but are applicable to economic evaluations in general within the field of health care.

Cost instructions

These guidelines cannot be interpreted without using the ‘Manual for cost research’, which was written at the request of the CVZ by the Institute for Medical Technology Assessment (IMTA) in Rotterdam. Guideline 5 (regarding the identification, measurement and evaluation of costs) refers to this cost manual.

Application for the reimbursement of drugs

The CVZ uses these guidelines as an assessment framework for pharmacoeconomic evaluations which are part of a reimbursement file. This assessment framework is used to check whether the cost effectiveness of a drug for which reimbursement has been requested has been sufficiently substantiated.

For reimbursement of drugs these guidelines are to be used in conjunction with the ‘Procedure for requesting drug reimbursement’, which amongst other things pays attention to the role of pharmacoeconomics in decision-making on the uptake of drugs in the Drug Reimbursement System (GVS).

Steering committee

Proposals for the updated Guidelines were drawn up by a steering committee set up for this purpose, comprising of Prof. dr. F.F.H. Rutten (chairman), drs. H.E.M. Rodenburg-van Dieten (CVZ, secretary), dr. R.M.C. Herings, Prof. dr. B.A. van Hout, dr. P.F.M. Krabbe, drs. J. van Loon, Prof. Dr. M.J. Postma, dr. W. van Rossum, Prof. dr. J.L. Severens, dr.J.F. van Sonderen, drs. L.J. Stokx, Dr. G.J. van der Wilt, Dr. G. van den Boom and Dr. J. Oltvoort (both on behalf of Nefarma).


Initiation date

Until April 1st 2006 the CVZ still assessed pharmacoeconomic evaluations that were part of a reimbursement file according to the original 1999 guidelines. After that date the updated
2. The updated guidelines

Composition of a guideline

A guideline is comprised of the actual text of the guideline, an explanation and literature providing further reading on the subject of the guideline. The quoted literature is not intended to be exhaustive.

Motivated departure from the guidelines

All pharmacoeconomic evaluations, submitted in support of a request for reimbursement, need to be carried out according to these guidelines. Departure from the guidelines is only allowed when the file contains arguments as to why the evaluation has not been carried out or could not be carried out according to the guidelines.

Guideline 1 - The perspective of the evaluation

Guideline 1

The pharmacoeconomic evaluation should be performed and reported from a societal perspective, in which all costs and benefits are included, irrespective of who actually bears the costs or receives the benefits.

Explanation

There is a broad consensus, both nationally and internationally, that on the grounds of welfare-theory the societal perspective should form the basis for pharmacoeconomic evaluation. In addition, the goal of the evaluation and/or the background question that needs to be answered with the evaluation is an important aspect that determines the perspective from which pharmacoeconomic evaluations should be carried out. Pharmacoeconomic evaluations are part of the reimbursement file on the basis of which the Minister decides whether a drug will be included on List 1B of the GVS. The reimbursement question involves the allocation of financial means and consequences for public health. For this reason pharmacoeconomic evaluations should be carried out from the societal perspective in order to obtain a clear insight into the results of placing drugs on list 1B.

Literature


Guideline 2 - Choice of comparative treatment/indication

Guideline 2

The drug for a certain indication should be compared with the standard treatment, or if that does not exist, the usual treatment. This can either be a medicinal or a non-medicinal treatment. The standard treatment is the treatment regarded in daily practice as first-choice, for which effectiveness has been proven.

The permit-holder should make use of the same comparative
treatment, medicinal or otherwise, for the pharmaco-economic evaluation as for the claim of therapeutic (added) value.

**Explanation**

The starting point in assessing new drugs is the comparative treatment and the indication for which reimbursement is being requested. The drug should be compared with the standard treatment, or, if this does not exist, the usual treatment. The standard treatment is the treatment regarded in daily practice as first-choice, for which effectiveness has been proven. The gold standard for determining the effectiveness of treatment is the randomised, double-blind, comparative study. If the effectiveness is as yet unproven or the experience insufficient then the term ‘usual treatment’ is used instead by the Committee of Pharmaceutical Aid (CFH). Usual treatment can be regarded as the treatment used in daily practice by a substantial number of patients for the indication concerned. The standard treatment is determined by the CFH. In determining the (medicinal) standard treatment, the Dutch Pharmacotherapeutical directory ‘Kompas’ forms the guiding principle. If the Kompas does not refer to a standard treatment or an usual treatment, then the subsequent guiding principles are: the Dutch General Practitioner (NHG) Standards, the Dutch Institute for Healthcare Improvement (CBO) Guidelines or the National Transmural Agreements (LTA).

Next most important are the guidelines of the professional groups within the Order of Specialists. Last of all, foreign guidelines are relevant.

The standard treatment for a certain indication can comprise of more than one drug or non-medicinal treatment. The registered indications of drugs form the starting point for determining the standard or usual treatment. Also important are drugs that are not registered for the indication concerned, but which are actually used in practice.

The starting point for assessment is the indication requested for reimbursement by the permit-holder. This indication may be narrower than the registered indication. Due to the assessment for uptake in the GVS, the CFH will in all cases also assess the drug for the registered indication. The pharmacoeconomic evaluation, on the other hand, does not necessarily have to be involved in the entire registered indication of the drug, but must be in accordance with the manufacturer’s claim. Ideally, the indication should be described according to an accepted classification system, for example, the ICPC.

In practice, a number of problems can arise in choosing the comparative treatment. The prescribing behaviour of doctors and therapeutic insights can both change with time. This means that views on the most suitable comparative treatment will also change. What was considered to be a well-founded choice of comparative treatment for a clinical study may, by the time the drug is being registered for inclusion on the list, prove to be no longer the most appropriate choice.

As it is sometimes difficult to determine the standard
treatment for a given indication, manufacturers are provided with the opportunity of consulting the CVZ at an early stage about the choice of comparative treatment.

**Guideline 3 - Analytical technique**

**Guideline 3** If the improvement in quality of life forms an important effect of the drug being assessed, then it is necessary to carry out a cost-utility analysis (CUA). If this is not the case, then a cost-effectiveness (CEA) has to be carried out. If the manufacturer does not expect the drug to have an added therapeutic value, nor that it will be mutually replaceable with (a) different drug(s), then a cost-minimisation analysis (CMA) can be carried out.

**Explanation** In the case of a new drug, research is primarily aimed at determining its therapeutic value and whether it mutually replaceable with another drug. If a drug is not mutually replaceable with another drug, then a pharmacoeconomic evaluation is necessary to assess the costs of the drug in relation to its therapeutic (added) value. All aspects of the treatment, such as intended effects, side effects and their costs, must be included in the evaluation.

When carrying out a pharmacoeconomic evaluation, a choice can be made from a cost-utility analysis (CUA), a cost-effectiveness analysis (CEA) or a cost-minimisation analysis (CMA).

**CUA** Cost-utility analysis (CUA)

A CUA is a specific form of cost-effectiveness analysis, in which the difference in costs (incremental costs) is compared with the difference in effects on health, measured in quality adjusted life-years (QALYs). QALYs combine changes in quantity and quality of life (mortality and morbidity) in a generically combined measurement. In this analysis the quality of life needs to be evaluated with a utilities instrument (see Guideline 6: Assessing quality of life and QALYs). These utilities need to reflect the preferences of society for length of life versus quality of life.

**CEA** Cost-effectiveness analysis (CEA)

In a CEA the differential costs (incremental costs) are compared with the differential effects (incremental effects). The effect measurements used to express that difference can vary considerably, from clinical measurements such as millimetres of mercury in blood pressure, to lives saved or life-years gained. In a CEA, the so-called intermediate outcomes, should preferably be translated into final outcomes, such as
life-years gained.

**CMA**

Cost-minimisation analysis (CMA)

The CMA is applicable if the clinical outcomes of treatment with a new drug and the comparative treatment are almost or completely identical. In the pharmacoeconomic evaluation these equal clinical effects must be sufficiently substantiated. In a CMA only the costs of both treatments are compared.

**Literature**

- Drummond MF et al. (1999), p. 96-225.

**Guideline 4 - Time horizon**

**Guideline 4**

The time horizon of a pharmacoeconomic evaluation must be such that it enables valid and reliable statements to be made regarding the effects and costs of the treatments being compared. This includes both intended and unintended effects and costs (e.g. side effects).

**Explanation**

The effects and costs of the treatments being compared must be measured over the same time-span. The time horizon should provide sufficient opportunities for measuring the most important effects and costs of the treatments being compared. As primary data usually provide insufficient insight into the cost-effectiveness of the treatments being compared in the medium- and long-term, modelling techniques can be used in order to obtain insight (see Guideline 7: Modelling)

**Literature**


**Guideline 5 - Cost identification, measurement and evaluation**

**Guideline 5**

Where possible, the Health Care Insurance Board’s ‘Manual for cost research’ should be applied for the identification, measurement and evaluation of costs. The aim of using this manual is to promote the uniformity and the standardisation of cost measurement and evaluation in pharmacoeconomic evaluations.

**Cost identification**

Pharmacoeconomic evaluations carried out from the societal perspective need to include both the direct and the indirect costs inside and outside the healthcare system. Indirect costs inside the healthcare system not related to treatment must be excluded. When indirect costs outside the health care system (also known as productivity costs) are involved, these need to be calculated using the friction cost method. All categories of costs need to be indicated separately. Separate analyses for productivity costs (an analysis including productivity costs and an analysis excluding productivity costs) should be performed and reported.

**Cost measurement**

After identifying the types of costs that need to be included in
the analysis, the costs are measured. This measurement comprises an inventory of the deployment of people and means during treatment. All cost data obtained from international studies must be validated for use in the Dutch situation.

**Cost evaluation**

The identified and measured cost units subsequently need to be assessed in monetary units.

**Explanation**

The following categories of costs can be distinguished:

**Direct costs within the health care system:**
This cost category comprises all medical costs resulting from the treatment, for example, the costs of medication, diagnostics, hospital admission, etc. It also includes the costs of treating side effects.

**Direct costs outside the health care system:**
An example of direct costs outside the health care system as a result of treatment are travelling expenses of the patient.

**Indirect costs within the health care system:**
These are the medical costs which may arise during life-years gained as a result of the treatment. Medical costs that are not related to the treatment of the disorder may not be included in the evaluation.

**Indirect costs outside the health care system:**
The indirect costs outside the health care system are mainly the costs incurred as a result of loss of productivity. However, costs in other sectors (e.g. education) can also be involved. There are two methods currently in use for calculating the costs resulting from loss of productivity:
1. The Human Capital Approach.
   This method assesses the loss of productivity by multiplying the time that the patient is absent from work by the patient’s income.
2. The Friction cost method.
   The period over which the production loss is calculated is limited to the friction period, i.e. the time that an employer needs to replace a sick employee. After this period, there are hardly any further productivity costs (in contrast to the Human Capital Approach).

The friction cost method results in the best approximation of the real costs to society. The Human Capital Approach by contrast may lead to an overestimation of costs. In pharmacoeconomic evaluations the indirect costs outside the health care sector should be assessed using the friction cost method.

**Literature**

- Oostenbrink JB et al. (2004).
- Drummond MF et al. (1999), p. 31-35.
- Drummond MF et al. (2001), chapt. 4-5.
Guideline 6 - Assessing quality of life and QALYs

Guideline 6

If improvement in the quality of life is an important effect of the drug being assessed, then a cost-utility analysis (CUA) should be performed.

When carrying out a cost-utility analysis, assessments for health states of patients need to be determined in order to calculate the number of ‘quality-adjusted life-years’ (QALYs). The assessments of the health states and the survival data need to be reported separately. The combination of these two elements into a QALY should be presented clearly.

Descriptive quality-of-life questionnaires (generic, illness-related and domain-related) cannot be used as a measurement of effect in pharmacoeconomic evaluations. It is often useful to add such questionnaires to the study, particularly in order to determine the health domains where alterations occur.

Explanation

The assessments (utilities) can be obtained in two ways:

1. In the case of empirical studies, health assessment systems such as EQ-5D, HUI 2/3 which are completed by patients or by proxy, can be used. The replies to the questions are subsequently used to calculate assessments with the aid of algorithms.

2. In case of modelling it is usually not possible to obtain assessments for (all) health states by using data from empirical clinical study (phase III). In this case there are two approaches in order to obtain valid assessments for health states.

a. The first and most appropriate approach is to value health states in the model by taking a representative sample survey from the population with one of the known assessment methods (standard gamble, time trade-off, visual analogue scale).

b. The second approach is to adopt utilities from published studies. If the utilities need to be taken from different sources, then at the very least the method of assessment must be identical, as well as the type of assessor and the context of the assessment task (this is because different assessment methods can result in different utilities). Utilities that have been taken from published studies must also have been assessed as described above.

Literature

- Krabbe PFM et al. (2003).

Guideline 7 - Modelling

Guideline 7

In order to be able to support decisionmaking, the model must be transparent: preferably based on 'peer-reviewed' publications and with a user-friendly electronic version. In
order to make a model transparent, the model must be as simple as possible, and obviously it must include all the most important processes. Modelling should be supplementary, and in line with pharmacoeconomic analysis of the clinical studies (preferably ones that have already been published).

**Explanation**

Use of modelling is often unavoidable in pharmacoeconomic studies for the following reasons: (1) to study and analyse effects and costs during a longer time horizon than that of the clinical studies; (2) to ‘translate’ the data on efficacy obtained from clinical studies into estimates of effectiveness in ‘daily practice’, taking into account, for example, therapy compliance, co-morbidity and the composition of the population; (3) and, to allow comparison of effectiveness and costs between drugs which are not directly compared in empirical studies.

Parameter values for extrapolation in the model study are obtained from empirical data, such as published (clinical) studies and, if possible, obtained from a meta-analysis. In addition to the point estimates, the distribution is indicated that represents the statistical uncertainty (95% reliability intervals) of the point estimates. This distribution is used in probabilistic sensitivity analyses (PSA). If no empirical data are available for parameter values, information will have to be obtained in some other way, such as via an expert panel (see Guideline 11). The uncertainty of the parameter values is then expressed by the spread of answers from the experts. With respect to assumptions in the discount rate, unit costs, sub-groups, patient characteristics and possible model structures, it is possible to conduct an extra analysis in which the PSA is carried out repeatedly.

The validity of the model (‘face validity’, internal and external validity) should be studied and described. Internal validity involves the internal (mathematic) logics of the model and the consistency with the model specification. External validity concerns the agreement of the results of the model with observations from ‘daily practice’ concerning comparable populations or settings as the research setting. The results of the model study have to be compared with studies for other countries and with the results of other pharmacoeconomic models available for the same drug.

**Literature**

- Weinstein et al. (2003).
- Philips Z et al. (2004).
- Buxton MJ et al. (1997).

**Guideline 8 - Incremental analysis**

**Guideline 8**

There should be detailed reports on the incremental values of effects and costs of the treatments to be compared.

**Explanation**

The cost effectiveness of the treatments to be compared is presented by reporting the incremental effects and costs between the treatments.
Guideline 9 - Discounting future effects and costs

Guideline 9
If data on effects and costs are collected over a period longer than one year, then the effects and costs need to be discounted after the first year. In the primary analysis the costs should be discounted at a constant discount rate of 4%. Future effects should be discounted at a constant discount rate of 1.5%.

Explanation
The use of the same discount rate for effects and costs in the first version of the Guidelines was based on three theoretical arguments: (1) the delay paradox, (2) the consistency argument and, (3) the argument of the perfect economic world. In recent literature there has been debate on the necessity of applying the same discount rate for effects and costs, and also on the validity of the abovementioned arguments. The choice of discount rates for effects and costs should be based on changing assessment of effects and costs over time. The choice of a discount rate of 4% for costs was based partly on current returns on obligations and the literature. The choice for a discount rate of 1.5% for the effects is also based on the literature, and on the fact that the (healthy) life expectation of the population is still increasing. The results need to be presented both discounted and undiscounted.

Literature
- Brouwer WBF et al. (2000).
- Gravelle H et al. (2001).
- Klok RM et al. (accepted for publication).

Guideline 10 - Uncertainty analysis

Guideline 10
In explaining the analysis methods, all underlying assumptions must be stated, arranged and substantiated. The most important limitations of these assumptions must also be stated. Sensitivity analyses must be used to show how the results depend on the assumptions made. With respect to the uncertainty of deterministic variables, univariate sensitivity analyses need to be conducted. In relation to the uncertainty of stochastic variables, probabilistic sensitivity analyses need to be carried out in a modelling study.
In the case of an empiric cost-effectiveness analysis based on primary, patient-related data, the uncertainty of costs, effects and the cost-effectiveness relationship need to be reflected with distribution measures. In addition to statistical uncertainty, within empirical studies there remains also the need of univariate sensitivity analysis in order to determine the effect of assumptions, such as the discount rate, estimated cost prices, etc.
The posterior probability of the cost-effectiveness relationship should be indicated in both modelling studies and empirical studies.
The methods used, the choice of parameters and the range of these parameters all need to be stated and substantiated.
Prior to the presentation of a definitive estimate of the costs, effects and a cost-effectiveness ratio, a number of methodological choices have been made and a number of parameters have been estimated. In a sensitivity analysis it is preferred to first formulate an upper and a lower limit for each estimate reflecting the uncertainty margins. Subsequently, one can determine the extent to which the costs, effects and the cost-effectiveness ratio change if the extreme limits are applied. If this procedure is followed successively for all parameters, it is known as a univariate sensitivity analysis. A multivariate sensitivity analysis examines the effect of simultaneous alterations in various variables thereby taking into account the correlation between these variables. When the chance distribution within these values is known, as well as the extreme values of the parameters, then simultaneous ‘random’ draws can be used to determine a new estimate of each parameter. Each combination of estimations results in a new estimate of the costs, effects and the cost-effectiveness ratio. This can be used to present a posterior chance distribution in relation to the results of the study.

All techniques for analysing the uncertainty of the incremental cost-effectiveness need to be extensively motivated with respect to the technique used, the substantiation of the data used, the assumptions made, etcetera.

- Briggs AH et al. (2002).
- Fenwick E et al. (2004).

**Guideline 11 - Use of expert panel**

If there is a lack of research data and an expert panel is consulted for obtaining data for input in a model or for the design of a model, then the (method of) compiling this panel and the way in which consensus is reached must be described in the pharmacoeconomic evaluation based on scientifically accepted methods.

In the pharmacoeconomic evaluation, the manufacturer first needs to demonstrate that the study data are missing. The Health Care Insurance Board needs to have access to this information relating to the expert panel in order to determine the composition and independence of the expert panel. Furthermore, this information provides insight into the way in which consensus is reached within the expert panel. Finally, the data used in the pharmacoeconomic evaluation provided by the expert panel should be clearly documented in the reimbursement file.

- Evans C et al. (2000).
3. Literature

8. Farmacotherapeutisch Kompas, College voor zorgverzekeringen, 2006
17. Krabbe PFM, Adang EMM, Stalmeier PFM. Health-state valuations have been core issues in the field of medical decision making. Medical Decision Making 2003;23(6):542; author reply 543.