Report

Dutch guidelines for pharmacoeconomic research

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1. Summary

On 8 September 1997 the Minister of Public Health, Welfare and Sport asked the Health Insurance Council (Ziekenfondsraad; ZFR) to start formulating guidelines for pharmacoeconomic research. The Minister stated that pharmacoeconomic research conducted according to these guidelines should provide a reliable, reproducible and verifiable insight into the therapeutic value of a drug, the costs that will result from its use and the possible cost savings compared with other drugs and/or treatments. In the future, the Minister intends to use the results of pharmacoeconomic research when making decisions regarding the reimbursement of drugs. Pharmacoeconomic research should therefore be carried out whenever a manufacturer claims that a new drug offers added-value compared with existing treatment options. The responsibility for carrying out and financing this research into new drugs lies with the manufacturer.

For the development of the pharmacoeconomic research guidelines, the Healthcare Committee of the ZFR has set up a Preparatory Committee on Guideline Development (Voorbereidingscommissie Richtlijnontwikkeling; VBR). This committee has focused mainly on the substantive aspects of the pharmacoeconomic guidelines, chosing the Canadian guidelines as their starting point. The Canadian guidelines were select because they are generally regarded as the scientific standard for pharmacoeconomic research. For the purpose of the Dutch pharmacoeconomic guidelines, the Canadian guidelines have been specially adapted to the Dutch situation. During the development process, the VBR submitted a draft of the pharmacoeconomic guidelines for consideration by the field on 30 November 1998. The comments received have led to the draft being revised on a number of points. The draft guidelines were also submitted to a number of foreign authorities on this subject. Their comments were also taken into consideration when amending the text.

The present report on pharmacoeconomic guidelines contains nineteen separate guidelines which together represent the state-of-the-art methodology for pharmacoeconomic research. The report also contains a short outline of the possibilities for incorporating the pharmacoeconomic guidelines into the current evaluation procedures for the inclusion of a new drug in the National Health Service’s list of drugs. In addition, an initial
standard format for reporting pharmacoeconomic research has been drawn up. The ZFR realises that it may take between 4 to 5 years to gain experience in applying these pharmacoeconomic guidelines in the Netherlands. It is also aware that, certainly in the initial period, interpretative differences might arise. The pharmacoeconomic guidelines will be evaluated and adjusted where necessary.
2. Introduction

On 8 September 1997, the Minister of Public Health, Welfare and Sport (VWS) requested the ZFR to start developing guidelines for pharmacoeconomic research (Appendix 1). Pharmacoeconomic research carried out according to these guidelines should provide a reliable, reproducible and verifiable insight into the therapeutic value of a drug, the costs that will result from its use and the possible cost savings compared with other drugs and/or treatments. The intention is that the Minister will be able to use this information to make a sound policy decision as to whether a new drug should be included on the National Health Service’s list of drugs. This means that pharmacoeconomic research will need to be carried out whenever a manufacturer claims that a new drug offers added-value compared with existing treatments. The Minister assumes that the ZFR, when drawing up the pharmacoeconomic guidelines, will make use of the various insights and experience that have been acquired in this field both within the Netherlands and abroad. Those parties most closely-involved should also be given the opportunity to contribute their expertise in this area.

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The pharmacoeconomic guidelines state which data should be provided and which analytical techniques should be applied. This does not mean that researchers need to confine themselves exclusively to what is asked for in the guidelines. For example, if there is sufficient justification to use other analytical techniques as well, these can be included in the report. As a minimum, however, the data and analyses requested by the guidelines should be presented. In very exceptional cases, it is possible to deviate from the guidelines, provided this is sufficiently substantiated.

Below we first explain briefly how the pharmacoeconomic guidelines came into existence. The pharmacoeconomic guidelines themselves will then be discussed. The report concludes with some brief final considerations.
3. **Procedure for the realisation of the guidelines**

At its meeting on 10 February 1998, the ZFR’s Healthcare Committee approved the procedural proposal for the development of pharmacoeconomic research guidelines. The VBR was set up to carry out the actual work on the guidelines. The VBR includes a number of experts who are supervising the development of the guidelines. For a list of the VBR members, please refer to Appendix 2.

At its first meeting (on 23 March 1998), the preparatory committee identified a number of key focal areas. The pharmacoeconomic guidelines must:

- be applicable to the Dutch situation; they must therefore take into account the regulations which apply in this field in the Netherlands,
- harmonise as closely as possible with the existing evaluation system,
- in the first instance be applicable to new drugs with an expected therapeutic added-value.

Responsibility for carrying out this research into new drugs lies with the manufacturer, who must produce the necessary evidence to justify inclusion of the new drugs in the National Health Service drugs list. The manufacturer will also need to finance the research. The Committee realises that some time will need to be allowed to enable the parties involved to acquire practical experience with these guidelines.

Initially the Committee focused on the content of the pharmacoeconomic guidelines, choosing the Canadian guidelines as the starting point. The Canadian guidelines have been selected because they are generally regarded as being the scientific standard for pharmacoeconomic research. Since they were drawn up for the various provinces of Canada, the Canadian guidelines are more general than the Australian guidelines, which were drawn up specifically for applying for inclusion on the Australian drugs list. For the purpose of the Dutch pharmacoeconomic guidelines, some parts of the Canadian guidelines have been adapted to the situation in the Netherlands. It was possible to combine certain aspects in some sections, and certain points have also been clarified. In some places the content differs from that of the Canadian guidelines.

Drawing up guidelines does not take place within a vacuum, but always requires integration into a certain procedure. For this reason, the Committee
has included a brief description of the decision-making process for the inclusion of new drugs on the drugs list in Appendix 3. This is an example of how the pharmacoeconomic guidelines could be incorporated into the present evaluation procedure.

On 30 November 1998, as part of the process of realising the guidelines, the VBR submitted a draft of the pharmacoeconomic guidelines for consideration by the field. The complete report of this conference is given in Appendix 4. The meeting was attended by representatives of the Dutch Organisation for Research-oriented Pharmaceutical Industry (Nefarma), The Royal Dutch Association for the Advancement of Pharmacy (KNMP), the National Organisation for General Practitioners (LHV), The Royal Dutch Association for the Advancement of Medicines (KNMG), the Dutch Association of Medical Specialists (OMS), the Association for Academic Hospitals (VAZ), the Dutch Association of Hospital Pharmacists (NZVA), the Dutch Federation for Patients and Consumers (NP/CF), the Dutch Organisation for Healthcare Insurers (ZN), the Council for Public Health and Care (RVZ), the Committee for the Evaluation of Medicines (CBG) and a number experts in the field. The draft guidelines were also discussed at a separate meeting with representatives of Nefarma only. The report of this discussion is enclosed as Appendix 5. The guidelines were also presented to a number of authorities in the field abroad, including Dr. A. Mitchell and Prof. M.F. Drummond. The reactions of these experts to the draft guidelines were predominantly positive. The text has been ammended in light of their comments.

At the conference on 30 November 1998, an interesting discussion took place on several parts of the pharmacoeconomic guidelines. This also resulted in a number of alterations being made to the draft. For example, discussion about the financial analysis led to the removal of this subject from the guidelines. Instead it was included in the description of procedures surrounding the guidelines (see Appendix 3). This was done in order to stress the difference between the two analyses. The pharmacoeconomic guidelines themselves only cover the scientific methodology of pharmacoeconomic research. The financial analysis is a policy-directed analysis, where choices tend to be based on the existing financing system and current healthcare policy. In view of the fact that incorporation into the evaluation procedure is a reflection of the policy framework surrounding the pharmacoeconomic guidelines, it is was felt that the financial analysis should
be included. However, this distinction certainly does not imply any difference in terms of the importance between the two analyses.

A second point of discussion was Guideline 4 which concerns who should perform the research. A satisfactory procedural description should be sufficient to guarantee the desired independence. This means that - other than stated in the draft - the pharmaceutical industry should be able carry out this research itself.

With respect to the choice of comparative treatment (the comparator), attention was drawn to the fact that many comparative studies are carried out on an international basis. It was also pointed out that the comparator can also be a non-medicinal treatment.

Furthermore, various parties stated that they found some of the methodological restrictions unnecessary. An attempt was made to address this objection as far as possible by including only the minimum of methodological requirements in the guidelines.

Based on Guideline 10 which deals with efficacy and effectiveness, several parties suggested temporary inclusion on the drugs list. This conditional admission has been suggested because only the use of an efficacious drug in practice will demonstrate whether it is effective in terms of treatment and cost. Moreover, such a conditional inclusion would improve the availability of new drugs. However, opinions on this matter still seem divided. Nefarma stated that it does not support the concept, and the ministerial representative explained that many considerations were involved in their rejection of the option of conditional inclusion. Notwithstanding the social unrest caused when a medicine is excluded from the reimbursement system at a later date, conditional admission in fact only means that the final decision being postponed. In addition, conditional admission also requires financial input and the definite evaluation of added-value status needs to be tested under controlled conditions, which can lead to a delay in the drug’s availability to all patients.

The last important point of discussion was the accessibility of confidential data. The conclusion was that it may sometimes be necessary to have access to additional, more detailed data in order to be able to make the appropriate decision concerning a drug’s inclusion on the drugs list. In providing such

1 This is in reference to the report concerning the inclusion of new drugs on the drugs list (ZFR publication no. 746). In this report the Ziekenfondsraad suggested the possibility of including new drugs on the list on a temporary basis in a so-called Appendix 1C.
additional data, confidentiality of patient information and the fact that clinical research dossiers are closed should obviously be taken into account. The importance of an evaluation of the pharmacoeconomic guidelines has been emphasised by several parties. In such an evaluation, the above-mentioned points in particular will be subjected to detailed examination. The results of the evaluation will, where necessary, lead to further clarification or adjustment of the guidelines. It is important to check whether the pharmacoeconomic guidelines are indeed able to guarantee transparency and correct execution of research.
4. **Guidelines for pharmacoeconomic research**

The guidelines for pharmacoeconomic research are presented below. They reflect ‘state-of-the-art’ methodology. The accompanying explanations provide further elaboration where necessary, as well as indicating the area of application for healthcare policy.

**Guideline 1 : Target groups**

The primary target of pharmacoeconomic research is the Minister of Health, who decides whether the costs of a drug are to be reimbursed. Secondary target groups include patients, prescribers, suppliers, hospitals, insurers and researchers.

**Explanation**

In the Netherlands, drugs are evaluated by the ZFR. The Minister of Health ultimately decides whether a drug will be included (and will remain included) on the drugs list. Pharmacoeconomic research will provide insight into the cost-effectiveness of the drug.

**Guideline 2 : The perspective**

All studies must be reported from a social perspective.

**Explanation**

Pharmacoeconomic research must be conducted from a social perspective. There is a broad consensus, both nationally and internationally, that on the grounds of welfare-theory the social perspective should form the basis for pharmacoeconomic evaluation. This social perspective means that the analysis should cover all costs and benefits, irrespective of who actually bears the costs or receives the benefits. This means that costs and benefits outside the field of healthcare should also be taken into consideration. Healthcare itself should therefore be considered as a whole (in other words, non-compartmented): additional costs for one budget section can be compensated, for example, by savings in another budget section. Pharmacoeconomic research can provide insight into such substitution effects.
Guideline 3 : Timing of the studies
Pharmacoeconomic studies can be performed at any stage (Phases II-IV) of the development of a drug. When the decision whether or not to include a drug on the list is to be made, the pharmacoeconomic data conforming with these guidelines must be available.

Explanation
The Dutch Health Minister is anxious to include information from pharmacoeconomic research in her decision-making concerning the inclusion of new drugs on the list. The research must therefore provide as up-to-date an insight as possible on the cost-effectiveness of the proposed drug.

Guideline 4 : Perpetrator of the study
Pharmacoeconomic studies can, in principle, be carried out by any qualified researcher. All research needs to be consistent with these pharmacoeconomic guidelines. There should be transparency concerning the perpetrator(s) of the study and the relationships between the perpetrator(s) and the contractor.

Explanation
Pharmacoeconomic studies can, in principle be carried out by the pharmaceutical industry, scientific institutes, consulting bureaux or any combination of these. A qualified researcher is a person with a research training and experience, who is familiar with the background and requirements of the study and who is known to be a person with high ethical standards and good professional ethics (GCP guidelines). The research protocol should always be consistent with these guidelines.

There must be transparency with respect to the perpetrator(s) of the study and the relationship between the contractor and the perpetrator(s) of the study. This means that if parts of the dossier (or the whole dossier) have been prepared by one or more research-groups, it must be clearly stated what conditions were applied. Information must be provided about the contractual relationship relating to financing, publication rights and other conditions and agreements. This can be achieved, for example, by providing a copy of the (standard) contract.
Sometimes extensive pharmacoeconomic research for a new drug may have been carried out abroad. In such cases a sound translation to the Dutch situation, accompanied by any necessary supplementary information, may suffice, provided that applicability of the results to the Dutch situation has been adequately demonstrated. Transparency, as described above, is also required for such translations of foreign results to the Dutch situation.

**Guideline 5 : Analytical technique**

If a drug has a therapeutic added-value compared with existing drugs, then the research must include a cost-effectiveness analysis and/or a cost-utility analysis, depending on the intended effect of the drug and the disorder for which it is intended. A cost-utility analysis is particularly appropriate if there are differences in the quality of life.

**Explanation**

In the case of a new drug, research is primarily aimed at determining its therapeutic value. If the drug has a therapeutic added-value, then its costs and how these costs relate to the therapeutic added-value must be defined by means of an economic evaluation. All aspects of the treatment, such as side-effects and their costs, must be included in the evaluation.

For the economic analysis of new drugs a choice can be made between a cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) or cost-benefit analysis (CBA).

**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 a CMA, only the costs of both treatments are compared.

**Cost-effectiveness analysis (CEA)**

In a CEA the differential costs are compared with the differential effects measured in physical units. These physical units can vary considerably, from clinical measurements such as millimetres of mercury in blood pressure, to lives saved or life-years saved. In a CEA, the so-called intermediate outcomes, such as the millimetres of mercury in blood pressure, should preferably be translated into final outcomes, such as life-years saved.
Cost-utility analysis (CUA)
A CUA is a specific form of cost-effectiveness analysis in which the (differential) costs are compared with the health effects measured in quality-adjusted life-years (QALYs). QALYs combine changes in quantity and quality of life (mortality and morbidity) in a joint measure which in principle is independent of the type of healthcare programme or disease process. In this analysis the quality of life needs to be evaluated with a utilities instrument. These utilities need to reflect the preferences of society (in view of the social perspective) for length of life versus quality of life.

Cost-benefit analysis (CBA)
In a CBA costs and effects are both expressed in monetary terms, making an overall comparison possible.

These guidelines stipulate that for each case either a CEA or a CUA should be presented. The CMA has not been included in the guidelines, because it is only appropriate if the clinical outcomes of treatment with the new drug and the comparative treatment are comparable.
Given that an economic analysis is only required when added-value is claimed for the new product, a CMA is irrelevant in this context. If the new drug has an equal therapeutic value to (a cluster of) existing drugs, it can be included in Appendix IA of the Pharmaceutical Aid Regulation (Regeling farmaceutische hulp), and it will be assigned a reimbursement limit.

For a CBA, the WTP (willingness to pay) method is currently regarded as the best evaluation method of the effects observed. The WTP approach is, however, still under development (i.e. experimental), and no consensus has yet been reached. For this reason, research with a CBA as the sole analytical method is presently considered to be insufficient. If the researchers consider that there are good arguments for using the CBA method, they can include it in the report. A CEA or a CUA must, however, be presented.
Guideline 6 : Indications
The patients for whom the drug is intended must be clearly specified. The starting points for pharmacoeconomic research are the registered indications. The subgroup analyses for patient groups, disease subtypes, degree of seriousness, presence or absence of comorbidity, etc., must all be stated. The economic evaluation must be performed on the entire study population and also on the subgroups that have been identified in the protocol on the basis of possible differences in effectiveness, costs and/or other arguments.

Explanation
Because a treatment can be cost-effective for some groups of patients but not for others, it is essential that a prior distinction is made in the protocol between the different subgroups. Sometimes these subgroups will already have been clearly described in the registration text. These will then be the subgroups on which clinical research has been performed and for which the efficacy-safety balance has been found to be positive. From the point of view of cost-effectiveness, the results of a pharmacoeconomic analysis may suggest that the field of application should be limited further within the registered range of indications. These results can be taken into account during the decision-making process.
In the case of subgroup analyses, care must be taken that the statistical power of the analyses, i.e. the group size, is guaranteed. The precision needs to be sufficient to enable decisions to be taken regarding the subgroups.

Guideline 7 : The comparative treatment
In principle, the drug should be compared with the standard treatment or the usual treatment. This can be either a medicinal or a non-medicinal treatment. The standard treatment is the treatment regarded in daily practice as the first-choice for which effectiveness has been proven.

Explanation
The economic evaluation of a drug is always based on comparison with another treatment. The outcome of that comparison will be largely determined by the choice of the comparator. Selecting the right comparative treatment is therefore vitally important, not only for the economic evaluation but also when evaluating the therapeutic value of the drug. In choosing the
comparator, it is important to adhere as closely as possible to the current guidelines and evaluation procedures. According to the Canadian guidelines, a pharmacoeconomic evaluation must compare the drug both with existing practice and with one of the two following alternatives: either the most cost-effective treatment or ‘doing nothing’. This means that it is usually not sufficient to make just one comparison, because cost-effectiveness needs to be compared not only with the treatments which the new drug will replace, but also with the most cost-effective treatment. Ideally, this means that the cost-effectiveness of the comparison treatments should also have been evaluated. This is certainly not always the case, and it is questionable whether the manufacturer wanting to market a new drug should be expected to carry out this additional research. The Australian guidelines are more pragmatic regarding the choice of comparator: if a new drug belongs to an existing pharmacotherapeutic group, then in principle the most frequently prescribed drug within that group should be chosen. If the drug belongs to a new pharmacotherapeutic group, but is intended for an indication for which other drugs are available, then the drug most frequently prescribed for that indication should be chosen. These considerations are in close agreement with the system used by the ZFR’s Central Medical Pharmaceutical Committee (Centrale Medisch Pharmaceutische Commissie - CMPC; to be known in the future as the Committee for Pharmaceutical Aid - CFH), when choosing comparative drugs for evaluating therapeutic value. The CMPC uses the concepts of ‘standard treatment’ and ‘usual treatment’. The standard treatment is the treatment regarded in common practice as the first-choice treatment, for which the effectiveness has been proven. If the effectiveness is as yet unproven and the experience insufficient then the term ‘usual treatment’ is used instead. The Dutch Pharmacotherapeutical directory ‘Kompas’ states which drugs can be regarded as standard or usual treatment. The comparative treatment can also be a non-medicinal form of treatment.

A number of problems can arise in the practical application of these guidelines. 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 comparator for Phase 3 studies may, once all the clinical studies have been concluded, or by the time the drug is being registered for inclusion on the list, prove to no longer be the most appropriate choice. It is also important that clinical research with new drugs has a markedly
international character; when choosing the comparison model, a manufacturer cannot be expected to take all possible views and desires into account. The choice made may deviate from what would normally be regarded as ‘standard’ in the Netherlands. This choice will have to be supported by arguments demonstrating a close a connection with generally-accepted guidelines and protocols.

Since it is so important that the comparative treatment should adhere as closely as possible to the Dutch situation, consultation on the choice will usually be necessary before carrying out pharmacoeconomic evaluation.

**Guideline 8: Incremental and total analysis**

Costs and effects must be reported in the form of incremental values (i.e. as differences between two alternatives). These incremental values must be used in the pharmacoeconomic evaluation. The study must also provide insight into the total values of the costs and effects of both treatments.

**Explanation**

In an economic evaluation we are concerned with an incremental analysis: what is the difference in costs and effectiveness when intervention A is replaced by intervention B? Two treatments need to be compared: the current treatment (standard treatment, see guideline 7) is compared with the new drug. From the incremental analysis one can deduce what the (net) difference in costs and effects will be when the new treatment replaces the existing one. In order to place the outcome of the incremental analysis in a broader context, the total costs and effects also need to be reported. The inclusion of total costs and effects will, moreover, improve the ability to translate the study to, for example, (future) situations with another comparative treatment.

**Guideline 9: Analysis period**

The analysis period of the study must be such that it enables valid and reliable statements to be made. If modelled data are necessary to meet this requirement, then the model’s structure and basis need to be described. The model must have a sound scientific basis at the time the study was performed.
Explanation
The costs and effects must be measured over the same time-span. This time-span should provide sufficient opportunities for observing the most important outcomes of the intervention. The time period within which effects and costs can be anticipated depends on the treatment goal and thus on the anticipated outcome. When a decision has to be made regarding the inclusion of a new drug on the list, there is often insufficient information available about its effectiveness. To obtain this information, the drug needs to be used in practice.

Because primary data usually provide insufficient insight into the value of a drug in the medium- and long-term, modelled data will often have to form an integral part of the dossier being submitted in application for inclusion on the drugs list.

Guideline 10: Efficacy versus effectiveness
Ideally, pharmacoeconomic studies should report on a drug’s effectiveness, and not on its efficacy.
Efforts should be made to collect information on the relevant end points in terms of morbidity and mortality. If possible, the data should be collected under realistic conditions. If no effectiveness data are available, then appropriate modelling techniques may be used to translate data from efficacy studies into what can be expected in practice (i.e. effectiveness). The model used needs have a sound scientific basis. All assumptions in such modelling techniques must be explicitly stated and evaluated with the help of a sensitivity analysis.

Explanation
Efficacy and effectiveness are two different concepts. However, both provide insight into the effect of a drug. In the case of efficacy, the effect is examined under ideal conditions in a homogeneous group of patients, and usually whilst making use of intermediate outcomes. Effectiveness data offer a clearer picture of actual value because an effect is studied under more realistic conditions, making use of a heterogeneous group of patients, and with aspects such as therapy (non-)adherence playing a role. This information about use in common practice also provides more insight into whether the treatment aim is ultimately being achieved. Effectiveness research is thus oriented towards final outcomes, such as reduction in morbidity and mortality.
The ZFR would like to have access to effectiveness data as soon as a drug is put forward for inclusion on the drugs list. However, from a practical perspective this is not usually possible. Phase 3 studies form the basis for registration and admission to the market. This research is carried out on a select group of patients using a clear treatment protocol, and tends to be done in specialised centres, for a limited period of time and without a follow-up after the study has finished. These are not ideal circumstances for pharmacoeconomic research, in view of the fact that research conditions need to match the practical situation as closely as possible. The most important problem with using clinical studies for pharmacoeconomic research is the extent to which an evaluation based upon intermediate outcomes provides any meaningful information on the reduction in morbidity and mortality. For this reason, it is necessary to obtain satisfactory insight into the relationship between the intermediate outcomes and the final outcomes. In order to be able to make a statement on a drug’s effectiveness, data from clinical studies can be modelled on the basis of realistic and explicit assumptions. All assumptions need to be carefully discussed and scientifically substantiated. Important variables in the study need to be examined for validity and reliability. Further studies after registration (Phase IV), will have to demonstrate the extent to which the modelling was performed responsibly.

Guideline 11: Quality of life and utilities
The quality of life (QOL) can be measured using generic and disorder-specific questionnaires. The quality of life can be evaluated using a utility instrument.
If a CUA is carried out, then the quality of life must be evaluated by means of a utility instrument. Given the social perspective, a representative random sample from the population is the most suitable source of data for the evaluation of the quality of life in utilities. The choice of instruments must be justified.

Explanation
If the quality of life is to be included in the research design, it needs to be reliably measured and evaluated. The decision of whether to include it or not needs to be supported by arguments.
When measuring the quality of life, two different sorts of questionnaires are usually distinguished: disorder-specific and generic questionnaires. The evaluation of the quality of life is carried out with the assistance of utilities.

Disorder-specific questionnaires
Items in these questionnaires are specifically aimed at the dimensions of the quality of life that are most affected by the disorder. This means that disorder-specific questionnaires are more sensitive to alterations in the quality of life than generic questionnaires. However, it is this very specific property that makes comparison between various diseases almost impossible. Economic evaluations are specifically aimed at comparing the costs and effects of different healthcare provisions with one another.

Generic questionnaires
These questionnaires cover the concept of quality of life as broadly as possible. They can therefore be used for any group of patients and the scores can be compared with data from other groups of patients and healthy subjects. Due to the fact that the quality of life is expressed in general terms, generic measurement instruments are less sensitive than those for disorder-specific measurements. To measure the generic quality of life the MOS 36-item Short Form Health Survey (SF-36) and the EuroQol are recommended.

Utilities
By making use of utilities, the quality of life can be expressed as a single figure. This is usually called the valuation of the quality of life. The value of such a valuation is usually referred to as a utility. There are various methods for determining the utility of a state of health. The most direct method is by means of interview techniques such as the Standard Gamble and Time Trade-Off. A Visual Analog Scale can also be used, and can be administered in writing as well. However, the validity of the Visual Analog Scale is open to question.

Some generic quality of life questionnaires allow valuations of the state of health to be made, i.e. utilities (indirect method). Two widely-used systems are the EuroQol and the Health Utility Index.

The utility of the state of health can be determined by the patient himself or by the general public. If the utility of the state of health is derived from the general public, it is known as the ‘social perspective’. The social perspective is preferred in economic evaluations of healthcare.
In an economic evaluation study it is generally advisable to include both a disorder-specific and a generic quality of life questionnaire. The disorder-specific questionnaire will be sensitive enough to detect the effects and the generic questionnaire will provide an impression of the extent of the effects.

For a CUA it is necessary to include a valuation instrument (utility instrument), to enable the calculation of quality-adjusted life-years (QALY’s).

**Guideline 12 : Outcomes for cost-utility analysis**

Survival and QOL-results must be reported separately. The method for combining the two must be clearly described. The recommended method for primary analysis is to combine survival data with the QOL valuation using quality-adjusted life-years (QALYs). Utilities must be used as quality-weighting for the calculation of QALYs, measured on an interval scale, where 0 represents the state of death and 1 represents good health.

**Explanation**

The choice of one uniform outcome measure, the QALY, makes it possible to compare the results of different pharmacoeconomic studies. At the moment the QALY is internationally the most widely used and most recommended method. Primary analysis should therefore be based upon QALY’s. Secondary analyses may be performed using a different outcome measure. The World Bank, for example, has proposed the disability-adjusted life-year (DALY) as an alternative to the QALY.

**Guideline 13 : Cost identification**

From the social perspective, the direct costs, both inside and outside healthcare, must form part of the analysis. As far as the indirect costs inside the healthcare system are concerned, any costs due to illnesses which are not related to the intervention must be excluded. If there are any indirect costs outside the healthcare system, then they should be stated separately (two analyses: one with and one without these costs). It must be stated why these costs are considered important and which method has been used to calculate them. The preferred method is the friction cost approach.

**Explanation**

The following cost categories can be distinguished:
Direct costs within the healthcare system:
From a social perspective, the direct costs within the healthcare system must form part of the analysis. These are the medical costs of prevention, diagnosis, therapy, etc.

Direct costs outside the healthcare system:
From a social perspective, the direct costs outside the healthcare system must form part of the analysis. An example of such costs are a patient’s travelling expenses.

Indirect costs within the healthcare system:
These are the medical costs which may arise during life-years that have been saved. It is increasingly recommended that these costs should only be included in the analysis if there is a clear relationship with the intervention. Costs of illnesses that are not related to the intervention should be omitted from the analysis.

Indirect costs outside the healthcare system:
In the case of indirect costs outside the healthcare system, the focus is mainly on the costs of production losses. However, it can also involve costs in other sectors (e.g., education). One approach for determining these costs is the human capital approach (HCA). This method is controversial, however, because it can lead to extremely high outcomes (for the savings made), which raises the question of whether the results are realistic. This is because in the HCA, the potential (and, in theory, maximum) production loss is calculated by totalling the loss of earnings from the moment of morbidity/mortality to the moment of retirement. There are various arguments in the literature that show why the HCA leads to overestimation. Whether actual production loss occurs (and the degree to which this occurs) depends on, for example:

- unemployment in the product market concerned (someone who is ill can be replaced by someone who is unemployed);
- the internal labour reserves within companies;
- ‘replaceability’: the more specialised a job is, and the more expertise or training it requires, the greater the loss of production will be.

An alternative approach to HCA is the ‘friction cost method’. The period over which the production loss is calculated is limited to the friction period, i.e. the period between the initial absence and the actual moment of
replacement. This period is currently estimated to be some 3 months on average. Due to the above-mentioned overestimation, the human capital method is not the method of choice. It is preferable to use the friction cost approach.

For the sake of completeness, it should be mentioned that costs incurred as a result of the research itself should not be included.

**Guideline 14 : Cost measurements**

The deployment of people and resources during a treatment must first be described in natural (non-monetary) units, such as hours, tasks, nursing days or daily doses. All cost data obtained from international studies must be validated for use in the Netherlands.

**Explanation**

A distinction should be made between volume and price when presenting the costs. The natural units should be shown in as much detail as possible. Showing the deployment of people/resources in volume units also makes the study more easily transferable to other countries/situations.

**Guideline 15 : Cost evaluation**

Economic definitions should be used for the costs. Ideally, uniform amounts should be used for certain cost categories in order to promote the comparability and extrapolability of the results of different studies.

**Explanation**

A standard cost list will be available in mid-1999. This list must be used.

**Guideline 16 : Discounting for future outcomes and costs**

Future outcomes and costs should be discounted at equal rates. The current discount rate must be applied. This discount rate must be varied in a sensitivity analysis. If other percentages are used as the basic discount rate, they need to be thoroughly substantiated.

**Explanation**

Internationally, different percentages are used as basis for discounting. At the moment the current discount rate in the Netherlands is 4% according to the ‘Cabinet’s standpoint on the reconsideration of the discount rate’ dated 9

**Guideline 17: Reliability and validity**

In explaining the analysis methods, all underlying assumptions must be listed, arranged and substantiated. The most important limitations of these assumptions must also be stated. A sensitivity analysis must be used to show how the results depend on the assumptions made. As a minimum, a univariate sensitivity analysis must be included. If this is insufficient, then multivariate techniques must be included. The methods used, the choice of the parameters and the range of these parameters all need to be stated and substantiated.

**Explanation**

Prior to presenting a definitive estimate of the costs, the effects and a cost-effectiveness ratio, a number of methodological choices will have been made and a number of parameters estimated. The methodological choices concern, for example, the calculation of indirect costs, the definition of the effects and the time window. The estimates relate to aspects such as the use of healthcare facilities, unit prices and the effect parameters.

In performing sensitivity analyses, it is desirable to first formulate an upper and lower limit for each estimate; these represent the uncertainty margins. One can then examine to what extent the costs and the cost-effectiveness ratio will alter if the extreme limits are applied. If this procedure is followed for all estimates successively, it is known as a univariate sensitivity analysis. A multivariate sensitivity analysis examines the effect of simultaneous alterations in various variables, taking into account the correlation between these variables. The most advanced method attempts to create probability distributions around each parameter and repeatedly makes a new estimation for each parameter according to the distributions. Each combination of estimations results in a new estimate for the costs, effects and the cost-effectiveness ratio. If this is repeated many times, a risk distribution can be presented for the results of the study.

If there are indications that a univariate sensitivity analysis is insufficient, then a multivariate analysis should be carried out.

It is important to adopt the perspective of the end-users of the information as a starting point. By making use of the sensitivity analyses results, policy-
makers can assess how much value can be attached to the results of the economic analysis, i.e. how reliable the results are.

**Guideline 18: Reporting the studies**

All the results must first be displayed individually in a detailed format. Reporting should adhere to the enclosed standard format.

**Explanation**

Results must be reported according to the enclosed standard format (Appendix 6). The enclosed standard format for reporting is a first draft and for the time being consists only of a set of headings. The standard format will be further elaborated later.

In principle, it should be possible to make a decision on inclusion on the drugs list based on the presentation of such data and the results of the research. Additional more detailed research data may be necessary to enable a thorough consideration when inclusion on the list is being decided. When providing additional data, the confidentiality of patient data and the closed nature of clinical research dossiers must be taken into account.

**Guideline 19: Modelling of results**

The use of modelling techniques is often unavoidable in pharmacoeconomic studies. There are two different and important situations in which the modelling of data is used. The first is to obtain effectiveness data from efficacy data. The second occurs if the data originated from a study which was carried out in another country with a different healthcare system. This is of particular importance in the context of multinational studies. The modelling of data must be carried out with great care. Choices made need to be substantiated.

**Explanation**

As far as the first aspect is concerned (i.e. the extrapolation of effectiveness from efficacy), the reader is referred to Guideline 10.

It is a fact in the Netherlands that studies are often carried out internationally. The results of these international studies must be translated to the Dutch situation according to the guidelines. The translation should take into account demographic and epidemiological differences, differences in the provision of healthcare, differences in (financial) incentives for healthcare providers and differences in relative prices.
5. **Final considerations**

After a brief introduction and description of how the Dutch guidelines came into existence, this report describes the Dutch guidelines for carrying out pharmacoeconomic research. A Preparatory Guideline Development Committee (Voorbereidingscommissie Richtlijnontwikkeling, VBR) was set up for the development of the guidelines. This Committee took the Canadian guidelines as its starting-point and drafted the Dutch pharmacoeconomic research guidelines. The necessary experience has already been acquired with the Canadian guidelines and this has led to a number of alterations. In the meantime the Canadian guidelines have received international recognition as a guiding principle for carrying out pharmacoeconomic research.

The VBR has tailored the Canadian guidelines to Dutch practice and has, where necessary, introduced certain modifications. A number of guidelines have been combined for extra clarity, although this has had no consequences in terms of their contents. In addition, the guidelines have been formulated somewhat more pragmatically with respect to the choice of the comparative treatment. On this issue the Australian guidelines were consulted.

The guidelines have adopted the social perspective as their starting-point. This means that direct costs, inside and outside the healthcare system, need to be included in the analysis. Indirect costs inside the healthcare system, which are not related to the intervention, can be excluded. If there are indirect costs outside the healthcare system, they should be mentioned separately. Use of the friction cost approach is preferred for calculating these costs. A new standard cost list will be available from mid-1999 for the purpose of uniformity of costs.

Pharmacoeconomic research needs to be carried out if a manufacturer is claiming added-value for a new drug compared with the existing treatment. Responsibility of carrying out and financing this research therefore lies with the manufacturer. The guidelines provide clear instruction as to how this research should be carried out.

The ZFR realises that that some experience (4 to 5 years) will need to be gained in the use of these pharmacoeconomic guidelines in the Netherlands.
The ZFR also recognises that differences in interpretation may occur, especially in the beginning. The pharmacoeconomic guidelines will be evaluated and adjusted where necessary.

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The Chairman of the Ziekenfondsraad

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L. de Graaf
Literature consulted

Baladi JF, Menon D, and Otten N. Use of economic evaluation guidelines: 2 Years’ experience in Canada. Health Econ. 7:221-227, 1998


Canadian Coordinating Office for Health Technology Assessment. Guidelines for economic evaluation of pharmaceuticals: Canada, 2nd ed. CCOHTA. Ottawa, 1997


Drummond MF. Guidelines for pharmacoeconomic studies; the ways forward. Pharmacoeconomics 6(6):493-497, 1994

Drummond MF and Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 313:275-283, 1996


Essink-Bot ML en Haes JCJM de. Kwaliteit van leven in medische onderzoek; een inleiding. Amsterdam, Amsterdam University Press, 1996


Koopmanschap MA en Rutten FFH. Berekening van kosten van zorg; Vaak onderschat in economische evaluatiestudies. TSG 76:83-88, 1998


Rutten FFH, Busschbach JJ van, Hout BA van, Koopmanschap MA en Michel BC. Economische evaluatie van gezondheidszorgprogramma’s; Principes en instrumentarium. TSG 76:74-82, 1998


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