HAS

HAUTE AUTORITÉ DE SANTÉ

A METHODOLOGICAL GUIDE

Choices in Methods for Economic Evaluation

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Department of Economics and Public Health Assessment

Contents

Abbreviations

Table 1: Abbreviations used in the text	
Abbreviation	**Meaning**
CEA	Cost-effectiveness analysis
CEESP	Commission for Economic Evaluation and Public Health
CES	French College of Health Economists
CUA	Cost-utility analysis
ENCC	National costs study
EQ-5D	The European Quality of Life 5-Dimensions questionnaire
DRG	Diagnosis-related group
HRG	Healthcare resource group
HRQL	Health-related quality of life
HAS	Haute Autorité de santé (French National Authority for Health)
HUI	Health utilities index
ICER	Incremental cost-effectiveness ratio
INSEE	National Institute of Statistics and Economic Studies
LDD	Long duration disease
LY	Life years
PMSI	French national computerised medical information system
QALY	Quality-adjusted life year
SF-36	Short-form 36

Foreword

The French National Authority for Health (*Haute Autorité de Santé* or HAS) was set up by the Health Insurance Law of 13 August 2004 to promote the quality of care for patients and help maintain a healthcare system based on solidarity and fairness. It therefore supports healthcare professionals in the continuous improvement of practices, and through its opinions HAS contributes to informing public decision-making to optimise the management of medical products and services which are reimbursable.

Maintaining a fair healthcare system that is also based on solidarity involves reconciling improvements in the quality of the healthcare system with severe public spending constraints. From this point of view, the Social Security Financing Act for 2008 gave HAS responsibilities in the area of economic evaluation: *"as part of its missions, HAS issues health economics assessments and opinions on the most efficient strategies for healthcare, prescribing or concerning more efficient care management"* (Article 41). In order to carry out this new task, a multidisciplinary committee dedicated to the economic evaluation and to the assessment of public health campaigns and programmes as been established. HAS' opinions contribute to optimizing the allocation of collective health resources, as a support to public decision-making.

Since 2008, HAS has included economic evaluations in its work programme with the aim of better formulating its methodology in the course of its work out and in dialogue with its partners.

Subsequently, HAS decided to set out a methodological framework for its economic evaluations. Drawing on its vast experience and the in-depth work on economic evaluation methods within the Economic Evaluation and Public Health Committee, HAS strives to present and share the principles and methods that it uses in economic evaluation analyses, comparing the health effects to be expected from health care with the resources used to produce such care.

Chair of the HAS Board

Summary of the Methodological Guidelines

The HAS reference case analysis complies with the 20 methodological guidelines presented here. To maintain a balance between scientific and operational concerns, some guidelines need to be applied systematically in an evaluation. Other guidelines may be preferred, but may not be followed when this choice is clearly justified. This methodological framework is for the reference case analysis, in accordance with HAS principles (see the presentation of the reference case analysis, page 12).

STRUCTURING HEALTH ECONOMIC EVALUATION

Guideline 1: The economic evaluation method

The reference case analysis uses cost-utility analysis and/or cost-effectiveness analysis as methods of evaluation. The choice of the method to use depends on the nature of the expected health effects of the interventions under study.

- If the intervention is expected to have an important impact on health-related quality of life (HRQL), cost-utility analysis must be used. The health outcome to use is patient's length of life weighted by a valuation of the HRQL. The cost-utility analysis is always accompanied by a cost-effectiveness analysis which uses length of life as health outcome.

- If health-related quality of life is not identified as a relevant health effect of the interventions studied, cost effectiveness analysis is the required form of economic evaluation and the health outcome is measured by length of life.

- Any other choice must be duly justified.

Cost-benefit analysis is not recommended in the reference case analysis, but it can be presented as an additional set of information.

Guideline 2: The perspective

The reference case analysis adopts a collective perspective that is sufficiently broad to take into account all stakeholders concerned by the treatments studied, in the French health system.

The economic evaluation has to be made under the real conditions.

The production costs of the interventions studied are identified, measured and valued independently of their source of funding.

The health effects are identified and measured from the perspective of individuals affected by the interventions. When preference-based scores are used for valuation of changes in HRQL, they are obtained from a representative sample of the general population.

Guideline 3: The population analysed

The population in the reference case analysis consists of all individuals whose health is directly or indirectly affected by the interventions studied. Any exclusion is to be justified.

The economic evaluation may justify the analysis of particular subgroups of the population for whom health effects or costs are expected to differ from the population.

Guideline 4: The interventions to compare

Economic evaluation is a comparative approach.

The reference case analysis identifies all interventions that compete with the intervention evaluated in the population analysed.

The arguments on which an intervention's inclusion or exclusion from the analysis is based are duly justified.

Guideline 5: The time horizon

The reference case analysis uses a time horizon which is long enough to reflect all expected consequences in costs and health effects between the interventions being compared.

The time horizon is identical for all the interventions being compared. It depends on the natural history of the disease, the chronology of the interventions, the occurrence of changes of health effects and costs related to the interventions compared.

Guideline 6: The discounting method

Future costs and health effects are discounted to reflect their present value.

The reference case analysis uses the French social discount rate which has been set at 4% since 2005, for time horizons of less than 30 years with a reduction of up to 2% thereafter. This rate may be reassessed.

In the reference case analysis, HAS considers that the relative prices of the health effects for the community do not change over time. The costs and health effects are thus discounted at the same rate.

A sensitivity analysis is needed to assess the robustness of the evaluation results concerning the chosen discount rate.

An anticipated variation in the relative price of a health effect over time may be considered in an additional analysis.

Guideline 7: The data used in economic evaluations

Economic evaluation reports include a systematic review of the clinical and economic studies conducted on the intervention in question, respecting good practices in terms of literature search, selection and critical analysis.

For both health effects and costs, economic evaluations draw on different types of studies, taking into account their relevance and ability to limit biases, while reflecting the realities of medical practice. Clear explanations of the limits of data make it possible to document the impact of data use on the conclusions of an evaluation.

Sources of variability and uncertainty concerning the health effects and resources use are identified and dealt with by suitable methods.

French data are preferred in the reference case analysis. When foreign data have to be used, a rigorous analysis is made of their relevance to the French context.

EVALUATING HEALTH OUTCOMES

Guideline 8: Identification and measurement of health outcomes

All the health effects likely to vary between the interventions being compared in the analysed population are identified for the appropriate time horizon.

In the reference case analysis, health outcomes are chosen according to the type of health effects previously identified. To measure the chosen health outcomes, HAS recommends the choice of generic criteria to promote the comparability of studies.

The health outcomes are identified and measured under conditions that are as close as possible to usual daily practice.

Guideline 9: Health outcome evaluation in cost-effectiveness analyses

In a cost-effectiveness analysis, length of life is the preferred health outcome, expressed in life years (LY), and calculated from all-cause mortality.

If the data needed to measure LY are unavailable or it is not possible to produce them at reasonable cost and within a reasonable time, a cost-effectiveness analysis can be made on the basis of another health outcome criterion. A criterion related to LY is preferred.

Inability to use length of life as a health outcome in the cost-effectiveness analysis as well as the choice of a criterion other than LY must be duly justified.

Guideline 10: Health outcome evaluations in cost-utility analyses

In a cost-utility analysis, the health outcome is the length of life weighted by health-related quality of life and is expressed in QALYs. This allows the life years to be weighted with a preference-based score.

It is recommended to use health status classification systems for which validated preference-based scores are available in France. At the time of writing this guide, only EQ-5D and HUI3 were available.

French empirical data on life expectancy and preference-based scores are preferred. In the absence of any such data, it is possible to use preference-based scores from foreign studies, subject to a critical analysis of their quality.

If the data needed to calculate QALYs are not available or cannot be produced at a reasonable cost and within a reasonable time, a cost-effectiveness analysis can be conducted. Inability to use QALYs and the choice of another criterion is duly justified.

EVALUATING COSTS

Guideline 11: The economic evaluation is based on production costs

The cost classification used by HAS is based on the distinction between resources used in the production process of an intervention (direct costs) and other resources (indirect costs).

Economic evaluation at HAS is based on the analysis of production costs. Consequently, only direct costs are taken into account in reference case analysis, and included in the incremental cost-effectiveness ratio. An analysis of the indirect costs, if considered relevant by the author of the study, is presented in an additional analysis.

Guideline 12: The identification, measurement and valuation of direct costs in the reference case

Evaluation of the costs requires identification, measurement and valuation of the resources used in the production process which must be as close as possible to usual daily practice.

All the resources which are likely to vary between the interventions being compared are identified over the time horizon selected. Future costs independent of the interventions being studied are not taken into account.

The measurement of resources used, in physical units, is made in the French healthcare context.

Resources are valued using production costs, as far as possible. When it is not possible, tariffs can be used.

Guideline 13: The identification, measurement and valuation of indirect costs in an additional analysis

When indirect costs are documented, they are included in an additional analysis and they are not combined into the incremental cost-effectiveness ratio.

DECISION MODELLING FOR HEALTH ECONOMIC EVALUATION

Guideline 14: An economic evaluation is in most cases based on a model

Modelling is the preferred approach in health economic evaluation. The author of the evaluation discusses the appropriateness and feasibility of modelling. Non-use of modelling is duly justified.

The quality criteria of a model are met, namely: relevance, transparency, internal consistency, consideration of uncertainty and reproducibility.

The methodology and results of the model as well as its implications and limitations are presented in an understandable manner.

Guideline 15: Type and structure of the model

Many types of model can be used in a health economic evaluation. The choice of the most suitable type of model that best fits to meet a specific evaluation question is justified on the basis of a comparative analysis of possible options.

The choice relating to the structure of the model is described and supported.

Guideline 16: Defining values for the model's parameters

The parameters included in a model are defined according to the methodological principles of HAS.

For each parameter, its statistical characteristics (distribution, central tendency, dispersion), the source of information and the quality of the estimation are documented.

When the value of a parameter is not known, it must be documented as well as possible, given the knowledge available, distinguishing between what is subject to debate, what is poorly known, and what is not documented at all.

The assumptions made for each parameter are duly justified.

Guideline 17: Validation of the model

The ability of a model to produce results that are consistent and suited to the reality of the decision-making process is tested.

Guideline 18: Assessing the robustness of the results of the model

The characterisation of uncertainty is part of the economic evaluation.

The sources of uncertainty are identified: uncertainty about the parameters, uncertainty about the model structure, and uncertainty about the methodological choices.

A probabilistic sensitivity analysis is preferred when the theoretical or empirical distributions of the parameters are known or can be estimated. The number of Monte Carlo iterations is stated and justified.

An univariate, deterministic sensitivity analysis is always made on parameters likely to influence the results of the model.

The choice of parameters subject to a sensitivity analysis and the range of values used to test these parameters are presented and justified.

If the model is based on the assumption of independence of parameters, the uncertainty associated with that assumption is discussed.

The author of the evaluation justifies the sensitivity analysis conducted.

PRESENTATION AND INTERPRETATION OF THE RESULTS OF THE ECONOMIC EVALUATION

Guideline 19: Economic evaluation to inform health care decision-making

Health interventions plotted on the efficiency frontier are identified and an incremental cost-effectiveness ratio (ICER) calculated for each one, by detailing the incremental health effects and costs. All interventions are represented in the cost-effectiveness plan.

A clear and reasoned discussion allows the robustness of the results of the economic evaluation to be assessed and the conditions under which the results would be different to be defined.

This discussion is based on a critical analysis of the methods and data used, and on statistical sensitivity analysis.

The breakdown of the total cost per healthcare payer identifies all possible transfers of expenditure.

Guideline 20: Presentation of the economic evaluation

The economic evaluation is presented in a clear, structured and detailed manner. The methods are transparent and the data and the sources used clearly reported.

For each of the interventions being studied, the undiscounted expected values of each component of costs and health outcomes are presented. The total costs and the chosen outcomes are then calculated and discounted.

HAS Reference Case Analysis

Table 1: Basic elements of reference case analysis

Reference case analysis defines the features of health economic evaluation at HAS and the recommended methodology for each component of an analysis. It distinguishes between "required" references, to which the author must strictly comply, and "preferred" references which allow the use of a different method when this is clearly justified.

	Reference case analysis	Status
The method of evaluation	Cost-utility or cost-effectiveness analysis according to the nature of the health effects of the intervention.	Required reference
	- If health-related quality of life is an important consequence, a CUA is used - If health-related quality of life is not an important consequence, a CEA is used	Required reference
Perspective - on costs - on health effects	Collective perspective - All health care funders - Population whose health is affected (identification and measurement of health effects) and general public (preference-based scores)	Required reference
Population analysed	All the individuals concerned, directly or indirectly.	Preferred reference
Intervention comparators	All interventions competing with the intervention studied are identified. The choice of interventions included as comparator is the responsibility of the author, and is justified.	Required reference
Time horizon	A time horizon which is long enough to reflect all expected differences in costs and health effects.	Required reference
Discount rate	Discounting is done at the public discount rate. It stood at 4% at the time of writing this guide and views the relative price of the health effects to the community as being invariable over time. After 30 years, the discount rate linearly declines to 2%.	Required reference
Summary of data	- Based on a systematic and critical review of clinical and economic studies	Required reference
	- Based on data from all relevant studies, subject to their ability to limit bias and to consider "real life" practice.	Required reference
	- French data	Preferred reference
Health outcome criteria	- QALY in CUAs	Required reference
	- Life years in CEAs	Preferred reference
Costs criteria	Production costs	Required reference
Conclusions of health economic evaluation	- Efficiency frontier and calculation of an incremental cost-effectiveness ratio for non-dominated interventions	Required reference
	- Analysis of transfers of spending between healthcare funders	Preferred reference
Critical analysis of the evaluation	- Analysis of variability and uncertainty, whatever the source	Required reference
	- Discussion of the conclusions and limitations of the evaluation	Required reference

Introduction

This guide presents the principles and methods used by HAS (the French National Health Authority) to carry out its mission of providing economic evaluations of health interventions. In this specific context, economic evaluation allows health interventions to be compared on the basis of their health effects and costs.

Following examples in other areas of evaluation covered by HAS, this work on formalising reference case analysis strives to guarantee rigour, transparency and methodological homogeneity in health economic evaluations. It also aims to ensure that the results of such evaluations are adopted by providing healthcare professionals and institutional decision-makers with the keys to understanding the approaches adopted.

This document provides guidance on the selection and analysis of scientific literature in the systematic reviews made by HAS and defines the basic methodology used in the economic evaluations which it undertakes, initiates or about which it is asked to give expert opinion.

This document contributes to the promotion of a shared culture of health economic evaluation in France which is understood by all players. Yet, it is not a guide for universally applicable economic evaluation methods. The selected methods presented in this document must be seen as part of a specific institutional and operational context.

▪ *The choices of methods are based on the founding missions and principles of HAS*

Economic evaluation at HAS must develop consistently with all other HAS missions. Consequently, the main principles of the institution form the cornerstone on the basis of which economic evaluation processes and methods have been defined. They are:

- independence and impartiality,
- scientific rigour,
- the need to be cross-cutting and multidisciplinary in evaluation.

These principles guide the methodology used by HAS to analyse or conduct an economic evaluation study.

▪ *The choices of methods are based on the scientific state of the art*

In this document HAS defines the methods it favours in carrying out its missions. Each of its choices is motivated by both scientific quality and operational functionality. To this end, HAS acknowledges the state of the art while recognising that the ongoing scientific debate necessarily results in changes of methods, with a view of improving them. Consequently, this methodological guide is likely to be updated regularly.

In the document, the expression "reference case analysis" is used to refer to an evaluation made using the methodology chosen by HAS. Such reference case analysis meets the scientific requirements applied by HAS, while leaving room for adaption to the specific features of a particular evaluation or to operational difficulties. That is why the reference case analysis adopted by HAS distinguishes two levels of recommendations: certain guidelines are "required" systematically in the evaluation, whereas others are "preferred" but may not be followed, where this choice is clearly justified. HAS is in fact aware that such economic evaluation in France is still in the development phase and that difficulties such as the lack of available data limit the strict application of these methodological principles.

Finally, additional analyses based on choices of methods not included in reference case analysis may be put forward, where these help to document any economic evaluation.

- *The choices of methods for the continuous improvement of economic evaluations*

An economic evaluation requires a large quantity of different types of data (epidemiological, demographic, clinical, economic, etc.) and from different sources (clinical studies, patients registries, administrative databases, etc.).

The use of French data is favoured wherever possible. Due to the insufficient availability of these data in France, HAS stresses the need to develop collaboration between the different stakeholders, to promote the accessibility of the existing data (in particular on costs), and to encourage the production of studies on French samples (especially for the calculation of preference-based scores). Obtaining these data would help to improve the relevance of economic evaluations.

HAS is committed to initiating a methodological monitoring procedure for the regular updating of this document and to the development of collaborative projects with its scientific and institutional partners in order to contribute actively to the development of economic evaluation in France.

Objective and Methods

Objective

The objective of this document is to set out the economic evaluation methods which HAS favours when determining the efficiency of a specific health intervention.

The methods described are applicable to the economic evaluation of all health interventions, meaning any activity intended to preserve or improve the health of a population, whether it is diagnostic, therapeutic, preventive, organisational, etc.

These methods cover all aspects that are considered in carrying out an economic evaluation: perspective, population analysed, comparators, time horizon and discounting process, data quality, measurement of the health outcomes and costs, modelling, management of uncertainty, presentation of the results and limitations of the evaluation.

The economic evaluation in health care needs to be carried out in a multidisciplinary environment. Some data used come from other disciplinary fields such as clinical evaluation and public health (evaluation of treatment effects, diagnostic performance, compliance, toxicity and safety, etc.). The methods for the production and the analysis of these data are discussed in specialised methodological guides to which HAS refers readers who wish to learn more about them. Similarly, this document does not contain any guidelines on methods for budget impact analysis: instead readers may refer to the *Guide méthologique pour la mise en place d'une analyse d'impact budgétaire* published by the French College of Health Economists.[1]

Methods

The document was prepared on the basis of an ongoing process of drafting working documents and discussions.

A literature search was carried out to identify guidelines on methods published by foreign health evaluation agencies. That search identified 14 references. Using a cross-sectional thematic analysis, an inventory was made of approaches to methods currently used at other evaluation agencies.

This analytical review of the existing guidelines was supplemented by a partial update of the "French guidelines for the economic evaluation of health care technologies" published in 2003 by the French College of Health Economists (CES). The update by the CES provided a snapshot of recent advances in methods. A summary is given in Appendix 4 of the French version of this guide: the complete working document is available on the HAS website (www.has-sante.fr).

Thematic summaries prepared by the Department of Economics and Public Health Assessment at HAS, and the working document produced by the CES, were discussed by the Committee for Economic and Public Health Assessment (CEESP) economists' technical group, set up prior to this project. The discussions also benefited from presentations by French and foreign experts invited to report their experience of using economic evaluation as an aid to public decision-making.

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[1] http://www.ces-asso.org/docs/Rapport_AIB.pdf

The compilation of these various studies resulted in the drafting of a first version of the document which was submitted to the Commission for Economic Evaluation and Public Health (CEESP) and to the HAS Board. It was then made public for the HAS "Rencontres" (a public event) in 2010.

Subsequently, that first version was released for comment in order to assess its readability and its reception by all stakeholders. It gave rise to hearings and a public consultation held between 2 December 2010 and 10 February 2011.

The hearings were organised at the invitation of HAS partners in economic evaluation or upon request: learned societies, government departments, compulsory health insurance schemes, manufacturers or manufacturers' representatives, and consultancy companies.

The public consultation was based on a questionnaire designed to collect general opinions on the document and comments on the different methods chosen by HAS in the field of economic evaluation. For each of the chosen methods presented, an opinion was sought on three points: the clarity of the wording, the relevance of the position adopted and the feasibility of the guideline proposed.

Twenty-three questionnaires were completed on the website and three spontaneous responses were sent to HAS.

All comments were analysed and discussed in the CEESP economists' technical group, in order to improve the final version of the document. A summary of the comments expressed during the public consultation and at the hearings is available on the HAS website (www.has-sante.fr).

The process of updating the document

HAS expects this methodological guide to be part of a continuous process of improvement and adoption by all parties involved.

Indeed, this first version of the guide to health economic evaluation methodologies at HAS will be updated as often as necessary. A monitoring procedure for methods has been organised to take into account advances in theories and methods in economic evaluation in the health care. In addition, practical implementation of the guidelines will be monitored, so that any weaknesses in this guide can be identified and addressed.

Structuring Health Economic Evaluation

Type of economic evaluation

Guideline 1

The reference case analysis uses cost-utility analysis and/or cost-effectiveness analysis as methods of evaluation. The choice of the method to use depends on the nature of the expected health effects of the interventions under study.

- If the intervention is expected to have an important impact on health-related quality of life (HRQL), cost-utility analysis must be used. The health outcome to use is patient's length of life weighted by a valuation of the HRQL. The cost-utility analysis is always accompanied by a cost-effectiveness analysis which uses length of life as health outcome.

- If health-related quality of life is not identified as a relevant health effect of the interventions studied, cost effectiveness analysis is the required form of economic evaluation and the health outcome is measured by length of life.

- Any other choice must be duly justified.

Cost-benefit analysis is not recommended in the reference case analysis, but it can be presented as an additional set of information.

The health economic evaluation methods can be classified in three main categories:[2] cost-effectiveness analyses (CEA), cost-utility analyses (CUA), and cost-benefit analyses (CBA).

■ *Cost-benefit analysis is not recommended in the reference case analysis.*

Cost-benefit analysis is the most suitable method of assessing the allocation of collective resources, since it can be used to evaluate the social value of public expenditure. Nevertheless, the methods used in this type of analysis, particularly in the healthcare field, are widely debated. At the present stage in the debate, HAS does not wish to favour such an approach in the course of its work, particularly as the paucity of cost-benefit evaluations in health, compared with CUAs and CEAs, limits the comparability of studies. Despite this, if evaluations of this type are available for the interventions studied and if they are considered relevant, they can be presented as an additional source of information.

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[2] Cost minimisation analysis is regarded as a sub-category of cost-effectiveness analysis, where the health effects are equivalent across interventions studied.

■ *The two methods recommended by HAS are cost-utility analysis and cost-effectiveness analysis*

The reference case analysis is based on cost-utility analysis and cost-effectiveness analysis as methods of evaluation. The choice of the method to be used depends on the nature of the expected health effects of the interventions studied.

- If health-related quality of life (HRQL) is identified as an important health effect of interventions[2], cost-utility analysis is the required form of economic evaluation and the health outcome to use is the length of life weighted by a valuation of the HRQL. The cost-utility analysis is always accompanied by a cost-effectiveness analysis which uses length of life as health outcome.

- If health-related quality of life is not identified as an important health effect of the interventions studied[2], cost-effectiveness analysis is the required form of economic evaluation, while length of life is the preferred health outcome.

In practice, the author of an evaluation decides whether the data needed to implement the more appropriate method is available, in accordance with the methodological requirements (see Methods for health outcomes evaluation, page 26). If not, the author decides if it is possible to produce the data at reasonable cost and within a reasonable period of time.

Failing that, a cost-effectiveness analysis can be conducted on the basis of a health outcome which is different to length of life, whether or not it is adjusted for HRQL. This choice and the reasons for this choice are supported with relevant arguments from the point of view of the methods set out in the section evaluating the health outcomes (see the cost-effectiveness evaluation section, page 27).

The perspective

> **Guideline 2**
>
> The reference case analysis adopts a collective perspective that is sufficiently broad to take into account all stakeholders concerned by the treatments studied, in the French health system.
>
> The economic evaluation has to be made under the real conditions.
>
> The production costs of the interventions studied are identified, measured and valued independently of their source of funding.
>
> The health effects are identified and measured from the perspective of individuals affected by the interventions. When preference-based scores are used for valuation of changes in HRQL, they are obtained from a representative sample of the general population.

In the context of HAS and its work, the aim of the economic evaluation is to shed light on public decision-making in the allocation of resources.

The reference case analysis adopts a collective perspective. This allows account to be taken of all stakeholders affected by the decision, either because they are affected by one of the health consequences of the health interventions, or because they are involved as healthcare funders.

The economic evaluation covers the costs and health effects of interventions under real conditions of use, whether observed or expected.

The evaluation of costs endeavours to identify, measure and value all the resources consumed in the production of the interventions studied, whatever the source of funding (patients, compulsory and supplementary health insurance schemes, the central government, etc.).[3]

Evaluation of the health outcomes identifies the health effects relevant from the point of view of the individuals concerned (see below). These are then measured in life years, possibly weighted by a valuation of HRQL (preference-based scores). In this case, preference-based scores are obtained from a representative sample of the general population (see the section on cost-utility evaluation, page 28).

The population analysed

> **Guideline 3**
>
> The population in the reference case analysis consists of all individuals whose health is directly or indirectly affected by the interventions studied. Any exclusion is to be justified.
>
> The economic evaluation may justify the analysis of particular subgroups of the population for whom health effects or costs are expected to differ from the population.

■ *Population selected in the reference case analysis*

The population analysed in the reference case analysis consists of all individuals whose health is affected by the interventions studied, either directly (sick persons, the screened population, etc.) or indirectly (the non-vaccinated population, etc.).

The individuals directly concerned are those initially targeted by the interventions studied. When interventions have no health effect on other individuals, the population used in the reference case analysis is limited to the individuals directly concerned.

The population concerned can be extended to include other individuals when their health is affected by the interventions studied, even though they were not targeted. Examples include: the positive effect of a vaccination programme for persons who are not vaccinated but are nevertheless protected; the negative effect of antibiotic therapies if antibiotic resistance develops.

Any inability to include in the analysis certain individuals whose health is likely to be affected by the interventions studied is duly justified.

■ *Analysis of subgroups*

Economic evaluation may necessitate considering specific subgroups of the population for whom the evaluation results are expected to differ from the overall population, in view of the heterogeneity of the health effects or the costs due to the specific characteristics of these subgroups.[4] This variability is documented and its consequences in terms of fairness discussed.

An analysis of the health effects for subgroups can be made if it is based on clinical studies or other types of studies which include a subgroup analysis in their protocol. Such an analysis can also be made if clinical studies or other types of studies are available for these subgroups.

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[3] Studies performed from a more restrictive perspective are taken into account by HAS, in so far as they help to document the HAS' opinion.
[4] For example, the analysis of subgroups is also important when the baseline risk for a certain event is different: with a similar relative treatment effect, the absolute benefit will be different.

When interventions generate different costs for identified subgroups, an economic evaluation of these subgroups is justified. In cases where these subgroups do not correspond to clinically studied subgroups, the economic evaluation is based on the assumption that the treatment effect is constant. The treatment effect in the subgroups is considered as similar to the effect obtained in the broader, clinically studied population.

The interventions being compared

> **Guideline 4**
>
> Economic evaluation is a comparative approach.
>
> The reference case analysis identifies all interventions that compete with the intervention evaluated in the population analysed.
>
> The arguments on which an intervention's inclusion or exclusion from the analysis is based are duly justified.

■ *All competing interventions are identified*

The approach in the economic evaluation is always comparative as the objective is to know whether one health intervention would be more effective to implement than another.

The reference case analysis identifies all relevant comparators in the population analysed for the defined indication. The interventions differ greatly and include: drug treatments, surgical treatments, nursing care, prevention, non-medical interventions, etc.

■ *The interventions used in the reference case analysis are justified*

The author of an evaluation justifies, among all the interventions identified, those which are included and those which are excluded in the analysis. The impact of these choices on the evaluation results is discussed. The omission of an intervention which *a priori* could be considered in the analysis may bias the conclusions of an evaluation.

Current best or consensus/routine practices are the most widely used comparators in health economic evaluations. However, other interventions can be included in the comparison, such as an emerging practice, best supportive care or no intervention at all. An analysis of all the interventions that can be considered may reveal that the usual practice is not efficient compared with other practices that are actually rarely used.

Procedures and technologies which are used without "EC" marking and drugs that have not obtained marketing authorisation are to be included in the reference case analysis, if they are regularly used in daily practice. The aim here is not to validate misuse but to take into account the fact that off-label use of health technologies is a genuine option in "real life" clinical practice. This can cover very different situations such as when therapies have reached a deadlock, when therapeutic options can be used which have not yet been completely assessed, or situations when scientific publications suggest a possible broadening of indications. Such choices must be justified.

The evaluation considers the changing nature of technology over time (performance, cost, etc.). Anticipated changes in practices, linked for example to the learning effect, must also be discussed.

If data from direct, comparative studies are not available or not sufficient, it may be necessary to make indirect comparisons by a specified and validated method presented with the appropriate degree of detail (see the Appendix in the French version).

The time horizon

> **Guideline 5**
>
> The reference case analysis uses a time horizon which is long enough to reflect all expected consequences in costs and health effects between the interventions being compared.
>
> The time horizon is identical for all the interventions being compared. It depends on the natural history of the disease, the chronology of the interventions, the occurrence of changes of health effects and costs related to the interventions compared.

The economic evaluation is set against a specific time horizon. Only the health effects that occur and the costs that are incurred during that period are taken into account in the evaluation. All the interventions being compared are evaluated over the same period.

The reference case analysis uses a time horizon which is long enough to include all expected differences in costs and health effects between the interventions being compared. This depends on the natural history of the disease, the chronology of the interventions, the occurrence of health effects and costs related to the interventions compared.

A lifetime horizon is applied if at least one of the interventions being compared has an impact over the patient's life time, either in terms of costs, length of life, health-related quality of life or after-effects (i.e. a chronic or disabling condition). A shorter horizon is appropriate if differences in costs and health effects are no longer observed beyond that horizon. Arguments must be presented to support the choice of this shorter time horizon. In some cases, a multigenerational time horizon is necessary (e.g. for vaccinations).

As follow-up periods in clinical trials are limited, calculating costs and health effects over the patients' lifetime may often require modelling methods based on extrapolations of short term data (see modelling section, page 40).

The discounting method

> **Guideline 6**
>
> Future costs and health effects are discounted to reflect their present value.
>
> The reference case analysis uses the French social discount rate which has been set at 4% since 2005, for time horizons of less than 30 years with a reduction of up to 2% thereafter. This rate may be reassessed.
>
> In the reference case analysis, HAS considers that the relative prices of the health effects for the community do not change over time. The costs and health effects are thus discounted at the same rate.
>
> A sensitivity analysis is needed to assess the robustness of the evaluation results concerning the chosen discount rate.
>
> An anticipated variation in the relative price of a health effect over time may be considered in an additional analysis

Discounting makes it possible to compare interventions at different times, by calculating future costs and health effects at their present value. In health economic evaluations, discounting is applied as soon as the time horizon exceeds 12 months.

The discounting process is based on two separate factors: the discount rate and the system of relative prices for health effects produced by the interventions.

- *The discount rate is a substitution rate between the future and the present*

Given that HAS seeks to provide technical assistance in public decision making, it conducts economic evaluations from a collective point of view, and considers that the discount rate used in the reference case analysis must be identical to the social discount rate for all areas of public investment, as prescribed by the French government's Strategic Analysis Centre (French Planning Agency, 2005).

This social discount rate reflects the "value of time" to the society, and has been set at 4% since 2005.[5] It is a real discount rate applied to sums of money expressed in constant terms (i.e. excluding inflation), and it may be revised regularly.

The social discount rate does not take into account the uncertainty relating to the interventions being studied, which must be considered on its own.

- *Discounting involves predicting the relative prices of goods*

In the reference case analysis, HAS advocates that the relative price of health effects for the society are assumed not to change over time.[6] The costs (expressed in monetary units) and the health effects (expressed in their own units of account) are therefore discounted at the same rate. The incremental cost-effectiveness ratio (ICER) obtained in this way directly reflects the hypothesis that the relative price of the health effects does not vary over time and must hence be interpreted accordingly.[7]

However, if the analyst expects there will be a change over time in the relative price of the considered health effects, an additional analysis based on that expectation can be made.

- *The value of the public discount rate is subjected to a sensitivity analysis*

The analyst provides a sensitivity analysis in order to investigate the robustness of the evaluation results to changes in the value of the discount rate. The sensitivity analysis can use a discount rate higher than the 4% social discount rate (for example, the maximum rate of 6% considered in the above-mentioned report). It may also be useful to present the calculations using a 3% rate, which is generally used in foreign guidelines.

- *The value of the discount rate may vary with the time horizon*

When the time horizon of an economic evaluation is very long, as is the case with vaccination programmes (WHO, 2008), it is necessary to adopt the recommendations of the above mentioned report (French Planning Agency, 2005), namely that the discount rate declines after 30 years. This decline is continuous and bottoms out at 2%.

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[5] The discount rate depends on:
- a pure preference rate for the present,
- an elasticity of marginal utility of consumption,
- a growth rate of per capita consumption.

[6] See footnote 6

[7] Published health economic evaluations currently present a discount rate for costs on the one hand and a discount rate for health outcomes on the other, which may be different. This presentation results from an explicit hypothesis regarding the evolution in the relative price of health effects over time.

The data used in economic evaluation

Guideline 7

Economic evaluation reports includes a systematic review of the clinical and economic studies conducted on the intervention in question, respecting good practices in terms of literature search, selection and critical analysis.

For both health effects and costs, economic evaluations draw on different types of studies, taking into account their relevance and ability to limit biases, while reflecting the realities of medical practice. Clear explanations of the limits of data make it possible to document the impact of data use on the conclusions of an evaluation.

Sources of variability and uncertainty concerning the health effects and resources use are identified and dealt with by suitable methods.

French data are preferred in the reference case analysis. When foreign data have to be used, a rigorous analysis is made of their relevance to the French context.

■ *The evaluation report includes a systematic and critical review of existing studies*

The evaluation report includes a systematic review of clinical and economic studies. Situations in which foreign studies are "generalisable" to the French context are very rare (see below, page 24).[8] Nonetheless, a review of available literature is useful to identify problems raised by the subject covered, as well as to take stock of current knowledge and of the availability and quality of published data.

The data search strategy, the collection and the quality evaluation of the data follow the usual rules applied in clinical or economic studies in each particular field.

- The search strategy is clear and reproducible, using explicit selection criteria (Institute of Medicine, 2011). It minimises publication bias by looking for documents which are not accessible through the conventional channels disseminating information (Chojecki, 2011). Unpublished studies are permitted if they are described in a way which allows their relevance and quality to be assessed by HAS.

- The use of a data extraction form specifically designed for clinical or economic studies is desirable (see the Appendix in the French version).[9]

- The evaluation of the quality of clinical and economic data is based on the principles of systematic review and critical analysis. It can be carried out using checklists for assessing the quality of clinical or economic studies (see the Appendix in the French version).

■ *Different types of studies are used according to the parameters to be assessed in an economic evaluation*

An economic evaluation documents the costs and health effects of health interventions under real conditions. Thus, it requires a large amount of data of different types (epidemiological, demographic, clinical, economic, etc.) from different sources (studies, registries, databases, etc.).

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[8] Studies are "generalisable" when no adjustments to the analysis are required to apply them to another context. They are "transferable" to another context if adjustments in the data and the structure of the model have to be made (Nixon 2009).

[9] Conducting such an inventory is not always possible if the study data contain little or poor details. This is the case particularly with cost data presented in a summary manner, where it is not possible to identify the different items studied or the unit costs used. It is therefore not possible to ensure that these costs calculated abroad are acceptable for France.

The reference case analysis is based on available data taking account of its relevance and its ability to limit bias. Data used give an account of interventions under real conditions of practice.

More specifically, evidence on health effects is obtained from randomised controlled trials, or meta-analysis of randomised controlled trials. Comparative observational studies might be used in the case of added value, in terms of relevance or bias limitation.[10]

Other aspects of the evaluation (compliance, volume of resources consumed, etc.) can be documented by using various sources (epidemiological surveys, registries, databases, *ad-hoc* studies, etc.).

Expert opinions are used with caution. As a general rule, a panel of experts is consulted only if the data required are nonexistent or imperfect. If use of such a panel is considered necessary, total rigour and transparency are required, both in the choice of experts (collegiality, independence) and in the method used to obtain and process their opinions.

■ *The sources of variability and uncertainty are identified*

Whatever efforts are devoted to obtaining the most robust data, the data on health effects and costs necessarily contain some degree of variability and uncertainty.

Inter-individual variability is purely random and is irreducible. It consists, for example, of variations in the response to treatment within a population of individuals with the same characteristics.

Uncertainty refers to a situation in which the information needed for the economic evaluation is divergent (ambiguity) or unavailable (ignorance). A distinction is made between three types of uncertainty:

- uncertainty about data which is linked to errors of measurement and to sampling methods;

- uncertainty about the choice of methods used to structure the economic evaluation (perspective, time horizon, discount rate, population analysed, etc.);

- uncertainty about the structure of the economic evaluation model.

All sources of uncertainty are identified and explained using suitable statistical methods so that the impact of the uncertainty on the results of the evaluation is documented. There is a section on uncertainty in the chapter on modelling (see page 44).

■ *Conditions for using foreign data or studies*

In most cases, it is necessary to use foreign evaluation studies to make up for the absence of French data or to limit the costs of conducting the evaluation.

An economic evaluation is rarely generalisable to a different context to the one in which it was conducted.[11] The use of an economic evaluation in another context can however be considered if the interventions being compared are relevant and if the methodology of the study is of good quality (Welte 2004). That said, adjustments to the structure or the parameters are always necessary, because of the specific characteristics of the population (incidence/prevalence, life expectancy, preferences, etc.), the healthcare system (organisation, professional practices, unit costs, etc.) or methods (time horizons, perspective, discount rates, etc.) which can lead to differences in the evaluation of the costs or health effects (Welte 2004; Drummond 2009).

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[10] Thus, a good quality observational study, performed on the population analysed and the primary outcome used in the economic evaluation can provide a level of evidence greater than that of a randomised study which is less well suited to the decision-making problem covered.

[11] See the distinction between "generalisable" and "transferable" in the footnote 11, page 24.

Economic evaluations can be transferred to another context using these adjustments only under certain conditions. The evaluation of the degree of transferability of studies can be used to select studies that meet the necessary explanatory and transparency conditions. Tools have been proposed to assess the transferability of studies (Boulenger 2005; Nixon 2009). The task of transferring a study is then complex; it is necessary to have the full report containing details of all the work and to contact the authors to discuss the conditions for the internal and external validity of their model.

Finally, whether transferring a model developed in another context or constructing a model from scratch, the use of foreign data to rate a model's parameters is often unavoidable. The degree of acceptability of foreign data varies according to the nature of the parameter for which information is provided. A distinction can thus be made between the following: i) variables for which French data are essential (e.g.: calculating the costs of interventions); ii) variables for which French data are preferable, while accepting the use of foreign data under certain conditions (e.g.: evaluation of quality of life, compliance); and iii) variables for which the use of foreign data are generally accepted (e.g.: evaluation of the relative risks). The author of the evaluation justifies the balance struck between the value of using foreign data and their validity for a French evaluation.

Evaluating health outcomes

Identification and measurement of health outcomes

> **Guideline 8**
>
> All the health effects likely to vary between the interventions being compared in the analysed population are identified for the appropriate time horizon.
>
> In the reference case analysis, health outcomes are chosen according to the type of health effects previously identified. To measure the chosen health outcomes, HAS recommends the choice of generic criteria to promote the comparability of studies.
>
> The health outcomes are identified and measured under conditions that are as close as possible to usual daily practice.

The identification and measurement of health outcomes refer to the real conditions under which interventions are carried out, rather than to experimental situations.

■ *All the health effects of the interventions studied are identified*

The reference case analysis identifies all the health effects in the population analysed, as previously defined (see page 19), and are therefore likely to vary between the interventions compared. The health effects of the interventions are identified over the chosen time horizon, whether positive or negative (for example: adverse effects of the intervention).

■ *The choice of the health outcome depends on the nature of the expected health effects of the interventions studied*

The nature of the expected health effects determines the health outcome and, consequently, the choice of evaluation method to use in the reference case analysis (see page 17). The analysis is based on the measure of length of life weighted or not by a valuation of the health related quality of life (HRQL).

To measure the health outcome of the interventions, the reference case analysis uses a generic criterion to promote the comparability of the studies. If cost-utility analysis is used, the health outcome criterion to be used is quality-adjusted life years (QALY). If cost-effectiveness analysis is used, the health outcome criterion to be preferred is life years (LY).

The choice of criterion also depends on the availability of appropriate data and, if it is not available, on the ability to produce such data at a reasonable cost and within a reasonable time. If this is not possible, assessment criterion other than LY or QALY can be used in a cost-effectiveness analysis, as a last resort, after careful consideration and based on clear supporting arguments (see below).

Health outcome evaluation in a cost-effectiveness analysis

> **Guideline 9**
>
> In a cost-effectiveness analysis, length of life is the preferred health outcome, expressed in life years (LY), and calculated from all-cause mortality.
>
> If the data needed to measure LY are unavailable or it is not possible to produce them at reasonable cost and within a reasonable time, a cost-effectiveness analysis can be made on the basis of another health outcome criterion. A criterion related to LY is preferred.
>
> Inability to use length of life as a health outcome in the cost-effectiveness analysis as well as the choice of a criterion other than LY must be duly justified.

As a reminder (see page 17), when HRQL has not been identified as the health outcome of the evaluation,[12] the reference case analysis is based on a cost-effectiveness analysis (CEA).

- *The health outcome preferred in the cost-effectiveness analysis is length of life, expressed in life years, calculated from all-cause mortality*

HAS recommends the choice of length of life as health outcome. The preferred criterion is the life years (LY) calculated from all-cause mortality.

According to the ISPOR Task Force on Good Research Practices (Weinstein, 2003), it is generally acceptable to derive all-cause mortality probabilities from national life tables without correction for the fact that all-cause mortality includes disease-specific mortality in the general population. Where a correction is made, this need to be argued and the method for modelling survival is specified and justified.

- *The choice of a different health outcome must be properly argued*

Two circumstances may justify the use of a health outcome other than length of life in a cost-effectiveness analysis.

If the data needed to measure the length of life in LY are unavailable or if it is not possible to produce it at reasonable cost and within a reasonable time, a cost-effectiveness analysis can be made on the basis of another health outcome using a different criterion. In this case, a criterion whose correlation with mortality has been demonstrated and, if possible, quantified, is preferred.

If the interventions studied are equivalent in terms of length of life, another health outcome can be selected to conduct a cost-effectiveness analysis in an additional analysis. The choice of this health outcome and of the associated criterion is supported with relevant arguments.

If it is not possible to use length of life as a health outcome in the cost-effectiveness analysis, then this needs to be supported with relevant arguments. In the same way, if a criterion other than LY calculated from all-cause mortality has been used, the reasons for doing so and for selecting that criterion need to be duly justified.

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[12] It is up to the author of the evaluation to set out the reasons why health-related quality of life should or should not be taken into account in the health outcome (see choice of economic method, page 17).

Health outcome evaluation in a cost-utility analysis

> **Guideline 10**
>
> In a cost-utility analysis, the health outcome is the patient's length of life weighted by health-related quality of life and is expressed in QALYs. This allows the life years to be weighted with a preference-based score.
>
> It is recommended to use health status classification systems for which validated preference-based scores are available in France. At the time of writing this guide, only EQ-5D and HUI3 were available.
>
> French empirical data on length of life and preference-based scores are preferred. In the absence of any such data, it is possible to use preference-based scores from foreign studies, subject to a critical analysis of their quality.
>
> If the data needed to calculate QALYs are not available or cannot be produced at a reasonable cost and within a reasonable time, a cost-effectiveness analysis can be conducted. Inability to use QALYs and the choice of another criterion are duly justified.

■ *In a cost-utility analysis, the health outcome is the length of life weighted by a valuation of the HRQL, expressed in QALYs*

As a reminder (see page 17), when health-related quality of life is identified as an important health outcome of the interventions studied, the reference case analysis is based on cost-utility analysis (CUA). HAS recommends the choice of length of life weighted by the HRQL as a health outcome, which is measured in QALYs (quality-adjusted life years).

The QALY is a measure of the length of life (expressed in LY) weighted by the health-related quality of life valued by a preference-based score.

■ *The evaluation of the health outcome is based on two distinct stages of description and valuation*

In a CUA, health outcome evaluation is based on two very distinct stages: i) a description of the HRQL experienced by the persons affected by the disease, together with the length of time spent in each successive state, and ii) a valuation of the HRQL by assigning a preference-based score to each health state. To be eligible for use in a CUA, these scores must have certain characteristics: they are based on the preferences of the general population (see page 30) and they are measured on an interval scale[13] which assigns a score of 1 to perfect health and a score of 0 to death.[14]

Different methods produce different scores. It is therefore necessary to use a single method of assessment for all the interventions being compared (i.e. an identical method of describing and valuing).

In the reference case analysis, HAS recommends describing the HRQL using a generic descriptive questionnaire validated in France and generating health-related utility values with associated preference-based scores that have also been obtained and validated in France.

The use of any other method must be duly justified and its validity must be demonstrated in France for the questionnaire describing HRQL and for the rating system.

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[13] An interval scale is a scale on which intervals can be compared (in particular, the intervals between scores have the same value if the differences between scores are equal). On an interval scale, zero is placed arbitrarily, following the example of a temperature scale (Celsius and Fahrenheit scales) and has no precise meaning. (http://www.irdp.ch/edumetrie/lexique/echelle.htm). Consequently, the value zero assigned to death is arbitrary and the ratio between two utility scores has no meaning.

[14] For the most part, the scoring systems currently used in the CUA assign a negative score to certain health states when they are regarded as worse than death.

The description of individual HRQL and its duration

■ *The description of HRQL uses a generic questionnaire which must be eligible for CUA*

To promote the comparability of economic evaluations, HRQL is described by means of a generic questionnaire. It is important to be careful as many generic questionnaires are available to describe HRQL, but very few of them may be appropriate for cost-utility analysis. In fact, even if they are valid to describe HRQL, they do not have a suitable rating system based on preferences (the best known example is SF 36).

The scores produced by a questionnaire describing HRQL and which are not associated with a preference-based scale cannot be used in a CUA, under any circumstances.

■ *Classification systems associated with a set of preference values obtained from the French population are recommended*

To quantify the health outcomes of interventions, the EQ-5D and the HUI 3 (two standardised and validated generic instruments) are preferred, in order to promote the consistency and comparability across CUAs. They are the only ones, to date, with a set of preferences values obtained from a representative sample of the French population (Chevalier, 2010; Costet, 1998; Le Gales, 2001). Other instruments do exist (QWB, SF6D), but they are not validated in France.

The choice between the two instruments depends on the suitability of their conditions of use for an ongoing study, for example in terms of population or in the method of administration.[15] If two tools are suitable, the one which is most commonly used to evaluate interventions is favoured.

It is possible to use a different, standardised generic description questionnaire in a CUA, when there is a French version whose psychometric properties (validity, reliability, consistency) have been demonstrated and published. That does however necessitate the production of a preference-based scale appropriate to the CUA (see below).

■ *The description of HRQL and its duration are preferably obtained from the population analysed*

The description of HRQL and its duration are preferably based on a survey carried out in France of a representative sample of the population analysed.

When it is not possible to obtain this description directly from persons concerned (for example: young children, people who are mentally ill, etc.), then data are obtained from other persons but use of such data is duly justified. The questioning of close relatives is preferred. If this is not possible, consultation of healthcare professionals may be considered as a last resort.

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[15] For example, the current version of the EQ-5D is not suitable for studying children. HUI3 is designed for use in children aged 5 and older (the questionnaire is completed by a close relative in a self-administered or administered version). An administered version is used for children who are 8 or older, and the self-administered version is used for children over 13.

■   *The results of a specific HRQL questionnaire can be used for informative purposes*

Disease specific questionnaires cannot be used in the reference case analysis.[16]

However, when it is clearly shown and argued that generic instruments lack sensitivity for a given disease, it may be relevant to present the results of a disease-specific HRQL questionnaire in the assessment report as supplementary information. In this case, several fundamental points need to be recalled:

- The references for publications on the psychometric properties of the questionnaire must be documented.

- The development of an *ad-hoc* questionnaire is not acceptable, given the complexity of the psychometric validation process of such a tool.

Valuation of HRQL: obtaining preference-based scores

■ *The health-related utility values are based on the public preferences*

The valuation of HRQL reported by patients or carers is based on public preference-based scores, obtained using a choice-based method with a representative sample of the general population.

The question of whether the utility value assigned to health states must be taken from the general population is a matter of debate. Some authors recommend questioning patients or former patients who have actually experienced the health conditions in question. HAS recognises the importance of this debate which underlines the distinction between different categories of utility, in this case in particular "*decision utility*" and "*experienced utility*". However, in the light of current knowledge and in accordance with the existing guidelines, HAS has adopted a position which focuses on operational feasibility, i.e. the health-related utility values are based on preference-based scores taken from the general population.

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[16] A quality of life questionnaire is said to be "specific" when it has been elaborated and validated for one disease. For example: the "St George questionnaire" is specific to chronic respiratory failure, the "KDQol questionnaire" is specific to end-stage renal failure, the "QOLOD questionnaire" is specific to obesity and its treatments, etc. These questionnaires have been translated and validated for use in France.

■ *The valuation method depends on the questionnaire used to describe HRQL*

When HRQL is described using EQ-5D or HUI 3, it is sufficient to link each of the health states identified to its corresponding preference-based score (see the Appendix in the French version).

If HRQL is described using a generic questionnaire which is validated in France but has no preference-based scale, the choice of the method used to generate the preference-based scores is supported with relevant arguments.

- Some recent publications describe methods to estimate EQ-5D preference-based scores by mapping it from other HRQL measures. There are for example several mapping functions to convert SF36 data into EQ-5D utility. However, such mapping functions are demonstrated and validated on the basis of foreign empirical data. There are still doubts about the reliability of these functions, in particular for more severe health conditions (Rowen *et al.* 2009), and there is no study to show that these functions are valid in France. Their use in the reference case analysis is therefore not recommended in their current state of development.

- Direct valuations of descriptions of health states based on a generic questionnaire, validated for France, may be considered. In such cases, health-related utility values are generated using a choice-based method with a representative sample of the French population. This obviously needs to be done in compliance with methodological standards regarding the sampling method, the techniques of analysis, the representativeness of the sample, etc. The two accepted choice-based valuation methods for revealing preferences are the Standard Gamble (SG) and the Time Trade-Off (TTO). However, this procedure is extremely complex and costly.

The calculation of QALYs

The number of QALYs is calculated by weighting the time spent in health states with the preference-based scores associated with those states.

When the health states resulting from an intervention are directly described by the individuals, duration and preference-based scores are to be linked to each state described. The number of QALYs associated with the intervention is calculated by weighting the time spent in each state of health identified by the corresponding preference-based score. Inter-individual variability is documented, both in the identification of health states and in their duration.

There are many unresolved questions regarding the weighting of the number of QALYs for the individual characteristics of the beneficiaries of the intervention (socio-demographic situation, severity of the condition, etc.). These relate in particular to methods and ethics. Given the current state of the debate, this type of weighting is not recommended.

Data on life expectancy and preference-based scores are presented separately.

The conditions for use of foreign data

■ *HAS encourages the collection of French data*

In the reference case analysis, it is recommended to calculate QALYs using French empirical data on life expectancy and preference-based scores collected by the methods described earlier.

■ *The use of foreign data is possible under certain conditions*

In the absence of French data, the use of foreign data is possible, provided that strict principles regarding methods are adhered to:

- the description of HRQL is based on EQ-5D or HUI3;

- the methodological quality of the foreign study is good;

- the external validity of the data is justified (in particular, data are collected from a population similar to the population analysed).

Two different situations may arise.

In the best case, it is possible to return to individual HRQL descriptions in the selected classification system. These data are rarely published and obtaining them necessitates contacting the sponsors of the foreign study. The described health states are then weighted by the French preference-based scores associated with the selected classification system.

Where the individuals HRQL descriptions are not available, French CUA can be performed on the basis of published mean preference-based scores for the condition in question.[17] In this case, scores from a single source are preferably used. If several good quality sources show different preference-based scores, they are included in a sensitivity analysis.

This use of foreign preference-based scores may be justified pragmatically, due to the scarcity of French studies. But there is no assurance that preference-based scores can be simply transposed from one population to another. This makes it all the more essential to conduct an ACE in parallel, and to discuss the results of both analyses.

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[17] For example, a recent publication reports mean preference-based scores associated with angina pectoris of between 0.8 for less severe health conditions, and 0.45 for moderate to severe cases (Dyer M, 2010).

Evaluating costs

Economic evaluation based on production costs

> **Guideline 11**
>
> The cost classification used by HAS is based on the distinction between resources used in the production process of an intervention (direct costs) and other resources (indirect costs).
>
> Economic evaluation at HAS is based on the analysis of production costs. Consequently, only direct costs are taken into account in reference case analysis, and included in the incremental cost-effectiveness ratio. An analysis of the indirect costs, if considered relevant by the author of the study, is presented in an additional analysis.

The economic evaluation of a health intervention is understood as the analysis of a production function in which resources are consumed to produce other resources.

Costs refer firstly to the resources consumed in the production of a health intervention, and secondly to resources those are not consumed but are made unavailable.[18]

■ *Direct costs: analysis of the production factors*

Direct costs take into account production factors, i.e. the resources consumed (goods, services and time) to produce the interventions being studied.[19] In particular, these include the consumption of hospital and outpatient care, medical goods, transport, the organisation of a healthcare programme or the time spent by people undergoing the interventions and the time spent by their carers.

Transition costs relate to the resources temporarily needed to pass from the current situation to the situation in which the evaluated intervention occurs routinely.[20] They are part of the direct costs.

The definition used corresponds to the wish by HAS to base its evaluation on the analysis of production costs, whatever the nature of the costs and whoever funds the intervention. For this reason, a reference to medical and non-medical direct costs is deliberately omitted.

■ *Indirect costs: analysis of the impact of the intervention on other resources*

While direct costs relate to the resources needed for the production of the interventions being studied, other resources may be made unavailable because of the mortality and/or morbidity. These lost resources are included as indirect costs.

Indeed, indirect costs cover the impact of the interventions evaluated for one specific resource: usually time devoted to work (whether or not that work is paid) or to leisure in the population analysed (excluding time devoted to the production of the interventions covered by direct costs). Indirect costs can be identified when health interventions concern life-threatening diseases or morbid conditions with total or partial incapacity in carrying out an activity, as differences in life expectancy or incapacity are accompanied by differences in work or leisure activity of the individuals concerned.

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[18] The term "resources consumed" is used broadly: compared to other interventions, some resources are consumed to a greater extent, while others are consumed to a lesser extent and so are saved.
[19] Times needed for the production of the interventions as far as these have not already been taken into account as a factor in the production of a service. This may for example be healthcare professionals' time in a micro-costing approach.
[20] These may be costs linked to the initial training of those involved in setting up an intervention, or to the coexistence of several interventions, while the new intervention becomes established, etc.

It must be noted that, when the interventions being studied differ in terms of mortality and/or morbidity, the recommended health outcome in the reference case analysis is patient's length of life, whether or not adjusted for HRQL. This covers the differences of time, without considering the way the time is used (working time, paid or unpaid, leisure time, etc.).[21]

Just as HAS does not wish to place a value on life years as a function of individual characteristics (see page 31), it recommends adhering to the measurement of the differences in life years without making any distinction according to the use of the time saved. It means not integrating indirect costs in the ICER. However, if the author of the evaluation considers this to be necessary, and can base it on solid arguments, then an evaluation of the indirect costs may be presented as an additional source of information.

The identification, measurement and valuation of direct costs in the reference case analysis

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Guideline 12

Evaluation of the costs requires identification, measurement and valuation of the resources used in the production process which must be as close as possible to usual daily practice.

All the resources which are likely to vary between the interventions being compared are identified over the time horizon selected. Future costs independent of the interventions being studied are not taken into account.

The measurement of resources used, in physical units, is made in the French healthcare context.

Resources are valued using production costs, as far as possible. When it is not possible, tariffs can be used.

The identification of production factors

All the resources used in the production process of the interventions studied and which are likely to vary between the interventions being compared are considered.

The resources to be taken into account depend on the perspective adopted. The reference case analysis endeavours to include all the resources used in the interventions studied, whatever the source of funding.

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[21] In a cost-utility analysis, the preference-based scores associated with health states do not refer to the use of time spent in those states.

The reference case analysis systematically identifies all resources incurred in the production of the interventions evaluated:[22]

- hospital care,

- outpatient care,

- medical goods (drugs, medical devices and equipment),

- transport,[23]

- care for elderly persons in an institution,

- organisation of a public health programme,

- aid for disability,

- carers' time, time devoted to the intervention by the beneficiaries,[24]

- changes in living environment or eating habits, etc.

The resources to be considered in the evaluation are not limited to the period in which the interventions evaluated are performed. The identification of resources covers the whole time horizon selected to take into account the long term cost consequences of interventions. Costs that are considered to be unrelated to the condition or intervention in question are excluded.

Measurement of production factors

The volumes of resources used in the production of interventions are given for France, preferably on the basis of publications or *ad hoc* studies, giving priority to data from current practice: prospective observational studies, databases, patient registers.

The use of cost data collected in a randomised controlled trial generally has to be justified, and usually need to be supplemented since such data rarely cover the full range of resources associated with a health intervention.

Several French sources exist, most of which have been set up with an objective other than evaluation such as: reimbursements by the health insurance schemes; invoicing of the establishments' activities; analysis of health product markets; medical registers, etc. They may nevertheless provide information which is useful for the economic evaluation. Some are available with open access and some are free of charge. Other data have to be paid for or has restricted access (see the Appendix in the French version). The most relevant source of data among those which are available to the author of the analysis must be used.

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[22] In comparison, the IQWIG guide recommends evaluating the costs from the perspective of persons insured in the statutory health insurance system ; the KCE guide recommends adopting the perspective of the Belgian health care funders (the federal budget and patients' co-payments), while the NICE guide recommends including costs for the National Health Service and personal social services.

[23] Ideally, all costs linked to travel are identified. In practice, it may be difficult and costly to identify travel when information is not collected by the health insurance system.

[24] It is important to take these resources into account in an economic evaluation adopting a collective perspective. HAS considers them as production factors, then as constituents in direct costs, although some evaluations regard them as indirect costs.

Valuation of the production factors

The valuation of a cost in monetary terms is generally the result of applying a unit cost to a quantity or a volume. The valuation of resources of different kinds in monetary terms allows comparisons to be made between the different interventions evaluated by an aggregate presentation of costs.

In the economic evaluation, the valuation of resources corresponds to their opportunity cost (i.e. the value of the best possible use of resources). Given the difficulties in implementing this approach, the most relevant approximation of the opportunity cost must be sought for each sector of activity considered.

As far as possible, the valuation of a resource must be based on the production cost of this resource.

In the absence of data on the production costs, tariffs are *a priori* an acceptable basis for valuation, since they in fact represent a price recognised by the community for the resources employed. When tariffs are used as a source of valuation:

-   expenditure over and above the tariffs are included in the reference case analysis (the perspective of all healthcare funders);
-   differences between the tariff and the acquisition price paid are documented and studied in a sensitivity analysis.

Resources for which there is no tariff (clinical procedures with no tariffs, medical devices or drugs that are not refundable, equipment, etc.) are valued at the average acquisition price paid if it can be identified, or by another method which must be specified.

■ *Hospital costs are valued as closely as possible to the cost of producing inpatient stays*

To approximate the production cost of a hospital stay, the preferred source of data is the National costs study (ENCC)[25]. Micro-costing studies provide other evidence that could be more appropriate in some cases[26].

The production costs from the ENCC represent average costs, masking major variations between establishments. They are also based on accounting agreements and little detail is available on some of these. The ENCC costs of production therefore do not exactly represent the actual production costs of a hospital and special attention must be paid to the uncertainty surrounding this data.

When the ENCC data do not reflect the characteristics of a hospital stay linked to an evaluated intervention, any change made to the components of the average cost issued from the ENCC must be explicit and well argued. It could for example concern the evaluation of two surgical interventions for which only a difference in the length of stay would be observed and valued; the cost of the hospital stay in the ENCC could be broken down so that only the difference in days in hospital (excluding surgery) could be taken into account.

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[25] There are two available French sources to valuate the hospital stays: i) the data from the ENCC (National cost study), based on the hospital cost accounting system by Diagnosis related groups, and ii) the data from the T2A (Payment by hospital activity), based on Healthcare resource groups and which must be viewed as tariffs.
[26] These cases are specified in the chapter considering innovation (page 38)

When recourse to the ENCC is not possible and the cost of the intervention is valued on the basis of the tariff for an HRG (healthcare resource group) or a flat-rate price (organ retrieval, for example), all resources not included in the tariff and likely to vary between interventions are valued in addition to it:

- medical fees when a private hospital tariff is used;

- drugs and medical equipment paid in addition to the HRG;[27]

- any supplementary user fees;

- any hospital services included in the extra funding envelope for general interest missions.[28]

Whatever the type of data used (valuation per DRG from the ENCC or per HRG for tariffs), the reference case analysis favours a valuation that is as close as possible to actual conditions of practice:

- when the interventions studied are likely to be funded across several DRGs (or HRGs),[29] the cost is valued taking into account the distribution of the interventions considered between DRGs (or HRGs)[30] observed in the PMSI database;

- it is preferable to weight the tariffs from the public sector and the private sector (including fees), according to the distribution of activity found in the PMSI database for the interventions considered.

A sensitivity analysis is made to assess the impact of the method chosen on the results of the evaluation.

■ *Costs in the outpatient sector are based mainly on tariffs*

Medical, paramedical and technical procedures can be valued on the basis of tariffs, to which excess fees are added, since they form part of the valuation for the medical service provided.

Medical devices and drugs are in most cases valued on the basis of their tariff, except in cases where the tariff does not fully represent expenditure:

- generic drugs are reimbursed on the basis of the reference tariff (the least expensive generic product, "tarif forfaitaire de responsabilité"), but can be marketed at a price which is freely determined by the manufacturer. They are valued at their average purchase price, all taxes included;

- drugs that are not reimbursed or medical devices invoiced at prices above tariff are rated at the purchase price actually paid.

Failure to take these factors into account must be justified.

When an evaluation includes the cost of a class of drugs,[31] that cost is valued considering the respective use of all the available drugs in the class for the indication.

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[27] Some expensive drugs and devices are not included in the hospital stay tariff. They are invoiced separately from the HRG. As previously stated, they are valued at their tariffs in the reference case analysis, and studied in a sensitivity analysis, on the basis of the average purchase price observed in the PMSI database.

[28] SAMU (mobile emergency medical services), SMUR (emergency medical intensive care units), reference centres for rare diseases, COREVIH (regional centres for coordinating action to control HIV), health education, memory consultations, genetics consultations, management of refractory chronic pain, mobile palliative care teams, addiction liaison and consultation teams, care for prisoners, innovative medical devices, medicines under a temporary usage authorisation (TUA), etc.

[29] For example, an intervention may be classified into four different DRG, depending on the severity of the patient's condition.

[30] The activity can be assessed as the number of stays in each HRG.

■ *Micro-costing techniques are particularly suitable in case of innovation*

When an evaluated intervention is likely to change the production cost of one or more components of medical products or services for which there is a tariff,[32] that tariff cannot be used.

It may also be necessary to evaluate a new intervention for which no tariff is available (a new drug, a procedure not included in the French public price list, etc.). In this case, it is necessary to use another source of evidence to identify, measure and value the costs of production for the intervention evaluated (an *ad hoc* study, a database, a publication, etc.). Micro-costing techniques are well suited to these situations and their use must be documented precisely.

■ *Certain resources are still difficult to value*

The sources of data that can be used to value direct costs other than inpatient and outpatient costs are heterogeneous, and few are published, apart from the costs of patient transportation reimbursed by health insurance: non-reimbursed transportation costs, cost of organising a healthcare programme, carers' time or patient's time.

Nevertheless, it is important to try to conduct a valuation when these costs are a significant part of the costs of the interventions evaluated.[33]

■ *Foreseeable cost changes are taken into account.*

If the evaluation covers an innovation and if the price of technology or of its use is likely to fall as the equipment becomes more widespread or because of a learning effect, then the foreseeable drop in costs is studied in a sensitivity analysis.

In the case of a drug, and if the patent is about to expire, the foreseeable fall in price is studied in a sensitivity analysis.

When some of the costs are linked to a particular organisation, any foreseeable change in that organisation is taken into account in the evaluation. This could for example be the concentration of the activity of several healthcare producers on a single site.

The identification, measurement and valuation of indirect costs in an additional analysis

Guideline 13

When indirect costs are documented, they are included in an additional analysis and are not combined into the incremental cost-effectiveness ratio.

When indirect costs have been identified (see page 33), these costs can be studied in an additional analysis.

In this case, the impact of the interventions on the activity of the people they are intended for, and/or their close relatives, is measured as the duration of the different categories of activities affected.

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[31] For example, if the evaluation makes it necessary to value the cost of a treatment with antihypertensive drugs as one of the components in an intervention.

[32] For example, in the evaluation of a new procedure which could change the consumption of the reagents needed to carry out a laboratory analysis, it is not possible to use the existing tariff to value the cost of the laboratory analysis.

[33] For example, carers' time can be valued on the basis of the market price of an equivalent service or on the basis of studies of willingness to pay.

Where indirect costs are to be valued, the choice of the valuation method is left to the discretion of the author of the study, but supporting arguments must be provided. For example: i) the human capital method, which consists in valuing the loss of productive potential, and ii) the friction costs method, which considers only the loss of production caused by the absence of an employee, during the time needed for the organisation to replace him/her and to regain the initial level of productivity.

This additional analysis is subject to the same level of methodological requirements, as the calculation of direct costs in the reference case analysis.

Decision modelling in health economic evaluation

Economic evaluation is usually based on a model

Guideline 14

Modelling is the preferred approach in health economic evaluation. The author of the evaluation discusses the appropriateness and feasibility of modelling. Non-use of modelling is duly justified.

The quality criteria of a model are met, namely: relevance, transparency, internal consistency, consideration of uncertainty and reproducibility.

The methodology and results of the model as well as its implications and limitations are presented in an understandable manner.

■ *Modelling is a currently used method in health economic evaluation*

Models are used mainly to structure knowledge and synthesise available data. They also allow situations where the available information is imperfect to be overcome, and make it possible to simulate variations in some parameters, in order to observe the consequences. The advantages of modelling are not limited to solving problems arising during evaluation. It may also be used for didactic or exploratory purposes.

Decision models are particularly suitable for health economic evaluation. Comparison of health interventions based on the criterion of efficiency does require the integration of different types of information obtained from different sources (clinical, economic, epidemiological, sociological, biological, technological, etc.).[34] By synthesising and integrating all these data, an economic evaluation model makes it possible to estimate the expected costs and health outcomes of the health interventions studied, including in situations in which information is imperfect (evidence which is incomplete or fragmented across different studies).

The use of different methods renders the available data suitable for economic calculation. Examples include evaluating the transferability of data from experimental studies to the analysed population, under real-life conditions, or the extrapolation over a long time horizon of data on effects or costs collected over a short follow-up period.

■ *The use of modelling in an economic evaluation is justified*

With very few exceptions, data obtained from clinical studies cannot satisfy the requirements of economic evaluation. Modelling is therefore required in most cases.

Constructing an economic evaluation model often implies a dialogue between economists, clinicians and specialists in other disciplines.

The author of the evaluation discusses:

- the contribution made by a model with regard to the question being examined and the level of knowledge on the subject, including its didactic and exploratory value;

- the feasibility of modelling in terms of the data and resources required producing the model (including time constraints).

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[34] These data may themselves be derived from different types of modelling studies, such as a model of the relationship between surrogate and final outcomes (e.g. HbA1c level and complications of diabetes), meta-analysis, etc.

The added-value of the model to the evaluation prevails over its feasibility; non-use of modelling is duly justified.

The model meets quality criteria such as relevance, transparency, internal consistency, consideration of uncertainty and reproducibility (see the Appendix in the French version).

The methodology and results of the model, as well as its implications and limits are presented to its users in an understandable manner.

The type and structure of a model

Guideline 15

Many types of model can be used in a health economic evaluation. The choice of the most suitable type of model that best fits to meet a specific evaluation question is justified on the basis of a comparative analysis of possible options.

The choice relating to the structure of the model is described and supported.

■ *Different types of model can be used in a health economic evaluation*

It is not possible to define *a priori* any one type of model that is inherently appropriate for all situations in health economic evaluation.

The most appropriate type of model for dealing with a specific evaluation task is chosen, taking into account four main considerations: i) how the model incorporates time; ii) its ability to take into account the uncertainty of parameters; iii) existence of inter-individual interactions; and iv) the most appropriate statistical unit between a group of people with the same characteristics or people as individuals, distinguished according to their individual characteristics.

These characteristics and taxonomy of existing models are given in the Appendix of the French version of this guide.

The models most often used in health economic evaluation are decision tree and Markov models.

The choice of the model(s) used is justified on the basis of a comparative analysis of the possible options.[35] Brennan *et al.* (2006) have proposed guidance for choosing the most appropriate model for the interventions being evaluated (see the Appendix in the French version).[36]

The possibility of carrying out sensitivity analysis dealing with parameter uncertainty is an important point to be taken into consideration (see below).

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[35] Different types of models may be combined.
[36] A similar work was carried out by the WHO in the specific field of vaccines (WHO 2008).

■ *The structure of the model makes it possible to represent the interventions being evaluated.*

Methodological choices concerning the model structure are based on a clear and argued trade-off between the real-life situation and the simplification inherent in any modelling process. In particular, three aspects are described and justified:

- the events or health states included in the model, related to the history of the disease and/or the consequences of the interventions being evaluated;

- their timing;

- the time horizon (and cycle length in the case of a Markov model). A long time horizon may require a two-period structure, with one period corresponding to the duration of follow-up in trials (observed parameter values), and an extrapolation period over a longer time horizon (parameter values estimated by extrapolation).[37]

A structure used in previous modelling (including in foreign studies) may be reused, once the external validity of the model structure is discussed and considered to be transposable to the interventions being studied, with regard to the aspects discussed below.

When there is uncertainty about the structure to be used, or when a number of structures may be suitable, the choice of one particular structure and the impact of this choice on the results of the evaluation are duly argued and discussed.

Definition of a model's parameter values

> **Guideline 16**
>
> The parameters included in a model are defined according to the methodological principles of HAS.
>
> For each parameter, its statistical characteristics (distribution, central tendency, dispersion), the source of information and the quality of the estimation are documented.
>
> When the value of a parameter is not known, it must be documented as well as possible, given the knowledge available, distinguishing between what is subject to debate, what is poorly known, and what is not documented at all.
>
> The assumptions made for each parameter are duly justified.

■ *The model's parameters comply with the methodological guidelines of HAS and an attempt is made to identify observed values*

Values for parameters included in the model (health effects, costs, discounting, etc.) are primarily defined in accordance with the principles stated in the sections of this guide dealing with the basic choices related to the evaluation method and the choices relating to identification, measurement and valuing of health outcomes and costs.

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[37] For example, there are three possible assumptions for extrapolating results of the efficacy of an intervention: i) the treatment effect disappears after the follow-up period, ii) the treatment effect remains unchanged over the follow-up and extrapolation periods, and iii) the treatment effect declines in the long term. Extrapolation of costs for the long term also requires assumptions, e.g. whether or not treatment is continued beyond a certain period.

These values are obtained from a systematic and comprehensive search process (see page 23) that may cover many sources of data.[38]

When several sources exist for the same parameter, the evidence is summarized, preferably using meta-analysis. If one particular source is retained, the reason for this choice is justified and the parameter is the subject of a sensitivity analysis which includes the other plausible data sources that were not used.

For each parameter, its statistical distribution (central tendency, location, and dispersion), the source of information and the quality of the estimate are documented. When the distribution of the parameter is not known precisely, elements that may provide information about it are presented. This information will be used when sensitivity analyses are carried out.

■ *Assumptions may be used to estimate the value of a parameter*

When the value of a parameter is not known or when it is ambiguous, the current state of knowledge is drawn, setting out as clearly as possible what is subject to debate, what is not well known and what is not documented at all.

It may be necessary to make assumptions about the value and the statistical distribution of a parameter.[39] Each assumption is justified in terms of its clinical and economic validity. For example, when assumptions are made about the distribution of a parameter (e.g. a normal, beta, or gamma distribution), the subsequent results are checked for coherence. Assumptions that are not retained are explored in a sensitivity analysis.

The use of expert opinions to determine the value of a parameter or its probability distribution complies with the conditions in which expert opinion may be used as specified page 24.

Under certain conditions, the value of a parameter may be estimated during model calibration. If a satisfactory estimate of the parameter cannot be obtained, parameter uncertainty is presented in the form of alternative scenarios.

The model validity

Guideline 17
The ability of a model to produce results that are consistent and suited to the reality of the decision-making process is tested.

The methodological choices and assumptions involved in building a model make it necessary to comply with good practice guidelines and to test the internal and external validity of the model (McCabe, 2000).

Internal validation explores the intrinsic consistency of the model, particularly the mathematical or mechanical logic of connections between the parameters and the outputs of the model. Repetition of tests, which allocate extreme values to the different parameters, makes it possible to identify any design deficiencies in the model, leading to incorrect outputs. Counterintuitive outputs are analysed.

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[38] Information about parameters may come from different sources, such as systematic literature reviews and meta-analyses, medical or administrative databases, randomised trials, observational epidemiological studies (cohort studies, case-control studies, cross-sectional studies), surveys, registries, etc.

[39] For example, calculation of initial cardiovascular risk using a risk equation (Framingham or SCORE); adjustment of data available to the population analysed; accounting for causal linkage between a co-morbidity and the occurrence of an event, etc.

External validation checks whether the structure, assumptions and parameters on which the model is based, produce reasonable results, compatible with scientific knowledge of the disease and the effect of the interventions being evaluated.

- Comparison of intermediate outputs with reliable, available, independent empirical data (calibration). For example, health outcomes modelled on the incidence of an event are consistent with known data (national statistics, epidemiological data). Calibration provides justification for the parameter values in the reference scenario, and for their range of variability. Any deviation is explained or used to document adjustments made to the model.

- Checking that outputs are consistent with intuitive judgment (face validity). The outputs of the model are analysed to ensure that they are intuitively correct.

- Checking that the outputs are consistent with those of models of the same interventions (cross-validity). The description of the model is sufficiently detailed to explain any discrepancies.

Assessing the robustness of the results of the model

Guideline 18

The characterisation of uncertainty is part of the economic evaluation.

The sources of uncertainty are identified: uncertainty about the parameters, uncertainty about the model structure, and uncertainty about the methodological choices.

A probabilistic sensitivity analysis is preferred when the theoretical or empirical distributions of the parameters are known or can be estimated. The number of Monte Carlo iterations is stated and justified.

An univariate, deterministic sensitivity analysis is always made on parameters likely to influence the results of the model.

The choice of parameters subject to a sensitivity analysis and the range of values used to test these parameters are presented and justified.

If the model is based on the assumption of independence of parameters, the uncertainty associated with that assumption is discussed.

The author of the evaluation justifies the sensitivity analysis conducted.

The concept of uncertainty refers to situations in which the events described by the model occur in a random manner, but that can be quantified in terms of probability (the situation is qualified as risky in the economic literature). It also refers to situations in which information required to build an economic evaluation model is imperfect, as they are divergent (ambiguity) or unavailable (ignorance).

Uncertainty is distinct from inter-individual variability (see page 24) and heterogeneity (see section 'subgroup', page 19).

■ *All potential sources of uncertainty are identified and discussed*

Quantification of the level of uncertainty affecting assessment of health outcomes, costs and conclusions of the economic evaluation is part of any modelling study.

Three types of uncertainty need to be analysed when discussing the results of the model (Bilcke 2011):

- structural uncertainty, which is related to the building of the economic evaluation model: the choice of the type of model, the selection of states in a Markov model or of compartments in a dynamic model, patterns of intervention, alternative methods for extrapolating health outcomes after the end of the observation period, the cycle length in a Markov model, etc;

- parameter uncertainty, which is related to measuring errors and to the sampling processes;

- uncertainty related to the basic methodological choices defined by HAS (perspective, time horizon, discount rate, population analysed, etc.).

■ *Analysis of plausible alternative scenarios are the main method used to characterise structural uncertainty*

Structural uncertainty inherent in the building of the model is documented when there are plausible alternatives in terms of type of model or model structure, corresponding to different representations of a phenomenon, which are plausible but uncertain, given the evidence available.[40] Alternative models are developed and the outputs of these different models are presented and compared. When different models suggest different decisions, the way in which structural uncertainty affects the decision is discussed. Model meta-analysis methods (model averaging) have been developed, and make it possible to weight the different scenarios explicitly, in order to represent their respective credibility.

■ *Sensitivity analysis are used to characterise uncertainty about parameters and methodological choices*

Sensitivity analyses are conducted both to assess how uncertainty about a model's parameters affects the estimation of costs and health outcomes and the robustness of the results of the economic evaluation, and also, in complex models, to specify the type of relationship between the parameter or parameters and the estimated costs and health outcomes.

An univariate deterministic sensitivity analysis is routinely used for parameters considered *a priori* to be able to influence the results of the evaluation.[41] Due justification for the choice of parameters and of plausible extreme values are provided. When a multivariate deterministic analysis is used, the author sets out the reasons for the choice of parameters and values. The process may be completed with a threshold analysis (parameter values that modify the results of an economic evaluation), but the probability (and relevance) of these thresholds remains a matter of judgement.

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[40] There may be for instance different hypotheses about the natural history of a disease, or about the transmission mode of a virus, that cannot be confirmed nor refuted by available evidence.
[41] These may be parameters that are *a priori* strong determinants of the model results, parameters with a wide range of variability, parameters derived from studies with a low level of evidence, parameters relating to behaviour for which there is potential for action, etc.

A deterministic sensitivity analysis is limited.[42] Consequently, a probabilistic sensitivity analysis is to be preferred as it incorporates uncertainty about all the parameters of the model, taking into account interactions.[43] It allows correct estimation of the expected value of costs and health outcomes and provides information useful for constructing acceptability curves and analyses concerning the expected value of perfect information (EPVI)[44] or the population expected value of perfect information (pEPVI).

A probabilistic sensitivity analysis is based on Monte Carlo simulations. The probability distributions associated with the parameters are presented together with the method by which they were obtained: i.e. statistical analysis of sample values (e.g. the distribution of costs of hospital stays within a DRG, or the distribution of the period between two clinical events), or a reasoned choice depending on the nature of the parameter, the information available about the distribution of the parameter and the way in which it was collected.[45]

If the model is based on the assumption of parameter independence, the reasons for adopting this assumption are presented. In particular, when the information required for the economic evaluation model is obtained from different sources, it can be very difficult to estimate correlations between parameters. The impact of this assumption on the results of the economic evaluation is discussed. This refers to the main parameters concerned, the expected direction of the correlation between the parameters, and the foreseeable consequences on estimation of costs and health outcomes.

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[42] If a univariate deterministic sensitivity analysis tends to underestimate uncertainty, in particular by not taking account of interactions between parameters (Claxton, 2008), it is difficult to carry out multivariate deterministic sensitivity analyses when the number of parameters in the model increases.

[43] For complex models, a probabilistic sensitivity analysis may require significant computational time.

[44] An analysis of the expected value of perfect information makes it possible to estimate the value of the additional information needed to reduce uncertainty about the decision and the cost of acquiring that information.

[45] Examples of factors that may guide the choice of distribution:
As the value of a probability is necessarily between 0 and 1, the use of a beta distribution is appropriate for characterising a probability.
A log-normal or gamma distribution is justified by the fact that the distribution of costs is often strongly skewed to the right.
If a parameter is obtained from an observational study or from a regression, the use of normal, beta-, gamma- etc. distributions is appropriate for the parameter itself or for the regression coefficients.

The presentation and interpretation of results

Economic evaluation to inform health care decision-making

Guideline 19

Health interventions plotted on the efficiency frontier are identified and an incremental cost-effectiveness ratio (ICER) calculated for each one, by detailing the incremental health effects and costs. All interventions are represented in the cost-effectiveness plan.

A clear and reasoned discussion allows the robustness of the results of the economic evaluation to be assessed and the conditions under which the results would be different to be defined.

This discussion is based on a critical analysis of the methods and data used, and on statistical sensitivity analysis.

The breakdown of the total cost per healthcare payer identifies all possible transfers of expenditure.

■ *Interventions studied are presented in terms of dominance and incremental cost-effectiveness ratios*

The main result of the economic evaluation is the definition of the efficiency frontier. The health interventions on the efficiency frontier are identified as not dominated by an alternative (strict dominance) or combination of alternatives (extended dominance). The credibility of a situation of extended dominance is discussed.

Standard decision rules are followed to calculate incremental cost-effectiveness ratios (ICER).

- Interventions are ranked in terms of costs (from the cheapest to the most expensive).

- If an intervention is more expensive and less effective than the previous one, then it is said to be strongly dominated and is excluded from further analysis.

- ICERs are then calculated for each intervention, compared with the next most-expensive, non-dominated option. If the ICER for an intervention is higher than that of the next most effective intervention, then it is ruled out by extended dominance.

- ICERs are then recalculated for the remaining interventions.

In terms of presentation, costs and health effects for all the interventions being studied are tabulated to demonstrate all the situations in which a position of strict dominance or extended dominance exists. Plotting the compared interventions in the cost-effectiveness plane permits the efficiency frontier corresponding to all the non-dominated interventions to be visualised.

Several series of ratios may be presented if various analyses are being carried out (e.g. cost per QALY gained and cost per life-year gained). The results of the evaluation are presented for the population analysed and for each of the subgroups, if such an analysis is performed.

In the absence of a cost-effectiveness threshold, interventions are qualified as efficient if they are non-dominated, without prejudging their acceptability in terms of the public decision-maker's maximum willingness to pay for health gain. Acceptability curves inform decision-makers about the probability that interventions are cost-effective at various cost-effectiveness thresholds (see the Appendix in the French version).

■ *Limitations and uncertainty associated with the conclusions of the evaluation are clearly analysed*

All evaluations contain some degree of uncertainty, inaccuracy or even controversy about the methods used. Whichever evaluation method is used, an explicit discussion is necessary to assess the robustness of the conclusions and to extrapolate the conditions under which the conclusion would be different.

First, the literature review included in the evaluation report contains a summary of the critical analysis of the studies selected, which makes it possible to assess their relevance and the soundness of the conclusions put forward. This assessment is based on compliance with standard methods for critical analysis in economic studies, and in analysis of the transposability of foreign studies (see page 24).

Second, the presentation of the results of the cost-effectiveness analysis is accompanied with a critical discussion of the methods, assumptions and data involved. The uncertainty associated with its results has to be properly described. Uncertainty surrounding the ICER estimates is systematically analysed using appropriate statistical techniques (sensibility analysis for the parameters of models, confidence intervals for ICER, cost-effectiveness acceptability curve, etc.).

■ *The potential impact on all healthcare funders of adopting an intervention is analysed*

HAS wishes to be able to identify changes in patterns of expenditure for each funder and to identify any transfers of expenditure which would be generated by choosing one intervention instead of another. This implies that the costs borne by the patients, compulsory health insurance and supplementary health insurance are identified separately. These costs are valued on the basis of current regulations concerning tariffs and reimbursement rates. For reasons of practicality and comparability, an agreement has been reached to recommend that the following breakdown of costs has to be applied:[46]

- compulsory health insurance pays for a reimbursed share of tariffs, after the deduction of any lump sum payments charged to users;

- supplementary health insurance pays for the co-payment (*ticket modérateur),* that is the share of the tariff which is not reimbursed by compulsory health insurance, and lump sum payments (excluding any deductibles that may not be covered by compulsory insurance);[47]

- patients pay any excess fee, deductible and non-reimbursable products and services.[48]

All the available data that could help to improve the description of the actual distribution of funding are taken into account, provided that they have been shown to be reliable.

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[46] For example, for a medical visit billed at €30 (€7 excess fee) the default breakdown will be:
* compulsory health insurance: €23 (tariff) x 0.7 (reimbursed rate) – €1 (medical deductible) = €15.10;
* supplementary health insurance: €23 (tariff) x 0.3 (co-payment) = €6.90;
* patient: €1 (medical deductible) + €7 (excess fee) = €8.

[47] Two types of lump sum payments coexist in France: i) sums that may be covered by complementary insurance (e.g. the daily lump sum payment towards hospital accommodation and subsistence expenses), ii) other deductibles may not be covered (e.g. deductibles on drugs, medical visits, nursing care, medical transport).

[48] This convention over-estimates the portion paid by patients, as supplementary health insurance policies may fund charges above tariffs, excess fees and costs of certain unreimbursed health products.

For example, individuals accepted into the LDD (Long Duration Disease) scheme benefit from a 100% reimbursement for medical products and services covered by the scheme, while individuals not accepted into the LDD scheme are insured at the usual rate. Analysis of funding sources reflects as accurately as possible the actual distribution of users inside and outside the schemes.

It is difficult to distinguish between the amount to be paid by the patient and the portion covered by supplementary insurance. The analysis can be improved when data are available on the proportion of users covered by a supplementary insurance fund, the degree of cover and the nature of products and services paid for.

If a funder cannot be included in the analysis (e.g. because of a lack of data), then the funder's relative weight in all financing of the interventions evaluated is discussed.

Presentation of the economic evaluation

Guideline 20

The economic evaluation is presented in a clear, structured and detailed manner. The methods are transparent and the data and the sources used are clearly reported.

For each of the interventions being studied, the undiscounted expected values of each component of costs and health outcomes are presented. The total costs and health outcomes are then calculated and discounted.

■ *The report is clear and detailed*

Particular attention is given to the writing and presentation of the evaluation to make the study accessible to potential users. This means complying with two requirements. Firstly, the report contains sufficient information to allow the reader to make a critical judgement on the validity of the analysis. Secondly, the report is written in a clear and understandable way.

A short summary (two pages) is included as an introduction, presenting in non-technical language the problem, the method used, the main results and the conclusion of the economic evaluation.

■ *Costs and health outcomes are broken down*

For all the interventions studied, the value of each component of the costs and health outcomes is first presented without discounting.

The level of detail will depend on the nature of the interventions being studied and the methods of measurement used. For example, the disaggregated presentation of costs could be based on the timing of health interventions (acute phase, re-intervention, chronic phase) or on the resources involved (hospital, physician visits, drugs and devices, transport, carers, etc.). If the health effects are expressed in QALYs, they are detailed in terms of their main contributing components (i.e. LY and HRQL).

The total health outcomes and costs for all the interventions studied are then calculated and discounted.

■ *The analysis is transparent and structured*

The report outline follows the logic of the evaluation, as this makes it more transparent and leads to a better understanding of the approach used. A number of documents propose detailed models for report structure (KCE 2008; ACMTS 2006, Drummond 2005), based on the same general outline (see below).

- The background and the problem addressed by the economic evaluation are presented clearly (what is the question being asked, and why) together with all the relevant information about the illness or health problem being considered (disease area, epidemiology, natural evolution of the illness, morbidity/mortality, treatment options, current clinical practice, cost of the disease, etc.).

- This makes it possible to define the scope of economic evaluation (target intervention, comparators, population analysed and subgroups) and to formulate a clear question in answerable form.

- A review of the clinical and economic literature is presented and discussed.

- The economic evaluation method is described in detail, in accordance with the methodological principles stated by HAS.

  - Description of the key elements of the evaluation, mainly: its perspective, the population analysed, and the interventions being compared, with reasons given for non-inclusion if appropriate (specific subgroup, particular form of the disease, etc.).

  - Description of the economic analysis method (CUA, CEA).

  - Technical description of the evaluation: time horizon, discounting, study design (based on a clinical trial and/or modelling), statistical analysis methods, sensitivity analysis.

  - Presentation of all the data included in the estimation of costs (quantity of resources consumed, unit costs) and health outcomes (relative treatment effects, preference-based scores, risk scores, etc.), together with the sources from which they were obtained (literature, *ad hoc* studies, databases, expert opinions).

- The results of the evaluation are reported in the form of incremental cost-effectiveness ratios accounting for uncertainty.

- Discussion of the results of the evaluation and its limitations.

Participants

This document was produced by members of the Economic Evaluation and Public Health Department, under the leadership of Catherine Rumeau-Pichon, in collaboration with the members of the Working Group of Economists in the Commission for Economic and Public Health Assessment (CEESP), chaired by Benoit Dervaux.

The project was coordinated by Fabienne Midy.

The section "Methods for evaluating costs" was coordinated and written by Véronique Raimond. The section on "Methods for decision modelling in health economic evaluation" was coordinated and written by Stéphanie Barré, Anne-Line Couillerot and Françoise Hamers. The other sections were written by Fabienne Midy, with the help of Clémence Thébaut.

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Members of the Economic Evaluation and Public Health Department	Members of the CEESP economists' technical group
- Stéphanie Barré - Isabelle Bongiovanni - Anne-Line Couillerot - Roselyne Delaveyne - Agnès Dessaigne - Françoise Hamers - Isabelle Hirtzlin - Grégoire Jeanblanc - Stéphanie Leclerc - Fabienne Midy - Célia Pessel - Anne-Isabelle Poullié - Véronique Raimond - Annie Rudnichi - Catherine Rumeau-Pichon - Cléa Sambuc - Olivier Scémama - Clémence Thébaut	- Luc Baumstark - Martine Bellanger - Marie-Odile Carrère - Roland Cash - Benoît Dervaux - Catherine Le Gales - Philippe Mossé - Marie-Christine Woronoff

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