KCE REPORT 183C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BELGIAN GUIDELINES FOR ECONOMIC EVALUATIONS AND BUDGET IMPACT ANALYSES: SECOND EDITION

Belgian Health Care Knowledge Centre

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
APR-DRG	All Patient Refined-Diagnosis Related Group
BCFI – CBIP	Belgisch Centrum voor Farmacotherapeutische Informatie – Centre Belge d'Information Pharmacothérapeutique
BIA	Budget impact analysis
B.S. – M.B.	Belgisch Staatsblad – Moniteur Belge
CEA	Cost-effectiveness analysis
CI	Confidence interval
CrI	Credibility interval
CTG – CRM	Commissie Tegemoetkoming Geneesmiddelen – Commission de Remboursement des Médicaments (Drug Reimbursement Committee)
CUA	Cost-utility analysis
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicine Agency
FOD – SPF	Federale Overheidsdienst – Service Publique Fédéral
HTA	Health Technology Assessment
IC	Incremental costs
ICD-9CM	International Classification of Diseases-9th Revision, Clinical Modification
ICER	Incremental cost-effectiveness ratio
IE	Incremental effects
IMA – AIM	Intermutualistisch Agentschap – Agence Intermutualiste
LY	Life year
MFG – RFM	Minimaal financiële gegevens – Résumé financier minimum
MKG – RCM	Minimaal klinische gegevens – Résumé clinique minimum
OCMW – CPAS	Openbaar Centrum voor Maatschappelijk Welzijn – Centre Public d'Action Sociale
OTC	Over the counter
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomized controlled trial

RIZIV – INAMI	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering – Institut National d'Assurance Maladie-Invalidité (National Institute for Health and Disability Insurance)
SD	Standard deviation
SG	Standard gamble
TCT	Technische Cel voor het beheer van de MKG-MFG data – Cellule Technique pour la gestion des données RCM-RFM
TRI – CTI	Technische Raad voor Implantaten – Conseil Technique des Implants (Technical Council of Implants)
TTO	Time-trade off
RVV – BIM	Rechthebbende op verhoogde verzekeringstegemoetkoming – Bénéficiaire de l'intervention majorée

SCIENTIFIC REPORT

1 BACKGROUND

Since 2002, a request for reimbursement of a class 1 pharmaceutical product by a pharmaceutical company has to be accompanied by an economic evaluation. Class 1 drugs are drugs with a therapeutic added value compared to existing therapeutic alternatives, class 2 drugs are those with comparable therapeutic value and class 3 drugs are mainly generics. Reimbursement requests are evaluated by the Drug Reimbursement Committee (CTG–CRM) based on the preparatory assessments by the experts of the RIZIV–INAMI administration. The decision to list and reimburse and the level of reimbursement of a class 1 drug is based on 5 criteria (art. 4 and art. 6 of the December 2001 Royal Decree).[37]

- The therapeutic value, taking into account the efficacy, effectiveness, side effects, applicability and user-friendliness of the product,
- The market price of the drug,
- The clinical effectiveness and likely impact of the product, taking into account therapeutic and social needs,
- The budgetary impact for the National Health Insurance,
- The cost-effectiveness of the product from the perspective of the National Health Insurance.

In contrast to cost-effectiveness, budget impact is not only a reimbursement criteria for class 1 drugs, but for all reimbursement requests.

From published data on class 1 requests in the period 2002-2004, it appeared that the claim of 'added therapeutic value' was approved after evaluation in only 48% of class 1 submissions,[1] which is of particular importance to the subsequent economic evaluation.

The definition of therapeutic value used in the Royal Decree is wider than the notion of effectiveness or outcome, as frequently used in clinical and economic literature. Besides morbidity, mortality and health-related quality of life it encompasses social and practical components such as applicability of the product and comfort of use. This larger definition has implications for the assessment of the cost-effectiveness of a product. While usual outcome parameters in economic evaluations are morbidity, mortality and/or health-related quality of life, additional reflections and analysis may be necessary to describe the therapeutic (added) value of a product.

Based on an evaluation by a competent experts committee of the reimbursement report submitted by the pharmaceutical company, the Drug Reimbursement Committee formulates a motivated advice for the Minister of Health & Social Affairs about the class of the product (class 1, 2 or 3), the appropriateness of reimbursement, the reimbursement rate and the conditions for reimbursement.

The legal basis for the assessment criteria for reimbursement requests of implants and invasive medical devices exists but is not implemented yet (Chapter III of the law of 14 July 1994 on the compulsory insurance of healthcare (B.S.–M.B. 27/08/1994)). So far, there is no requirement to perform an economic evaluation nor an assessment of the budgetary impact of new devices for which reimbursement is requested. Even if this is not an obligation (yet), economic evaluations are nonetheless usefull for medical devices and other health care interventions in order to stimulate the efficient use of our limited resources. Therefore, these guidelines are also useful to devices and other medical interventions.

In 2008, the KCE published a set of guidelines for pharmacoeconomic evaluations in Belgium. This set of guidelines has now been tested extensively by both independent researchers and pharmaceutical companies. These experiences have highlighted the need for clarification of some specific guidelines, and the further development of others. Moreover, the need for specific guidelines for budget impact analyses has been expressed. This report presents an update and extension of the guidelines developed in 2008. Compared with the previous report, the updated guidelines add a new set of recommendations for budget impact analyses and extend to all medical interventions. All guidelines were critically reviewed. Major amendments relate to guidelines on quality of life, costs and the comparator.

2 OBJECTIVES

The objective of this study was to develop methodological and reporting guidelines for economic evaluations and budget impact analyses of medical interventions, be it pharmaceutical, medical device or other interventions, submitted to expert committees at the RIZIV–INAMI, advising the health minister about reimbursement. An economic evaluation is defined as a comparative analysis of at least two health interventions in terms of their costs and health consequences. A budget impact analysis (BIA) is defined as the application of methods to estimate planned resource use and expenditure of a budget over a period of time.[2] The aim of BIA is to measure the impact of a (possible) policy decision concerning a certain intervention on the healthcare budget.

Any intervention for which a health economic evaluation or a budget impact analysis is required by the RIZIV–INAMI for reimbursement, should be assessed following these guidelines. Any deviation needs a clear and detailed justification.

The aim of these guidelines is to increase the methodological quality, transparency and uniformity of the economic evaluations and budget-impact analyses of medical interventions in Belgium. They do not relate to the procedures for the evaluation of reimbursement request dossiers, or to the methods used to arrive at a recommendation for reimbursement. Hence, compliance with the methodological and reporting guidelines for economic evaluations and budget-impact analyses as specified in this report does not imply a positive reimbursement advice. The better transparency and quality of the files will help the appraisal committees in formulating a better informed advice, but the advice itself remains entirely the committee's responsibility.

These guidelines will assist both the performers and assessors in making and evaluating economic evaluations and BIAs. Furthermore, it may assist researchers in identifying relevant parameters that should be gathered in their study protocols in order to allow robust economic evaluations.

3 METHODS

The development of this second version of the guidelines was done in *three phases*.

Phase one consisted of the development of a set of draft guidelines in 2006. These guidelines were developed by eight health economists from Belgium and abroad, two pharmacists, one medical doctor with training in health economics and one statistician. Existing guidelines from other countries were reviewed. Only guidelines issued or updated after July 2003 were considered, because the field of health economics is continually evolving and regular updates are necessary. The guidelines were mainly based on the Dutch (College voor Zorgverzekeringen, CVZ), French (Collège des Économistes de la Santé, CES), Australian (Pharmaceutical Benefits Advisory Committee, PBAC) and British (National Institute for Clinical Excellence, NICE) guidelines.[a] Other guidelines were identified, but did not add knowledge or recommendations to the ones reviewed.

Phase two consisted of a practical implementation of these guidelines during a 6 to 12-month test period. This pilot phase lead to conclusions about the practicality and usefulness of the guidelines and to potential improvements in the guidelines. Participation in the pilot test was voluntary. One company submitted an adaptation according to the draft guidelines of an earlier submitted economic evaluation of a product for which the reimbursement decision was already taken. This approach was taken to strictly separate the evaluation of the feasibility and usefulness of the guidelines from the procedural evaluation of the content of the reimbursement request file. Based on the experience of this company and the extensive feedback of about 20 pharmaceutical companies through the representative organization of the pharmaceutical industry in Belgium *Pharma.be*, the guidelines were adapted and finalized in 2008.[3] These guidelines were applicable to all new reimbursement request dossiers that (have to) include a pharmacoeconomic evaluation. Companies were strongly recommended to follow these guidelines for every economic evaluation submitted in the context of a reimbursement dossier.

Phase three involved the updating of the guidelines based on external feedback from users of the guidelines and personal experience, as well as the development of a guideline for budget impact analysis. The update was performed by three KCE health economists and discussed with a multidisciplinary team consisting of external health economists, experts of the Drug Reimbursement Committee and the Technical Council for Implants of the RIZIV–INAMI, representatives of Belgian databases, *Pharma.be* and UNAMEC. The guideline on budget impact analysis was developed by KCE health economists. In order to collect practical experiences with budget impact guidelines, a workshop was organized with three health economists from The German Institute for Quality and Efficiency in Healthcare (IQWIG, Germany). The budget impact guideline was adapted accordingly.

For most methodological aspects, different approaches exist. To improve consistency in the files, we present a “reference case”, including the essential elements for each economic evaluation or budget impact analysis together with the most appropriate methodology. The expert committees could request an economic evaluation and/or a budget impact analysis according to these “reference case methods” in order to enhance consistency between submissions. Additional analyses are allowed, but should be distinguished from the results of the reference case analysis. Variations to the reference case should be justified and well-argued. It is then up to the committee to decide how much weight it attaches to the additional analyses.

For each guideline, a short bibliography is provided in Chapter 11. The core text of the guidelines is deliberately kept relatively brief, especially for items for which there is little discussion about the most appropriate methodology. The document aims to serve as an easy working document for both evaluators and applicants. Therefore, the executive summary accompanying this report simply lists all guidelines to provide a quick overview. The appendices provide supportive documents for the economic evaluations and BIAs, and elaborate on some technical aspects of the guidelines.

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[a] Full references to these guidelines can be found in Chapter 11.

The guidelines for the economic evaluations and budget impact analyses are treated in Chapters 5 and 6, repsectively. A general discussion related to the guidelines and the use of economic evaluations and budget impact analyses is provided in Chapter 7. Recommendations for Belgian policy makers are formulated in Chapter 8. Chapter 9 and Chapter 10 present reporting guidelines for health technology assessments and models, respectively.

4 OVERVIEW OF THE BELGIAN GUIDELINES AND GENERAL REMARKS

4.1 Overview of the Belgian guidelines

The reviewed guidelines show very limited differences amongst each other. Differences relate for instance to the perspective to be taken, the cost items to be included and the discount rate for costs and outcomes.

The reference case defines the elements of an economic evaluation or budget impact analysis and the recommended methodology for each component. We are aware that discussion about the appropriateness of the recommended methodology is possible. Such discussion may relate to value judgments (e.g. the choice of the perspective or time preference for health benefits) or technical aspects (e.g. the choice of the uncertainty analysis). The reference cases for economic evaluations and budget impact analyses are presented in Table 1 and Table 2, respectively.

Table 1 – Reference case methods for economic evaluations

Component of an economic evaluation	Reference case	Guideline
Literature review	Systematic review of up-to-date clinical and economic literature following methodological standards: reproducible search strategy, transparent selection criteria, critical appraisal.	1
Perspective of the evaluation	Costs: Health care payers (federal government + communities + patients). Outcomes: Society. For health-related quality of life, health states should be described by patients on a generic instrument. Health state valuations for these states should come from the general public.	2
Target population	Consistent with the clinical file. Relevant subgroups need to be defined. Post-hoc subgroup analyses only in case of statistical proof of difference in costs or baseline risk between the post-hoc subgroups.	3
Comparator	Economic relevant comparisons are performed on the efficiency frontier.	4

Analytic technique	Cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), choice should be justified.	5
Study design	Economic evaluation based as much as possible on data from head-to-head comparisons between the study product and the comparator.	6
Calculation of costs	Health care costs paid out of the health care budget, by the federal government, the communities and the patients.	7
Valuation of outcomes	Final endpoints. Cost-effectiveness analyses: life years gained for interventions with an impact on mortality. Cost-utility analyses: QALYs, with quality-of-life weights based on empirical data obtained with a generic quality-of-life instrument such as the EQ-5D for which public preference values exist.	8
Time horizon	The appropriate time horizon for the economic evaluation depends on the duration of the impact of the study intervention on relevant outcomes as compared to the comparator intervention.	9
Modelling	Based as much as possible on data from clinical studies comparing the study medication and the comparator, data from validated databases and/or data from literature. Model inputs and outputs consistent with existing data. Face validity checked. Clear presentation of structural hypotheses, assumptions and sources of information.	10
Handling uncertainty	Probabilistic sensitivity analyses for parameter uncertainty. Scenario analyses for analyses of methodological and structural uncertainty. Presentation of uncertainty around the incremental costs (IC), incremental effects (IE) and ICERs by means of confidence or credibility intervals. Results shown on the cost-effectiveness plane and cost-effectiveness acceptability curve.	11
Discount rate	3% on costs and 1.5% on outcomes.	12

Table 2 – Reference case methods for budget impact analyses

Component of a budget impact analysis	Reference case	Guideline
Perspective of the evaluation	See economic evaluation guideline.	2 13
Target population	See economic evaluation guideline. Calculate the yearly budget impact up to the steady state. The size of the population may vary over time.	3 14
Comparator	The current situation that might change if the intervention under consideration is introduced in the healthcare system.	15
Calculation of costs	See economic evaluation guideline.	7
Costs of health outcomes	The cost consequences of the treatment effect, side effects and other short- and long-term consequences should be included in the BIA.	16
Time horizon	The time needed to reach a steady state budget impact, with a minimum time horizon of 3 years (if the steady state is already reached in the short-term).	17
Modelling	See economic evaluation guideline. Consistent with the clinical and economic assumptions in the economic evaluation.	10 18
Handling uncertainty	See economic evaluation guideline.	11 19
Discount rate	No discounting.	20

Before starting with the actual guidelines, some general remarks are made about economic evaluations and budget impact analyses of medical interventions.

4.2 General remarks

Data requirements for good economic evaluations and budget-impact analyses are high. However, even though good quality data for Belgium are often available at the company's level or at the governmental level, these data are not always easily accessible. For example, companies may find it difficult to estimate the average costs of treating a specific complication in Belgium without access to individual data on health care expenditures; while governmental agencies may find it difficult to perform or verify economic evaluations of medical interventions without access to complete data of all clinical trials. Confidentiality, secrecy and publication bias hamper the quality of economic evaluations and budget impact analyses in Belgium as well as their relevance for reimbursement decisions. Access to essential public data for the measuement and valuation of resource use for the people performing economic evaluations, including companies, their sub-contractors for the economic evaluation and other experts performing health economic evaluations that serve resource allocation decisions is often limited.

Full access to relevant study results should be pursued. Currently, there is no legal framework that obliges manufacturers to provide all relevant evidence, e.g. both positive and negative trial results. It is desirable that the producer submits a list of all studies and provide transparency about the results. This is essential to perform a balanced assessment of the intervention. Current obligations to register trials seem not sufficient. Not all trials are registered at onset, nor are all results presented in due time.[4] It should be explicitly stated if companies are not able or willing to provide the requested information.

Analogous to the clinical file, the document describing the model should be signed by the author(s) taking the responsibility for the model. Their contact details should be provided.

For reimbursement decisions, it is preferred that the outcome data used in economic evaluations reflect the interventions' effectiveness in daily practice (i.e. effectiveness in contrast to efficacy). Because effectiveness data are usually not available (yet) at the time of the initial reimbursement request, efficacy results are often transposed to the real life target population to estimate effectiveness in a cost-effectiveness analysis. This is acceptable, as long as adjustments are made for baseline risk in the real life target population.[5]

For reimbursement revisions, e.g. 1.5 to 3 years after the initial submission for class 1 pharmaceutical products and orphan drugs, real life effectiveness data should be made available. In cases where it has been decided to temporarily reimburse an intervention, however, e.g. because of uncertainty about the efficacy of the intervention, it is more important to strengthen the evidence-base for the efficacy by means of an RCT.

It is clear that at the initial submission, such evidence is rarely available, as the new intervention is not (yet) widely used. Therefore, if companies or providers would start early with thinking about the organization of an effectiveness evaluation study and the collection of economic data alongside this study (e.g. at the time of submission of the drug or device registration request), this kind of evidence may be available at the time of the initial reimbursement request. This would strengthen the economic evaluation. If still insufficient data are available from the study at the time of the initial submission, more data will nevertheless be available at the time of the revision 1.5 to 3 years after the initial submission. Especially for drugs and devices with potentially long-term effects, which would not be observed in a one or two year clinical study, it may be particularly interesting to start organizing an active control study at the time of registration of a product.

Each economic evaluation and budget impact analysis should be accompanied by an adequate description of the disease and the therapy. This description should provide information about the illness or health problem, including a specification of the disease area (pathology/problem), epidemiology (incidence and prevalence, in absolute and relative figures, e.g. per 100 000 inhabitants), the natural evolution of the illness, its morbidity and mortality and the current clinical practice. The information provided should be as relevant as possible for Belgium.

Whenever extrapolations are performed, e.g. from Flemish, Walloon or foreign data to Belgium, methods for extrapolation should be clearly described.

Belgium does not use an explicit discrete threshold value for incremental cost-effectiveness ratios below which an intervention is considered worthwhile and above which it is not.[6, 7] Referring to such thresholds from other countries should be avoided. A cost-effectiveness threshold -if we assume that it exists- is very context dependent. It depends, for instance, on the available health care budget and the interventions already financed in a country. Therefore, it does not make sense to refer to a previously stated threshold or a threshold from another country in a Belgian economic evaluation. Comparisons with other currently (non-)reimbursed interventions are difficult to interpret, since it is not clear whether economic or other arguments have been considered or played a decisive role.

Key points

- **Access to good quality Belgian data for the measurement and valuation of resource use should be facilitated to allow for economic evaluations with higher relevance for health care policy makers.**
- **In order to avoid bias and formulate balanced recommendations, initiatives should be taken to have access to all relevant evidence.**
- **Companies might consider the organisation of an active control study already at the time of registration of a product to increase the relevance of the economic evaluation either at initial submission or at revision.**
- **Belgium does not apply a threshold value for the incremental cost-effectiveness ratio. Referring to threshold values applied in other countries or based on previous decicions should be avoided.**

5 GUIDELINES FOR HEALTH ECONOMIC EVALUATIONS

5.1 Guideline 1: Literature review

Each economic evaluation should be accompanied by a description of the disease and the interventions studied and a systematic review of the existing relevant clinical literature. The review should reveal up-to-date evidence for clinical effectiveness of the intervention relative to its appropriate comparator(s). A review of economic studies is useful to identify relevant input parameters for the economic model and to support the assessors. The medical and economic search strategies should be reproducible and selection criteria and procedures clearly presented. The evidence should be critically appraised, its quality assessed and data presented in summary/evidence tables. A clear and concise synthesis, substantiated with references, should be provided. Ongoing studies should be mentioned.

For a full overview of the clinical effectiveness of a medical intervention, it is crucial to start with a thorough and systematic literature review on the safety and efficacy and/or effectiveness of the interventions. The review should be based on the best available up-to-date evidence for clinical effectiveness of the intervention and the comparator(s). Besides published literature, an overview of ongoing studies should be provided. The relationship with the clinical literature review submitted for the registration on the Belgian market should be clear.

The value of an economic evaluation crucially depends on the value of the evidence it is based upon. A review of economic studies is therefore useful to identify relevant input parameters for an economic model and to support the assessors.

Unless there is evidence about their clinical efficacy and safety, "off-label" medical treatments are not acceptable as comparators in the formal economic evaluation. The evidence on their (cost-)effectiveness can nevertheless be described in the literature review. This is not a formal requirement, but for the Drug Reimbursement Committee the existence and current use of an "off-label" used product can sometimes be a consideration in its advice to the minister. The applicant therefore has an interest in presenting the evidence on off-label used products in his literature review. This increases the transparency of the dossier.

Selective presentation of evidence is a pitfall. From the point of view of the applicant it may be felt that selective presentation of evidence provides a stronger case for the economic evaluation, but from the point of view of the assessor this creates suspicion about the validity and reliability of the economic evaluation. Therefore, it is important to even include studies in the review that are not directly used in the economic evaluation if they are relevant for the topic. The reason for not using the information provided by these studies in the actual economic evaluation should be explained. The literature review forms the basis of the economic evaluation. As for economic models, transparency and reproducibility is the key to a good literature review.

The best available up-to-date evidence can be found following the methodology of systematic literature reviews. Systematic reviews of clinical and economic literature should be carried out following the guidelines of the Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/finding_studies_systematic_reviews.htm for clinical reviews, http://www.york.ac.uk/inst/crd/econ.htm for economic reviews[b]). A literature review is an iterative process. A first search might reveal the existence of a high-quality systematic review. In that case, the literature review can be limited to an update of the existing review with more recent primary studies.

A good review starts with identification of the review questions. This includes specification of the population, the intervention, the comparator(s), the outcomes and the study designs selected (PICOS: Patient, Intervention, Comparator, Outcome, Study Design). As for the outcomes, it is worth considering (1) disease-specific outcomes, (2) adverse events, (3) overall survival and (4) quality of life, for both the intervention and the comparator.

The review should moreover contain the search strategy, study selection criteria and procedures followed for selecting studies, study quality assessment, data extraction sheets, and a synthesis of the evidence found. The approach to find general HTA reports will be the same for both the clinical and economic search strategy, e.g. searching CRD's HTA database and websites of HTA institutes. However, to retrieve primary clinical and economic studies, different databases and search strings will be used.

Databases searched for clinical evidence should include at least:

- Medline,
- Embase,
- The Cochrane Controlled Trials Register,
- The Cochrane Database of Systematic reviews and
- The NHS CRD Database of Abstracts and Reviews of Effectiveness (DARE).

Next to Medline and Embase, the economic search strategy should also search the public CRD's NHS Economic Evaluation Database (NHS EED). The KCE process note "Search for evidence and critical appraisal: Health Technology Assessment (HTA)" provides further details and methodological advices on how to perform literature searches for HTAs.[c]

[b] The search algorithms proposed in the CRD guidelines may have to be updated to current MeSH terms.

[c] Formulation of the review questions, study location, study selection, critical appraisal and data extraction, https://kce.fgov.be/content/kce-processes

The methodology used for the literature search should be clear and reproducible. Selection of articles is part of the review process. The selection criteria could relate to the years of publication, population size, publication type, language, indication, etc. The main requirement is transparency in selection criteria and argumentation why certain selection criteria were applied. Therefore, exclusion of articles is not problematic *per se* as long as the arguments for exclusion are well-justified.

Not being from Belgian origin is not an appropriate exclusion criterion for studies. Also clinical and economic studies from other countries may provide useful and relevant information for a Belgian economic evaluation. For instance, the design and assumptions of earlier published economic evaluations on the same intervention may provide a good cross-check of the assumptions and design of the submitted economic evaluation. This does not mean that the same design and assumptions must be used, but they allow argumentation for or against a specific approach.

The search algorithm should be presented, including search terms used for each database. A flow diagram, specifying the yield and exclusions (with the reason for exclusion) should be presented. Both clinical and economic literature should be critically appraised..

Data extraction sheets and/or checklists (e.g. Appendix 2) can be useful tools to collect the relevant data from the selected literature. The submission dossier must contain a synthesis of the relevant input variables, including the uncertainty measures (e.g. 95% CI, p-value). should be provided for all the studies retained for the synthesis. Appendix 3 provides examples for data extraction sheets for economic studies.

If modelling is used for the primary economic evaluation, all (clinical) studies that served as a basis for the modelling input parameters' valuation should be described in detail (including methodology used, assumptions, results). Relevance and appropriateness should be discussed in detail. The use of unpublished material in an economic evaluation is allowed but then the material should be sufficiently described to allow evaluation of its appropriateness.

The statements and data presented in the literature review should always be accompanied by the references from which they are derived. The external validity of study results included in the review, and their applicability to Belgium, should be assessed, especially if these results are afterwards used in the economic evaluation. In this context it is worth noting that clinical practice guidelines can be but are not necessarily evidence-based. Issues affecting external validity of RCTs are discussed by Rothwell.[8] They relate to the setting of the trial, selection of patients, characteristics of selected patients (e.g. baseline risk), differences between the trial protocol and routine practice, outcome measures, follow-up, and adverse effects of treatment. A full list of the issues highlighted by Rothwell[8] is found in Appendix 4.1. The analysis of the external validity and hence the relevance of study results for Belgium is mainly descriptive in nature.

The literature review will be critically appraised by the Expert Committee.

5.2 Guideline 2: Perspective of the evaluation

In economic evaluations submitted in the context of a reimbursement request, the reference case analysis should only include direct health care costs from the perspective of the health care payers. This includes payments out of the federal government's and the communities' health care budget as well as patients' co-payments. Health outcomes should be measured in patients but health state values should come from the general public.

In the literature, it is often recommended to use the societal viewpoint for the economic analysis, i.e. costs and outcomes for society as a whole should be valued. This would include costs borne outside the health care sector, such as productivity losses and travel expenses, and *stricto sensu* also outcomes for patients' family.

The decision maker, however, is usually more interested in the costs of a treatment from the point of view of the health care sector. This includes costs paid out of the health care budget (be it federal or from the communities) and patients' out-of-pocket expenses for health care.

The aim of the health care decision maker is to maximize health within the constraints of limited resources and taking into account additional decision elements. In the allocation of scarce health care resources, it is important to know how these resources can be allocated in the best possible way; in principle across disease areas.

To be of interest to the decision maker the calculation of the incremental cost-effectiveness ratio should be based on the aggregated costs of the health care payers, i.e. the patients, the federal government *and* the communities. An incremental cost-effectiveness ratio for either the government or the patient only does not make much sense as its value will depend basically on the level of reimbursement of the product. Therefore, the cost-effectiveness ratio should be based on the aggregated costs of *all* health care payers.

For the health care policy makers' information, it is nevertheless useful to report costs for the different categories of health care payers also in disaggregated form, i.e. as the costs borne by the different categories of payers (cfr. guideline 7).

Outcomes included in the analysis should be relevant for the patient population involved in the treatment and valued from a societal perspective. If health-related quality of life is used as an outcome measure, health states should be described by patients but values of health-related quality of life should be values allocated to these states by the general public.

This does not mean that broader consequences of a treatment cannot or will not be taken into account in resource allocation decisions. Decisions are not necessarily made on the basis of cost-effectiveness information alone. Other considerations, such as substantial reductions in the absence from work, may be important factors in determining the value of a therapy.[7,9] In addition, the decision maker will take other consequences into account: medical and therapeutic need, equity considerations, organizational issues, population characteristics, budget impact, etc. If these consequences are expected to be important for a specific treatment, additional analyses can be presented. However, these complementary analyses cannot replace the reference case analysis.

In conclusion, the base-case analysis should be performed from the perspective of the health care payers (federal government + communities + patients). Analyses from a broader perspective are allowed but should be clearly distinguished from the reference case.

5.3 Guideline 3: Target population

The patient population to which the economic evaluation applies should be consistent with the patient population defined in the clinical part of the reimbursement request submission.

If the intervention's effectiveness and/or costs differ between subgroups, separate subgroup analyses should be performed. A scientific justification for subgroup analysis should always be provided.

Post-hoc subgroup analyses are only allowed if the safety, effectiveness or costs between the subgroups are proven to be different based on appropriate statistical analyses or if the baseline risk for events differs between subgroups of the target population. Relative effectiveness should be assumed equal across subgroups in the latter case. The validity of this assumption should be checked.

Epidemiological data for Belgium should be presented if available for both the total target population and the relevant subgroups.

The economic evaluation should follow the clinical evidence. The target population described in the economic file should be consistent with the target population identified for routine use of the intervention in the clinical data or information provided in the reimbursement request dossier (hereafter called the 'clinical file'). The definition of the target population for routine use of an intervention is not necessarily identical to the population included in clinical trials, where selection criteria are often very strict and not applicable to routine care (e.g. Phase I, II or III studies). This would imply that the actual target population is larger than the population included in the trials. The opposite is also possible, i.e. that the target population is actually smaller, for instance if a treatment is only cost-effective in a subgroup of the patients

studied in the trial. Sometimes the implications of an intervention on the costs or effects of treatment are different between subgroups. These subgroups may already be described and analyzed in the clinical file. In this case, subgroup analyses are also indispensable in the economic evaluation.

While for the clinical file subgroup analyses are only allowed under specific conditions, there is more room for subgroup analyses in economic evaluations. The evaluations must consider the cost-effectiveness of an intervention for different indications and characteristics of the affected population. Even if subgroups were *not* analyzed in the clinical study, subgroup analyses might still be useful for the economic evaluation, e.g. if there are variables affecting cost-effectiveness which are different from the variables affecting clinical efficacy. Such analyses should always properly be referred to as post-hoc subgroup analyses. Post-hoc subgroup analyses are often explorative.

This does not mean, however, that choices should not be justified. Ad hoc data mining in search of subgroups with significant results is not acceptable. There should be a clear rationale behind the choice of subgroups and an answer should be provided to the question of why a differential effect is expected.

Post-hoc subgroup analyses always go with certain assumptions, e.g. about the treatment effect in the different subgroups. It is essential to use an assumption of constant relative treatment effect if the subgroups were not defined a priori and included as such in the clinical trial design. This means that the relative effectiveness in the different post-hoc subgroups is assumed to be equal to the relative effectiveness found in the complete sample of the clinical trial(s), while the baseline risks between the subgroups are different.[d,5] Other assumptions cannot be justified in the absence of clinical effectiveness data for the different subgroups.

Again, appropriate justification should be provided for the subgroup analyses and uncertainty associated with assumptions related to the analyses assessed. Specification of patient characteristics in the different subgroups should be detailed enough to allow the evaluator to assess the appropriateness and relevance of the subgroups.

Subgroups should be clearly defined groups that *can* be identified in real-life. For the policy maker it is of utmost importance that the sub-groups are identifiable based on objective criteria. If not, it is impossible to apply specific reimbursement rules to the subgroups. The application of objective selection criteria might be difficult. In that case, this should be explicitly discussed in the economic evaluation and budget impact analysis.

Outliers can therefore never be considered as a separate subgroup, as they are not a clearly identifiable homogenous group of patients with specific characteristics. Separate analyses on outliers are not acceptable.

Two reasons for (post-hoc) subgroup analysis are acceptable:

1. Differences in safety, effects or costs between clearly defined subgroups, as demonstrated by appropriate statistical analyses.
2. Heterogeneity in baseline risk of clearly defined subgroups.

Coincidentally observed differences in relative effectiveness between subgroups are not sufficient for post-hoc subgroup analyses, because it is impossible to say whether the differences observed are true differences if the study was not designed to observe such subgroup differences in effectiveness. Therefore, the relative effectiveness of an intervention should always be assumed equal in post-hoc subgroup analyses. The validity of this assumption should be checked by considering, for instance, the face validity of the outcomes of the model when applying this assumption. For example, a relative mortality risk reduction in a patient group of a specific age with severe co-morbidities cannot lead to a lower overall mortality risk than in the healthy population of that age.

Epidemiological data for Belgium for the target population or relevant sub-populations is part of the clinical submission. If epidemiological data are not available for Belgium, data from other European countries should be presented and be well described. In this case, the relevance of these data for Belgium should be assessed.

[d] For example, if a clinical trial finds a 10% increase in survival due to treatment, and if it is expected that the cost-effectiveness of the treatment will differ according to the age of patients, the cost-effectiveness analysis should assume a 10% increase in survival in all age groups. The relative effect is hence the same in the different subgroups, but the absolute effect will differ, due to the higher baseline survival in younger patients.

5.4 Guideline 4: Comparators

For the identification of the appropriate comparator, the efficiency frontier should be constructed. This involves the identification of all relevant treatments for the targeted indication and population, the removal of dominated or extendedly dominated interventions from the list of relevant comparators, and the calculation of the ICERs of all interventions compared to the next best alternative.

The comparators can be medical and/or non-medical treatments "Off-label" used products or services should not be used as a comparator in the reference case analysis, unless there is evidence about their clinical safety and efficacy.

The choice of the comparator(s) should always be justified.

Indirect comparisons are only allowed under specific conditions. The choice for an indirect rather than a direct head-to-head comparison between the study treatment and the comparator should be explained, together with the limitations of the indirect comparison.

The intervention should be compared with an alternative intervention with proven efficacy (in RCTs) that is considered a clinically recommended intervention for the target indication. It can be a medical or non-medical treatment, best supportive care, watchful waiting or doing nothing. Note that the "doing nothing" approach is usually not associated with zero costs and effects. The evidence should not be restricted to interventions supported by the manufacturer, but should also include alternative treatment options studied (in RCTs) by e.g. independent governments or academics.

In order to avoid the fallacious improvement of the cost-effectiveness ratio of an intervention by comparing it to a non cost-effective intervention, comparisons and thus calculations of incremental cost-effectiveness ratios should be performed on the efficiency frontier.[10] The efficiency frontier is the line on the cost-effectiveness plane connecting the non-dominated treatment alternatives (see Appendix 5). It can be constructed as follows:

1. Make a comprehensive list of all possible therapeutic strategies for the target indication and population.
2. Exclude interventions that are dominated by other interventions with lower costs and greater therapeutic benefits.
3. Exclude extendedly dominated alternatives, which means that linear combinations of other strategies can produce the same (or greater) benefit at lower (or the same) cost.
4. For the remaining alternatives, calculate the cost effectiveness by comparing each strategy with the previous less costly and less effective intervention.[11,12]

It is possible that the current treatment approach is not cost-effective itself, e.g. because it received a positive reimbursement decision in the past for reasons that now no longer apply (e.g. because at that time no other treatment was available for that indication or economic considerations were not taken into account). Striving to make calculations on the efficiency frontier avoids situations in which interventions are made cost-effective by comparing them with non-cost-effective alternatives, further stimulating non-efficient use of limited resources. The appropriate economic approach compares every alternative with the previous most cost-effective alternative. In practice, this means that next to the current treatment situation, alternative more cost-effective comparators should be included in the analysis. This can be a generic product, lifestyle adoptions (e.g. smoking cessation), or a new evidence-based intervention that has shown to be more cost-effective than the current treatment practice. Note that clinical practice guidelines usually do not consider cost-effectiveness. This implies that the recommended intervention in the guidelines is not necessarily situated on the efficiency frontier. However, guidelines may point to the different interventions that should be considered for constructing the efficiency frontier.

The choice of the comparator should always be justified and supported by clear arguments. Consistency between the clinical and the economic

submission should be pursued. Off-label used pharmaceutical products can be used as valid comparators in a pharmacoeconomic evaluation if evidence is available about the clincial safety and efficacy of the off-label use, e.g. from government sponsored trials. The value of these products should then be described in the literature review. The same applies to non-pharmaceutical interventions used beyond their described indication.

At first sight, it may seem strange that an evidence-based off label use or an intervention that is currently not applied in everyday practice is included in the analysis as a comparator. Nevertheless, this may be very relevant in order to stimulate efficient use of resources. If e.g. more cost-effective alternatives are currently not registered or reimbursed, than pointing this out could have an impact on regulations, reimbursement decisions, or supporting/requiring further research.

In some cases, the choice of the comparator will be difficult due to, for instance, changes in prescription behaviour and therapeutic insights over time. The comparator defined at the time of the clinical trials may no longer be the relevant comparator at the time of the economic evaluation. In this case, indirect comparisons and/or modelling may be required. Indirect comparisons are second best solutions and are only accepted if no single trial of appropriate quality or relevance to the Belgian target population has been performed and under specific conditions regarding the analyses. Appropriate statistical techniques must be used for indirect comparisons (i.e. adjusted indirect comparisons[13,14,15]). Useful reports about indirect comparisons is available on http://www.hta.ac.uk/fullmono/mon926.pdf[16] and on https://www.iqwig.de/download/General_Methods_4-0.pdf.[38]

Comparators for which no direct or indirect evidence is available cannot be included in the economic evaluation. All other interventions for which evidence is available can be included in the analysis. Evidence about the relative effectiveness of the two treatments is indispensable for an economic evaluation. Without such evidence, an economic evaluation will not be informative for the health care decision maker.

5.5 Guideline 5: Analytic technique

Cost-effectiveness analysis should be used if improving life expectancy is the main objective of the treatment and also the most important outcome from the patient's point of view. Outcomes of cost-effectiveness analyses should be expressed in euro per life-year gained.

Cost-utility analysis should be used if the treatment has an impact on health-related quality of life that is significant to the patient or if there are multiple patient-relevant clinical outcome parameters expressed in different units that cannot be translated into one common unit in a valid way. Outcomes of cost-utility analyses should be expressed in euro per quality-adjusted life year gained.

Given the continuing controversy over the appropriate methodology for cost-benefit analyses, cost-benefit analyses are not accepted as a reference case for economic submissions.

Results should be expressed as incremental costs, incremental effects and incremental cost-effectiveness or cost-utility ratios with their associated uncertainty. If a cost-utility ratio is presented as the result of a reference case analysis, the corresponding cost per life-year gained should also be presented.

The report should specify whether a cost-effectiveness or cost-utility analysis is used. Justification for the choice of analytic technique should be provided.

Cost consequence analyses, i.e. descriptions of costs and consequences without calculation of an incremental cost-effectiveness ratio, are insufficient for an economic evaluation but may be considered as a logical first step towards a formal economic evaluation. A table classifying the different types of economic studies is provided in Appendix 1. Separate reporting of incremental costs and incremental effects (both life-years gained and QALYs gained), besides the incremental cost-effectiveness ratio, is always recommended.

5.5.1 Cost-effectiveness analysis

In cost-effectiveness analyses the outcome should be expressed in terms of life years gained. The choice of the outcome measure should be consistent with the objectives of the treatment and the impact on patient-relevant outcomes.

The result of a cost-effectiveness analysis is expressed as an incremental cost-effectiveness ratio (ICER). The ICER reflects the additional (incremental) cost per additional unit of outcome achieved. If the effectiveness of a drug is better and the costs lower than the comparators', or vice versa, the ICER is negative. In that case, the intervention is either dominant or dominated and the ICER should not be presented. Independent of the sign of the ICER, incremental costs and incremental effects should always be presented in disaggregated form, with their respective credibility intervals (cfr. guideline 11).

If different patient-relevant clinical outcomes are expressed in different units (e.g. life years gained and complications avoided), cost-effectiveness analysis is less appropriate. For example, a cost-effectiveness analysis of a drug treatment that prolongs life expectancy significantly albeit at a high cost in terms of co-morbidity should present its results in terms of quality-adjusted life years that includes the impact of the drug on symptoms related to the treatment. Although this case for cost-utility analysis is strong, the cost per life year gained should nevertheless be presented to provide the most complete information to the decision maker.

5.5.2 Cost-utility analysis

In these guidelines, the term cost-utility analysis is used for economic evaluations that include health-related quality of life in the assessment of treatment outcome.[e] A cost-utility analysis should always complement a cost-effectiveness analysis if:

- the treatment has an impact on health-related quality of life that is significant to patients or,
- the treatment is associated with multiple clinical outcomes that are expressed in different units (e.g. side effects versus survival).

Cost-utility is not relevant in all disease areas or treatment situations. For instance, for very serious infections, leading to a high short term mortality rate but little quality-of-life consequences in survivors, it is more important to look at survival than to health-related quality of life and hence cost-effectiveness analysis may be more appropriate.

While it is easy to find at least one argument to use a cost-utility analysis, the outcome measures used in cost-utility analyses are much more subject to variation according to the measurement methods than the outcome measures of cost-effectiveness analyses. As a consequence, the comparability of different cost-utility analyses is limited. Validity of the utility values cannot be assessed because there is no golden standard for measuring utility. In order to stimulate the use of generic utility instruments and to promote consistency, the Belgian guidelines explicitly encourage the use of the EQ-5D instrument. If researchers feel that an intervention will have an impact on a patient's quality of life, including this instrument in the study protocol should be considered. This does not replace the use of disease-specific instruments, but rather complements them. If the EQ-5D instrument is not considered suitable, then the use of another generic utility instrument or direct measurement of utilities by means of time-trade-off (TTO) or standard gamble (SG) can be considered. This should then also be justified.

[e] Note that health-related quality-of-life values do not necessarily represent utility values. Measurement of utilities is subject to specific requirements. Therefore, more strict definitions of cost-utility analysis could be used. In these guidelines, however, we use the term "cost-utility analysis" for all analyses that include quality-of-life considerations in their outcome measure, to contrast them with cost-effectiveness analyses where this element is not taken into account.

To increase the usefulness of a cost-utility analysis for health care decisions, the applicant must provide sufficient detail about the methods used for valuing utilities.

5.5.3 Cost-minimisation analysis

Cost-minimisation analyses are used if the effects of two treatments are identical. Hence, cost-minimisation analysis can only be justified by proof of equal outcome.

Pharmaceutical products for which a pharmacoeconomic evaluation is needed have, by definition, claimed an added therapeutic value (as defined by the aggregate value of the 5 items mentioned in the background section). Nevertheless, due to the multiple outcomes considered in the definition of "therapeutic value", the outcome value in terms of life years gained (LYG) or QALYs gained can be identical for two interventions compared in an economic evaluation, while other elements of the therapeutic value (e.g. applicability or user-friendliness), which are not captured in the QALY or LYG-estimate, are still different. In that case, cost-minimisation analysis is recommended and additional reflections on the impact of the treatment on the other non-health outcome parameters should be provided.

In practice, it is often impossible to know a priori that cost-minimisation analysis is appropriate. The analysis will therefore usually be preceded by a cost-effectiveness or cost-utility approach, during which it becomes clear that health outcomes are identical. In this sense, a cost-minimisation analysis can be interpreted as a special case of cost-effectiveness or cost-utility analysis with equal outcomes.

5.5.4 Cost-benefit analysis

Unlike cost-effectiveness and cost-utility analyses, cost-benefit analyses express outcomes in monetary terms. The monetary valuation of clinical and non-clinical outcomes has been debated since long. As a consequence, cost-benefit analyses have not been used as frequently as cost-effectiveness or cost-utility analyses. Given the methodological difficulties and controversies associated with this technique, cost-benefit analysis is not acceptable as a stand-alone reference case analysis, but may be presented as an additional analysis to cost-effectiveness analysis or cost-utility analysis to illustrate societal benefits accruing from non-health impacts.

5.6 Guideline 6: Study design

Whenever possible, health economic evaluations should always be based on data from randomized controlled trials comparing the study intervention and a relevant comparator. Economic evaluations based on active control studies are preferred.

If modelling is needed because clinical trials provide insufficient information for the economic evaluation, the number of assumptions not based on clinical evidence should be reduced to a minimum and be fully justified.

Cost-effectiveness or cost-utility analyses can be performed alongside a clinical trial (e.g. piggy-back trial) or an observational study or can be based on a model. Clinical studies, as defined in the Law of 7 May 2004 regarding experiments on human beings, where a product under study is compared to its relevant comparator, are preferred as they offer a direct comparison between products. Each design has its peculiarities and specific caveats. Analyses should be explicit about the limitations of the design and should explain the methods used to overcome these.

5.6.1 Trial-based economic evaluations

There are basically two types of trial-based economic evaluations: *piggy-back* studies, i.e. an evaluation alongside a randomised controlled trial (RCT), and economic evaluations alongside *non-interventional trials*.

The weaknesses of **piggy-back studies** are directly related to the purposes of the RCT. RCTs are not set up for economic evaluation but rather for evaluating treatment efficacy. For economic evaluations, information is needed on the effectiveness in routine practice. As a consequence the information provided in RCTs is often insufficient for the economic evaluation. Some of the weaknesses of RCT for the purpose of economic evaluations are:

- a potentially inappropriate comparator,
- an inadequate sample size,
- a limited time horizon,
- the occurrence of protocol-driven costs or outcomes,
- inappropriate outcome measures and
- patient selection.

Note that these weaknesses do not apply to RCTs only. Other study designs often have worse limitations (e.g. biases and confounding factors, lack of comparator group).

When using results from RCTs performed in other countries, the treatment protocol may be different from the protocol that would be followed in Belgium. Some weaknesses, such as the problem of protocol driven costs, can be overcome with adequate methodology but others will require some extent of modelling.

Besides weaknesses, piggy-back studies may also have important strengths, which should be exploited if certain conditions are fulfilled. An RCT design is the strongest design to demonstrate differences in clinical efficacy, which can be causally linked to the treatment. Before reimbursement of a product it is often the only information available on efficacy.

Piggy-back studies are useful if the weaknesses are made explicit and whenever possible tackled in advance:

- either the economic evaluation is planned a priori, in which case the economic evaluation should be included in the study protocol and appropriate measures be taken to tackle the potential weaknesses of economic evaluations alongside RCTs,
- or the economic evaluation is performed retrospectively, using data gathered in the RCT, in which case appropriate measures to tackle the weaknesses should be taken before the actual economic analysis is performed. The analyst should evaluate the appropriateness of the sample size for measuring differences in costs and outcomes, develop methods to deal with protocol driven costs, assess the availability of an appropriate comparator and a relevant outcome measure for the economic evaluation.

The Drug Reimbursement Committee developed guidelines for **non-interventional studies**, defined as studies where procedures are not protocol-driven but rather by usual care. Such trials are considered complementary to randomised controlled trials, and especially useful to demonstrate the experience with the product in routine care (effectiveness rather than efficacy) as well as for the post-registration evaluation of the real cost-effectiveness of the product after 1.5 to 3 years. At the time of the initial reimbursement request, non-interventional studies will usually not be available yet, at least not for Belgium. Therefore, they will be more important for the revision file submitted after 1.5 to 3 years of use of the product in routine care. However, it should be reminded that if there is no comparator group in a non-interventional study, the relative effectiveness of an intervention cannot be assessed. Non-interventional studies avoid some of the weaknesses of RCTs but may nevertheless be insufficient to demonstrate long-term (cost-)effectiveness of a product, e.g. if there is no comparator group. In designing a non-interventional study, it is important to include the specific features for the economic evaluation in the protocol.

In some cases, additional data may be necessary to support better decision making. For example, temporary reimbursement may be allowed while gathering better data. In such cases, the remaining research questions should be clear and the research design should be appropriate to tackle these questions.

E.g. registries, without comparison group, are unable to provide reliable information on efficacy/effectiveness. On the other hand, they may be useful to provide e.g. safety or incidence/prevalence information.

For economic evaluations alongside RCTs or non-interventional trials, original data should be provided to the Expert Committee evaluating the reimbursement file upon request.

5.6.2 Modelling

Even if a trial-based economic evaluation exists, some modelling is likely to be needed (e.g. to extend the time horizon to longer time spans or to model comparators which have become more relevant in practice since completion of the trial). Very often, already in the analysis of a piggy-back study, certain assumptions will be made (e.g. assuming that the study population and observed resource use are representative for Belgium, while only a small portion of the study was set in Belgium), which turns it de facto into a model. However, modelling should never be used as a substitute for a bad RCT.

Health economic models allow the analyst to combine information from a variety of sources and to link these data to outcomes of interest to decision makers. Computer based models allow the simulation of various policies. They are therefore distinct from statistical models such as regressions or meta-analyses.

Models are used for different reasons: extension of time horizons, extrapolation of intermediate outcome parameters to final outcome parameters, consideration of externalities associated with a treatment, translation of foreign data to the Belgian context, pooling data from multiple trials, etc. The major weakness of models is that data from different sources are combined and assumptions have to be made (e.g. about the comparability of the data derived from different sources, resource use in Belgium, etc). The arguments to use a modelling approach should be set out clearly and sources for hypotheses should be presented.

A separate guideline is devoted to modelling (see guideline 10).

5.7 Guideline 7: Calculation of costs

The identification, measurement and valuation of costs should be consistent with the perspective of the Belgian health care payers. The reference case should only include direct health care costs. Direct costs outside the health care sector, productivity costs and health care costs associated with unrelated diseases should not be included in the reference case, but may be reported as a separate analysis. In this case, the impact of the intervention on these elements should be demonstrated by means of hard data. Validated sources should be used for the unit costs.

Where products under the reference pricing system or generic pharmaceutical products exist, the lowest priced product should be used in the economic evaluation, even if the cheapest products are not frequently used in Belgium.

For co-payments, the general rule is to use the official co-payments for patients without preferential reimbursement. Deviations from this rule should be justified.

The perspective for the cost calculation is that of the health care payers (government and patient). Health care costs borne by the government (RIZIV–INAMI, FOD–SPF, communities) and costs borne by the patients, as far as available, should be reported both separately and aggregated. Valuation of resource use in monetary units must be consistent with the perspective of the analysis.

5.7.1 Cost categories

Table 3 specifies the cost categories that should be included in or excluded from the cost analysis in the reference case.

Table 3 – Included and excluded costs in the reference case analysis

	Health care costs	Non-health care costs
Direct costs	*Included*. e.g. health services, medications, hospitalisations…	*Not included.* e.g. travel expenses to and from hospital, informal care, invalidity/incapacity allowances…
Indirect costs	*Not included.* e.g. health care costs in life years gained (unrelated health care costs)	*Not included.* e.g. productivity losses

This report uses this classification although other cost classifications exist.

The reference case should only include direct health care costs. These encompass costs directly related to the treatment of the disease as well as direct health care costs related to the disease in life years gained. Indirect health care costs – these are health care costs in future life years associated with unrelated diseases – should not be included. Costs borne outside the health care sector should not be included in the reference case analysis.

If productivity losses, non-health care costs and/or unrelated health care costs are deemed important for a specific treatment, they may be presented in a separate analysis.

5.7.2 Measurement of resource use

Measurement of resource use should be done by means of observations or derived from literature. Observations offer the best guarantee for appropriateness of the resource use estimates for the Belgian context. Different sources can be used to obtain observational data: clinical trials, prospective observational studies, databases and patient charts.

Use of expert panels for resource use measurement is subject to specific conditions (Appendix 4.3). Expert panels are preferably only used as a complementary source of information rather than as the sole source of information on resource use. If they are used, it is essential to provide a desciption of the way experts are selected.

Transparency in the methods used to obtain resource use estimates from experts is crucial. If questionnaires are used, these should be provided in appendix as well as descriptive statistics and in case of small samples (<10 experts) individual responses. Names and affiliations of experts should be disclosed.

If derived from literature or studies from other countries, resource use estimates should be validated for Belgium. This validation process must be described in the submitted file.

For the measurement of mean length of hospital stay per All Patient Refined Diagnosis Related Group (APR-DRG), data can be found on the web-site of the "Cellule Technique pour la gestion des données RCM-RFM–Technische cel voor het beheer van de MKG-MFG data"[f], under the heading "Feedback Financier par pathologie–Financiële Feedback per pathologie". The database also provides distributional parameters for each APR-DRG. This information should be used in the sensitivity analysis of the economic evaluation. Other databases can be used, provided that they are compliant with legal requirements about privacy and provided that the data in the database are validated, for instance against the data of the Cellule Technique–Technische Cel. An overview of health care related databases in Belgium can be found in Appendix 6.

[f] https://tct.fgov.be/etct/index.html

Each database has its weaknesses, such as for instance the cross-sectional nature of the data, discrepancies in the computation of length of stays, imperfect registration, etc. These weaknesses can generally not be remedied without some assumptions. Therefore it is recommended to discuss these weaknesses and their potential impact on the cost estimates in the text rather than trying to solve them by means of ad hoc assumptions.

For all analyses of data, methods to handle missing data should be described. For longitudinal RCT or observational studies in particular, information should be provided on the proportion of missing cost data, the reasons for these missing data, and the methods used to handle them in the analysis.

5.7.3 Valuation of resource use

5.7.3.1 General principles of cost estimation

The principle of the cost analysis is that costs are valued at opportunity costs. In practice, the opportunity costs will be approximated by market prices or some kind of mechanism used for the reimbursement of procedures (e.g. the Belgian per diem hospitalization price). In the absence of a better alternative and for reasons of uniformity between analyses, it is suggested to use these proxies in the reference case, knowing that these proxies do not always reflect real opportunity costs. Alternative cost estimates, e.g. based on micro-costing approaches, can be presented in alternative scenarios, supported with arguments of why the analyst thinks these alternative cost estimates are more appropriate.

If the health intervention to be valued is the intervention under investigation (i.e. for which a reimbursement request is introduced), there will be no official market price publicly available yet. A plausible price should then be estimated using alternative sources of information (contact with manufacturer, *ad hoc* study, literature, micro-costing…). Details on how the price was estimated should be clearly reported. This also applies to interventions which are relevant in the economic evaluation (e.g. follow-up treatments) and for which no official prices are published.

The values should reflect Belgian prices/costs for each resource input rather than foreign prices converted to euros. Valuation of resource use by means of simple currency conversion of values found in literature or in studies from other countries is not acceptable.

All costs should be expressed in values for the current (or most recent) year, e.g. by using current prices. If this is not possible and costs from past years are used, these costs should be inflated using the appropriate Health Index figures, if relevant. In some cases, indexation will not be relevant for particular products or services. For example, the reimbursement basis of pharmaceuticals is not necessarily indexed and might even decrease for products entering the reference price system. Index figures can be obtained from the web-site of the ministry of Economic Affairs[g].

Co-payments for the regularly insured should be used and not those for special categories of insured citizens, such as “patients with preferential reimbursement” (Rechthebbende op verhoogde verzekeringstegemoetkoming – Bénéficiaire de l’intervention majorée, RVV–BIM), unless there are good reasons to make the distinction. For instance, if an intervention is targeted at specific population groups that typically belong to one of these special categories, the distinction may be made between the groups in the cost analysis. For the calculation of the ICER, which is done from the perspective of the health care payers, the distinction will not have an impact as the total costs, born by the patients and the government, are the same for the different groups. Hence, the distinction is only relevant for the disaggregated reporting of costs.

g http://economie.fgov.be/fr/statistiques/chiffres/economie/prix_consommation/indice_sante/

5.7.3.2 Valuation of health care services

Unit prices/costs for ambulatory and hospital health care services (honorarium fees) can be found in the Belgian reimbursement scheme (Nomenclatuur–Nomenclature), which is publicly available on the RIZIV–INAMI website. [h]

Standard fees should be used for regularly insured patients. No account should be taken of additional charges (the so-called "supplements") for specific patients (e.g. in a private hospital room).

5.7.3.3 Valuation of drugs

Unit prices (reimbursement basis and the patients' share) for reimbursed drugs are publicly available at the RIZIV–INAMI website. [i] Unit prices for reimbursed and non-reimbursed (e.g. over the counter) drugs are available on the BCFI–CBIP website. [j]

Where products under the reference pricing system or generic pharmaceutical products exist, the lowest priced product should be used in the economic evaluation, even if it is not frequently used in Belgium. The rationale of this approach is that the limited use of the lowest priced product is a policy issue that is outside the scope of the economic evaluation. The aim of the economic evaluation is to assess the ICER relative to the appropriate comparator. If the comparator encompasses two kinds of products with a different price but equal outcomes, the least costly product should be used in the evaluation, as this product is more cost-effective than its more expensive counterpart. For follow-up treatments, a distinction is made according to the source of the data. If secondary cost data are used, e.g. from the Intermutualistic Agency (IMA–AIM), real-life data could be used, even though these real-life data might also contain the costs of brand products where generic products could have been used. Although theoretically possible, converting all costs of brand products to costs of generic products would require lots of effort for probably limited benefit. If follow-up treatments are simulated based on hypotheses, costs of generic pharmaceuticals should be used. Hypothetically constructed follow-up scenarios are simplified versions of real-life follow-up treatments. It is therefore feasible to use generic cost in these scenarios.

5.7.3.4 Valuation of devices

The list and prices (reimbursement basis and patients' share) of reimbursed implants and invasive medical devices (per category) is to be found on the RIZIV–INAMI website (Articles 28, 35 and 35bis of the RIZIV–INAMI nomenclature). [k] They also can be found in the Belgian reimbursement scheme (Nomenclatuur–Nomenclature). [l]

The list and prices of implants and invasive medical devices (per producer and per product) listed on the so-called "limitative lists", also published on the RIZIV–INAMI website. [m]

5.7.3.5 Valuation of per diem hospitalization prices

Belgian per diem hospitalization prices (in euro) are available on the RIZIV–INAMI website. [n] The per diem prices are reported per hospital and per type of hospital stay (acute, burns, geriatrics, palliative, psychiatric and specialized stays). This break-up per type of hospital stay is the one used in the Belgian hospital financing law. A description on how per diem hospital prices are computed in Belgium is provided in Appendix 4.4.

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h http://www.riziv.be/care/fr/nomenclature/index.htm

i http://www.riziv.fgov.be/drug/fr/index.htm

j http://www.cbip.be/

k https://www.riziv.fgov.be/insurer/fr/rate/index.htm

l http://www.riziv.be/care/fr/nomenclature/ index.htm

m http://www.inami.fgov.be/care/fr/other/implants/ information-topic/listart35_35bis/index.htm ("listes par type d'implant – Lijst per type-implantaat").

n http://www.riziv.fgov.be/care/nl/hospitals/specific-information/prices-day/index.htm

Based on this published list of per diem prices, a *mathematical* average across hospitals could be computed to derive Belgian average per diem prices per type of hospital stay. However this method does not account for the volume effect of each hospital such that big hospitals with higher hospitalization days and per diem prices would have the same weight as smaller hospitals with lower per diem prices. The simple mathematical average of the per diem prices should therefore not be used.

Rather the *weighted* average per diem prices that account for disparities in the case-mix (different levels of activities) of the hospitals should be used. Data over the number (volume) of stays per hospital are available (not publicly) from the MFG–RFM database. Data for the years 2004 to 2010 were obtained and weighted average 100% per diem prices were computed for those years.

Table 4 – Weighted average of the 100% per diem hospital prices per type of stay, Belgium (2004-2010)

Type	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013*
Acute	€289	€288	€308	€322	€355	€376	€390	€415	€432	€445
Burns	€1 061	€1 075	€1 135	€1 155	€1 208	€1 253	€1 296	€1 411	€1 584	€1 576
Geriatrics	€174	€179	€179	€196	€213	€214	€215	€244	€258	€252
Palliative	€402	€402	€418	€426	€446	€461	€470	€499	€533	€535
Psychiatric	€178	€177	€186	€196	€210	€215	€222	€240	€261	€273
Rehabilitation	€194	€194	€208	€220	€229	€235	€247	€261	€276	€284

More recent values will be published on the KCE website when data become available.

** 2013 are preliminary results*

Standard weighted average per diem prices should be used and no account should be taken of supplements related to extra-ordinary services, such as private room. Lump sums for drugs, medical imaging and clinical biology should be added to the per diem price (see the methods for valuation below).

5.7.3.6 *Valuation of lump sums for drugs, medical imaging and clinical biology in hospitalized patients*

Hospital lump sum for drugs

Since 1 July 2006, a prospective budget for pharmaceuticals administered to hospitalized patients in a general acute hospital was introduced by means of lump sum allocations.[17]

This prospective system covers reimbursed pharmaceuticals (classes A, B, C, Cs, Cx, Fa, Fb) and prophylactic (i.e. before surgery) antibiotics, with the exclusion of the drugs listed on a so-called "exclusion list".

Drugs excluded from the prospective system are:

- drugs highly relevant to medical practice, in terms of therapeutic needs, social values and innovative character,
- and whose high costs can strongly delay their administration to a hospitalized patient if it is included in the prospective budget.

Other specific products are excluded by law from the prospective budget (e.g. orphan drugs, cytostatics, immunoglobulins and albumins, retroviral drugs, radioisotopes, etc.). The list of excluded pharmaceuticals is updated monthly and is publicly available.[o] The RIZIV–INAMI database on the pharmaceutical specialties also mentions if the drug belongs to the prospective budget or is excluded.[p] Excluded pharmaceuticals are reimbursed by a retrospective fee-for-service system.

The prospective pharmaceutical budget is limited to inpatients (patients who stay at least one night in hospital) in acute hospitals. It is not applicable to psychiatric or chronic hospitals, nor for one-day hospitalisations.

For the pharmaceuticals integrated in the *prospective budget*, payments to the hospital are two-fold:

- Fee-for-service: the hospital retrospectively charges the sickness funds 25% of the reimbursement basis of each delivered drug.
- Lump sum: the hospital receives prospective lump sum allocations per inpatient admission, regardless of the magnitude (even absence) of the drugs administered.

Unit prices for (reimbursed and over-the-counter) drugs (100% of the reimbursement basis) administered during a hospitalization are publicly available from the RIZIV–INAMI and BCFI–CBIP websites.[q]

Lump sums per admission are hospital-specific and depend on the case mix (APR-DRG) of each hospital, taking into account the severity of illness. In 2011 lump sums varied from €62.11 to €170.6 per admission. Lump sums per admission are published on the RIZIV–INAMI website.[r]

The contribution of the patient is limited to a lump sum payment of €0.62 per inpatient day, which is charged irrespective of his actual consumption.

Drugs administered in the hospital are thus financed through the following channels :

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o http://www.riziv.fgov.be/care/fr/hospitals/specific-information/forfaitarisation/index.htm, ("liste des spécialités pharmaceutiques"–"lijst van farmaceutische specialiteiten" and "explications"–"uitleg")

p http://www.riziv.fgov.be/drug/fr/index.htm

q http://www.riziv.fgov.be/drug/fr/index.htm; http://www.cbip.be/

r http://www.riziv.fgov.be/care/fr/hospitals/specific-information/forfaitarisation/index.htm ('Anonieme lijst van alle forfaits'–'Liste anonyme de l'ensemble des forfaits')

Table 5 – Sources of financing – Hospital drugs for patients in general acute hospitals

	Sickness funds	Ordinary patient
Drugs included in the lump sum	Lump sum per admission (varies per hospital) 25% of the reimbursement basis as fee-for-service	€0.62 per inpatient day
Drugs outside the lump sum (exclusion list)	Reimbursement as fee-for-service (according to the reimbursement categories A, B, C, Cs, Cx, Fa, Fb).	
Drugs in reimbursement class D	-	100% out of pocket

In order to value the full cost of the pharmaceuticals delivered during an inpatient stay, taking into account the dual system of financing (25% fee-for-service and lump sums), the following procedure is suggested:

1. If IMA–AIM population data can be used (or IMA–AIM data from the "Permanent Sample" - Echantillon Permanent–Permanente Steekproef - which is a representative subset of the IMA–AIM population data), the drugs reimbursed as fee-for-service (at 25% of their reimbursement basis) should be identified in the IMA–AIM database and multiplied by 4. As a consequence, the lump sum per admission should be identified and removed from the computations. The patients' share and the drugs on the exclusion list are also recorded in the IMA–AIM database. Their total costs should further be added. The multiplication factor was obtained by computing the yearly (2000-2011) RIZIV–INAMI expenses (in lump sums, fee-for-service and in total) for inpatient drugs included in the lump sum based on full RIZIV–INAMI accountancy records (Doc N, "financial year–boekjaar–année comptable"), see Table 6. This multiplication factor clearly demonstrates a trend towards the value 4 over the years. This factor will be checked regularly by KCE and updated if necessary (publication on KCE's web-site).
2. If IMA–AIM population data cannot be used, the number and type of drugs administered per inpatient stay should be obtained from clinical trials, observational studies or be simulated based on literature about patient health care pathways. Drugs included in the lump sum and drugs on the exclusion list should be valued at 100% of their reimbursement basis. The patient share of €0.62 per inpatient stay (taking into account an average length of stay per pathology) should be added, as well as expenses for class D drugs.

Table 6 – Total RIZIV–INAMI expenses on inpatient drugs (drugs included in the prospective budget only)

Year	Lump sum expenses*	Fee-for-service expenses	Total expenses	Extrapolation factor **
2006* **	€81 965 692	€21 545 320	€103 511 011	4.80
2007	€258 548 716	€77 780 783	€336 329 499	4.32
2008	€263 207 655	€79 711 734	€342 919 389	4.30
2009	€246 271 579	€77 723 673	€323 995 253	4.17
2010	€230 943 715	€72 597 774	€303 541 489	4.18
2011	€217 654 214	€70 708 529	€288 362 743	**4.08**

** Lump sums per admission; ** Extrapolation factors from fee-for-service expenses to total expenses (= Total expenses / Fee-for-service expenses); *** Six-months period*

Hospital lump sum for laboratory testing

Laboratory testing for patients hospitalized in a general hospital is financed through a mixed system of fee-for service and (for the greater part) lump sum payments.[17]

- Fee-for-service: the hospital retrospectively charges the sickness funds 25% of the honorarium fees of each test performed.
- Lump sum 1: the hospital receives prospective lump sum allocations per inpatient day, inclusive the first day.
- Lump sum 2: the hospital receives lump sum allocations per inpatient admission.

Fee-for-service charges per laboratory test (25% and 100% of the honorarium fee) and lump sums per admission can be found on the RIZIV–INAMI website.[s]

The *lump sums per inpatient day* are hospital-specific and depend on the case mix of each hospital (APR-DRG). In November 2011 they varied from €0.27 to €37.94. Lump sums per day for each hospital can be found on the RIZIV–INAMI website.[t] Lump sum per inpatient day are charged irrespective of the actual number of performed tests (and even for days without tests performed).

Basic *lump sums per admission* are fixed at €31 (March 2012 values). If the laboratory works 24 hours a day and consists of 2 biologists full time, the lump sum reaches €54.25, and €73.63 with 3 full time biologists. Of these lump sums, the patient charge is €7.44, irrespective of the actual number of tests performed.[u]

Laboratory tests performed in patients hospitalized in a general hospital are thus financed through the following channels :

Table 7 – Sources of financing – Hospital laboratory testing for patients in general hospitals (2012 values)

	Sickness funds	Ordinary patient
Laboratory tests	Fee-for-service: 25% of the honorarium fee Prospective lump sum per inpatient day (varies per hospital)	-
"Remuneration for the biologists"	€23.56: basis lump sum per admission €46.81: lump sum per admission 24h service + 2 biologists €66.19: lump sum per admission 24h service + 3 biologists	€7.44 per admission

In order to value the full cost of the laboratory tests performed during an inpatient stay, taking into account the dual system of financing (25% fee-for-service and lump sums), the following procedure is suggested:

1. If IMA–AIM population data can be used (or IMA–AIM data from the "Permanent Sample" - Echantillon Permanent–Permanente Steekproef - which is a representative subset of the IMA–AIM population data), the lump sums per day and per admission, the patients' share, as well as the tests reimbursed as fee-for-service (25%), are available in IMA–AIM records (all have a RIZIV–INAMI (pseudo) code). Although there is no link with actual consumption (as the lump sums are paid to the hospitals irrespective of the actual services delivered) for simplicity we recommend to aggregate all the costs appearing in the IMA–AIM records for a specific hospital stay,

s https://www.riziv.fgov.be/insurer/fr/rate/index.htm ("médecins - biologie clinique"–"Artsen - klinische biologie").

t http://www.inami.fgov.be/care/fr/hospitals/specific-information/pseudo/index.htm ('Forfaitair honorarium per verpleegdag voor verstrekkingen klinische biologie'–'Honoraires forfaitaires par journée pour les prestations de biologie clinique')

u https://www.riziv.fgov.be/insurer/fr/ rate/index.htm ("Médecins - Biologie clinique"–"Artsen - Klinische biologie")

2. If IMA–AIM population data cannot be used, the number and type of laboratory tests performed per inpatients stay should be obtained from clinical trials, observational studies or be simulated based on literature about patients health care pathways. The 25% fee-for-service charge of each laboratory test performed should then be multiplied by 5 in order to account for the lump sum allocations prospectively paid by the sickness funds. The patient share of €7.44 per inpatient stay should further be added from a health care payers perspective. The multiplication factor was obtained by computing the yearly (2000-2011) RIZIV–INAMI expenses (in lump sums, fee-for-service and in total) for inpatient laboratory tests based on full RIZIV–INAMI accountancy records (Doc N, "financial year–boekjaar–année comptable"), see Table 8. This factor will be checked regularly by KCE and updated if necessary (publication on KCE's web-site).

Table 8 – Total RIZIV–INAMI expenses on inpatient laboratory testing

Year	Lump sum expenses*	Fee-for-service expenses	Total expenses	Extrapolation factor **
2000	€270 811 853	€65 754 539	€336 566 391	5.12
2001	€298 866 969	€72 041 667	€370 908 636	5.15
2002	€308 482 633	€71 007 877	€379 490 510	5.34
2003	€311 901 044	€74 876 818	€386 777 862	5.17
2004	€318 008 470	€79 464 354	€397 472 824	5.00
2005	€343 076 050	€79 743 404	€422 819 454	5.30
2006	€310 148 434	€80 470 707	€390 619 141	4.85
2007	€331 763 720	€84 663 406	€416 427 127	4.92
2008	€369 195 737	€89 113 191	€458 308 928	5.14
2009	€394 811 197	€94 737 538	€489 548 736	5.17
2010	€380 370 502	€95 455 303	€475 825 805	4.98
2011	€411 539 641	€88 385 028	€499 924 669	5.66
Total	€4 048 976 251	€975 713 831	€5 024 690 082	**5.15**

** Lump sums per inpatient day and lump sums "remuneration for the biologists"; **Extrapolation factors from fee-for-service expenses to total expenses (= Total expenses / Fee-for-service expenses).*

Hospital lump sum for medical imaging

Medical imaging for patients hospitalized in a general hospital is financed through a mixed system of fee-for service (about 70% of the hospital budget) and lump sum payments (about 30% of the hospital budget):[17]

- Fee-for-service: the hospital retrospectively charges the sickness funds the honorarium fee of each medical imaging act performed.
- Lump sum 1: the hospital receives prospective lump sum allocations per inpatient admission.
- Lump sum 2: the hospital charges a "consultancy" lump sum per inpatient stay from the first day on. This "consultancy" fee is a remuneration for the intellectual act of the performing radiologist.

Fee-for-service charges per medical imaging act and consultancy lump sums can be found on the RIZIV–INAMI website.[v] *Consultancy lump sums* are fixed (€15.83 and €16.83 for non-accredited and accredited radiologist in 2012, respectively). Of this lump sum, hospitalized patients pay €6.20 per admission, irrespective of the actual consumption.

The *lump sum per admission* is determined by the case mix of each hospital (APR-DRGs and severity level). In 2011 they varied from €0.58 to €124.16 per admission. This lump sum is chargeable whether or not any medical imaging act is performed. Lump sums per admission for each hospital can be found on the RIZIV–INAMI website.[w]

[v] http://www.inami.fgov.be/insurer/fr/rate/index.htm ("Médecins - Imagerie médicale"–"Artsen - Medische beeldvorming")

[w] http://www.inami.fgov.be/care/fr/hospitals/specific-information/pseudo/index.htm ("Honoraires forfaitaires par admission pour les prestations d'imagerie médicale"–"Forfaitair honorarium per opneming inzake medische beeldvorming)

Medical imaging acts performed in hospitalised patients are thus financed through the following channels :

Table 9 – Sources of financing – Hospital medical imaging for patients in general hospitals

	Sickness funds	Ordinary patient
Medical imaging acts	Fee-for-service per act Lump sum per admission (varies per hospital)	-
Remuneration for the radiologist "Consultancy lump sum"	€9.63: lump sum per admission for non accredited radiologist €10.63: lump sum per admission for accredited radiologist	€6.20 per admission

In order to value the full cost of the medical imaging acts performed during an inpatient stay, taking into account the dual system of financing (fee-for-service and lump sums), the following procedure is suggested:

1. If IMA–AIM population data can be used (or IMA–AIM data from the "Permanent Sample" - Echantillon Permanent–Permanente Steekproef - which is a representative subset of the IMA–AIM population data), the lump sums per admission and for consultancy, the patients' share, as well as the acts reimbursed as fee-for-service are available in IMA–AIM records (all have a RIZIV–INAMI (pseudo) code). Although there is no link with actual consumption (as the lump sums are paid to the hospitals irrespective of the actual services delivered) for simplicity we recommend to aggregate all the costs appearing in the IMA–AIM records for a specific hospital stay,
2. If IMA–AIM population data cannot be used, the number and type of medical imaging acts performed per inpatients stay should be obtained from clinical trials and/or observational studies or be simulated based on literature about patients health care pathways. The fee-for-service charge of each medical imaging act performed should then be multiplied by 1.7 in order to account for the lump sum allocations prospectively paid by the sickness funds. The patient share of €6.20 per inpatient stay should further be added under a health care payers perspective. The multiplication factor was obtained by computing the yearly (2000-2011) RIZIV–INAMI expenses (in lump sums, fee-for-service and in total) for inpatient medical imaging acts based on full RIZIV–INAMI accountancy records (Doc N, "financial year–boekjaar–année comptable"), see Table 10. This factor will be checked regularly by KCE and updated if necessary (publication on KCE's web-site).

Table 10 – Total RIZIV–INAMI expenses on inpatient medical imaging

Year	Lump sum expenses*	Fee-for-service expenses	Total expenses	Extrapolation factor **
2000	€97 007 111	€173 769 938	€270 777 050	1.56
2001	€99 233 648	€179 041 295	€278 274 943	1.55
2002	€98 800 265	€164 329 045	€263 129 310	1.60
2003	€102 475 616	€170 112 091	€272 587 707	1.60
2004	€101 204 649	€182 282 412	€283 487 061	1.56
2005	€122 653 467	€176 320 522	€298 973 989	1.70
2006	€98 001 155	€175 651 862	€273 653 017	1.56
2007	€104 823 792	€180 422 669	€285 246 460	1.58
2008	€114 356 262	€184 257 405	€298 613 667	1.62
2009	€123 063 728	€190 071 715	€313 135 443	1.65
2010	€109 876 769	€191 173 726	€301 050 495	1.57
2011	€138 703 898	€188 603 565	€327 307 464	1.74
Total	€1 310 200 361	€1 967 432 678	€3 277 633 039	**1.67**

** Lump sums per admission and "consultancy lump sums"; **Extrapolation factors from fee-for-service expenses to total expenses (= Total expenses / Fee-for-service expenses).*

Example: Valuation of an inpatient stay.

A patient is hospitalized for 6 days in an acute hospital. During his hospitalization he undergoes the following tests: a urine test, a blood test, a chest radiograph, an abdominal echography. He also receives the following medications: ACE inhibitors (25mg per day), aspirine (Acide acétyl salicylique 80 mg per day) and immunoglobulins (1 perfusion per day).

What is the cost of his hospital stay, from the perspective of the health care payers?

Laboratory tests	RIZIV–INAMI nomenclature	25% honorarium fee (1/1/2012)	Multiplication factor	Cost
Urine test	543723	€1.19	5	€5.95
Blood test	120061	€0.40	5	€2.00
Patients share	-	-	-	€7.44
Total costs laboratory tests				**€15.39**

Medical imaging acts	RIZIV–INAMI nomenclature	Honorarium fee (1/1/2012)	Multiplication factor	Cost
Chest radiograph	452701	€12.58	1.7	€21.39
Abdominal echography	460165	€26.46	1.7	€44.98
Patients share	-	-	-	€6.20
Total costs medical imaging acts				**€72.57**

Hospital per diem prices	Per diem price	Number of inpatient days	Total cost
Acute hospital	€388	6	€2 328

Medication	Drug included in the lump sum or on the exclusion list?	(Extrapolation to) 100% reimbursement basis (1/1/2012)	Nbr of inpatient days	Cost
ACE inhibitors (Captopril Apotex)	In lump sum	€0.0715/25 mg	6	€0.43
Acide acetyl-salicylique (Asa Mylan)	In lump sum	€0.0257/80 mg	6	€0.15
Immunoglobulin (Gammagard)	Exclusion list	€222.8 / perfusion	6	€1 336.80
Patients share	-	€0.62	6	€3.72
Total costs medications				**€1 341.10**

In this **example**, the total cost of the hospital stay is: €15.39 + €72.57 + €1 341.10 + €2 328 = €3 757.06.

5.7.3.7 *Valuation of the average transport costs to health care services*

Transport costs are not direct health care costs and as such should not be included in the reference case. For some interventions, however it may be important to quantify the travel expenses incurred by the patient or the RIZIV–INAMI (e.g. dialysis) to and from the caring institution or physician. These expenses may then be reported as a complementary analysis, *separate from the reference case*.

Travel expenses belong to the direct non-health care costs category. In order to increase the consistency across the economic evaluations, the following standard travel costs are suggested:

- Transport costs are estimated to be €0.30 (2010 value) per kilometer, which corresponds to the travel fee reimbursed by the RIZIV–INAMI to patients admitted in a day care centre (KB–AR 12/10/2010). This fee is indexed each year with the health index. No adjustement is done for the type of transport (personal car, public transport…) and the number of kilometers is limited to a maximum of 15 per journey (i.e. 30 kilometers per day).

Although these standard costs contribute to reduce some price difference between studies, deviations from those values are allowed if the researcher can demonstrate that the values relevant for his/her study considerably differ.

5.7.3.8 *Valuation of productivity costs (societal perspective)*

Productivity costs are not direct health care costs and as such should not be included in the reference case. If relevant, indirect productivity costs can be presented as a complementary analysis, *separate from the reference case*. In any case, the impact of the medical intervention on the level of productivity must be real and well documented.

Productivity costs are costs arising from production losses due to:

- Unfitness to work/sick leave (in the case of treatment/illness),
- Early retirement/incapacity to work (in the case of long-term illness or disability),
- Premature death.
- Productivity costs are divided into paid and unpaid work (i.e. voluntary job, house keeping…).

Short-term lost productivity during ***paid work*** has to be valued using the Human Capital Approach. The human capital approach values the time during the whole period of work inability due to sick leave, early retirement (potentially up to retirement) or premature death (up to retirement). Productivity costs in the Human Capital Approach are to be computed by multiplying the total number of days of work absenteeism by the national average labour cost per day. Labour costs include employee wages and/or salaries and employers' social security contributions, The Belgian average labour cost per working day was estimated at €257 (costing year 2010; Source Eurostat, Monthly labour costs,[x] and assuming 18.8 working days per months: 52 weeks * 5 working days minus 24 days (legal holidays and agreed extra holidays) minus 10 public holidays).

[x] http://epp.eurostat.ec.europa.eu/portal/page/portal/labour_market/labour_costs/database

In case of long-term absence from work or death, instead of accounting for the whole period of work inactivity, it should be considered that vacant workplaces can be filled again within a certain period of time. In that case, only the period until the workplace is filled again by a previously unemployed person will be valued. The Friction Cost Method should then be used. The friction-cost method is based on the idea that organizations need a certain time span (the friction period) to restore the initial production level after an employee becomes absent from work.

The amount of production lost due to disease depends on the length of this friction period. Productivity costs are then calculated by multiplying the labour costs per day (i.e. €257, see above) with the duration of the friction period. Unfortunately precise data on the length of the friction period could not be identified for Belgium. Productivity costs should then be computed by varying the friction period from 2 to 6 months.

Unpaid work such as voluntary jobs or housekeeping can be considerable, especially in those with chronic diseases. It is recommended to present the incremental number of unpaid working days. As there is currently no consistent method to value unpaid working days, it is recommended not to include them in the cost estimates.

5.7.3.9 Valuation of informal care costs

Informal care costs are the value of the time spent, by family and relatives, caring for a sick relative. Informal care can be important particularly for long-term diseases requiring non-specialized care (e.g. Alzheimer disease).

Informal care costs may belong to two cost categories. Informal care costs are direct non-health care costs if they are related to the intervention/disease under consideration (e.g. relatives caring for a sick parent after hospital discharge). Informal care costs are indirect non-health care costs if they are unrelated to the disease/intervention under consideration and occur in future life years gained (e.g. relatives caring for the same now older parent years after the intervention succeeded).

If relevant, informal care related to the disease/intervention under study can be presented as a complementary analysis, *separate from the base-case*. For reasons of consistency with unpaid work, informal care should only be measured (i.e. in number of days spent caring) but not valued.

Costs of informal care that is not related to the intervention/disease in life-years gained (indirect non-health care costs) should not be measured nor valued.

5.8 Guideline 8: Estimation and valuation of outcomes

Outcomes in economic evaluations should be expressed in terms of final endpoints instead of intermediary outcomes. Clearly defined outcome measures, for which there is little debate about the measurement methods, are recommended.

For cost-effectiveness analyses, outcomes should be expressed in terms of life years gained. For cost-utility analyses, QALYs should be calculated. Life expectancy should be estimated based on Belgian age- and gender-specific life tables. Health-related quality-of-life weights should be based on empirical data, obtained in patients with a descriptive system for health status for which corresponding preference values exist from the general public such as the EQ-5D. The use of Belgian preference values is preferred. Scenarios with disease-specific measures for health-related quality of life and scenarios including effects on caregivers' health-related quality of life can be presented as complementary analyses but are not acceptable in the reference case.

The aim of an economic evaluation is to assess the additional costs associated with the better outcome of a health intervention. It is important to include all cost and outcome consequences, including those associated with positive and negative effects of the treatment (e.g. adverse side effects).

The valuation of outcomes depends on the analytic technique used. In cost-effectiveness analyses, outcomes are expressed in clinical units such as life years gained, in cost-utility analyses outcomes are expressed in QALYs gained.

5.8.1 Effectiveness evaluation in cost-effectiveness analysis

For cost-effectiveness analyses, the outcomes should be consistent with the results of the clinical file. If this file contains only short term outcomes and long term outcomes are considered important for the economic evaluation, modelling may be needed (cfr. guideline 10). For an intervention with a impact on short- or long-term mortality, outcomes should be expressed in terms of "number of life years gained". Age- and gender-specific life tables for Belgium should be used to estimate life expectancy. These data are available at the National Institute of Statistics.[y]

The estimated effectiveness should be based on all-cause mortality in the reference case analysis. Effectiveness estimates based on disease-specific mortality can be presented in complementary analyses. If the disease has a major impact on overall mortality in the population examined, all-cause mortality figures should be corrected for the fact that they include disease-specific mortality (see ISPOR's Principles of Good Practice for Decision Analytic Modelling in Health Care Evaluation.[z] All-cause mortality should be modelled non-parametrically based on life table data. The functional form of the chosen disease-specific mortality function should be explained and justified in a complementary analysis.

5.8.2 Utility assessment in cost-utility analysis

In cost-utility analyses, the valuation methods for health-related quality of life should be equal for all comparators. Data on survival and health-related quality of life should be presented separately. As no weights that represent distributional preferences of the general public according to the populations affected are available, QALYs should not be weighted in the economic analysis. This means that in submitted economic evaluations a QALY is a QALY, no matter to whom it accrues.

Quality-of-life assessment in specific health states, needed for the calculation of QALYs, should be done in two steps. The first step is to obtain patients' health state description (5.8.2.1). Health states should be described on a standardised descriptive system such as the EQ-5D. The second step consists of assigning a value between 0 (= value for dead) to 1 (= value for perfect health) to these health states (5.8.2.2).

To avoid possibilities for manipulation of the quality-of-life values, it is strongly recommended to use the EQ-5D and the same set of utility values for the EQ-5D health states (so-called "EQ-5D tariff" or index values) across all economic evaluations. Moreover, it is strongly recommended to calculate QALYs based on original Belgian empirical data. If this is not possible, e.g. because the original clinical study was performed in another country, two options exist:

- either primary data on the health state descriptions should be obtained and "translated" into utility values based on the Belgian tariff scores,
- or – in case of secondary data analysis – health-related quality of life and utility data used in the economic analysis should originate from the same country.

Similar to the requirement for adjustment for baseline risk in estimating the incremental effectiveness of an intervention, adjustment for baseline (age- and gender-specific) health-related quality of life is required in estimating the incremental utility of an intervention. Unfortunately such data are not (yet) available for Belgium. When quality-of-life data from another country are used, baseline health-related quality-of-life data should also be from that country. For treatments leading to complete remission to normal health, reference data on health-related quality of life from the general population should ideally be used. However, in Belgium such data are not available as of yet. Therefore, reference data from another country should be used for now.

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y http://www.statbel.fgov.be

z http://www.ispor.org/workpaper/healthscience/tfmodeling.asp

5.8.2.1 Health state description

In the reference case, a generic health-related quality-of-life measure should be used for the description of health states. The health state description should be made by patients on a generic descriptive system such as the EQ-5D (for adults) and the EQ-5D-Y (for youngsters) or SF-6D.[aa] If justified by the disease or the intervention (e.g. care for disabled persons, terminal care, vaccination…), also informal caregivers' health states can be considered in a complementary analysis, but not as part of the reference case. It should then be explicitly stated that the QALY estimates include the effect on caregivers' health-related quaity of life. Other instruments than the EQ-5D exist, e.g. the HUI or QWB scale, but these have not been validated in Dutch or French for Belgium. Health state descriptions with the EQ-5D or SF-6D in similar patient populations in other countries may be used, provided that the criteria for valuation as explained in 5.8.2.2 are fulfilled. The use of a generic utility instrument should be considered in the phase of designing a clinical study when a future economic evaluation is envisaged. The study protocol should specify which instrument willl be used to obtain utility values and when it will be used (at prespecified endpoints and events).

If it is thought that a generic instrument is insufficiently sensitive to relevant changes in health in a specific disease, additional (disease-specific) quality-of-life results can be described in separate analyses. It is not acceptable though to create an ad hoc disease-specific questionnaire for a single economic evaluation and use this in the reference case analysis to estimate the number of QALYs gained. Such ad hoc created instruments, defined as a set of alleged relevant questions about a disease state and its associated health-related quality of life, are not sufficiently validated and tested to offer reliable and consistent results. If disease-specific instruments are used, references to publications that document the psychometric properties should be provided. Description of health states on a disease-specific quality-of-life instrument by proxies should be avoided as long as patients in the target population are able to complete a survey themselves or can be interviewed. There is evidence that expert opinions are not always close to the descriptions given by patients. Therefore, the use of proxies to describe patients' health states is only accepted if patients cannot describe their health state themselves (e.g. mentally ill patients, very young children, unconscious patients…). The reason for using proxies for the description of health states should always be justified with clear arguments.

5.8.2.2 Health state valuation

Values assigned to the health state descriptions should come from (a representative sample of) the general public. If the EQ-5D is used it is recommended to use the Flemish tariff values. For other instruments a similar preference valuation set is not available yet for Belgium. If the primary data are not available but only health-related quality-of-life results from trials from another country are used, index values from that country should be used for consistency (cfr. supra).

Mapping valuations from other health-related quality-of-life instruments (e.g. disease specific instruments or another generic instrument) to EQ-5D or SF-6D public preference values should be avoided. The direct use of a generic utility instrument is recommended. If primary data on health state descriptions cannot be obtained, mapping is still only allowed if mapping functions are based on and validated with empirical data.

If no original Belgian data are collected and mapping is not possible, generic health state descriptions and valuations from other countries in the same patient population can be used, provided that the source of the valuations is transparent and that potential problems of transferability are discussed. A basic requirement is that health states are valued from a societal perspective, i.e. derived from a representative sample of the general public. Details should be provided on the population to which the valuations refer, and references to publications describing the general population survey should be given.

[aa] The SF-6D consists of a subset of the SF-36. When the SF-36 has been used in a clinical trial, and SF-6D tariff values are available, the SF-36 data can be used to calculate QALYs. In other words, the SF-36 is sufficient but not necessary for calculating QALYs. The advantage of the complete SF-36 instead of the SF-6D is that it offers more detailed insight into the dimensions of health-related quality of life affected by an intervention, as compared to the more limited SF-6D or EQ-5D.

In the reference case, generic health state descriptions and valuations should be used. Newly set-up studies should therefore preferably always include a generic utility instrument such as the EQ-5D (alongside a disease-specific instrument if a disease-specific instrument is considered necessary), in order to increase the potential usefulness of the data for later economic evaluations.

Health state values from different (clinical) studies should be treated with utmost caution. Only if measured with the same instrument and in a similar patient population are the values comparable and can they be used in one and the same economic evaluation. Consistency in methodology for the valuation of utilities of different health states in the economic evaluation should be pursued.

5.9 Guideline 9: Time horizon

The appropriate time horizon for the economic evaluation depends on the duration of the impact of the study intervention on relevant costs and outcomes as compared to the comparator intervention.

The time horizon of the economic evaluation should be in concordance with the period over which the main differences in costs and health consequences between the intervention under consideration and its comparator are expected. Health consequences include intended as well as unintended consequences (e.g. side effects).

Treatments for chronic diseases or acute diseases with long term sequelae mostly have consequences over a patient's lifetime. In these cases, a lifetime time horizon should be adopted for the economic evaluation. However, even in chronic diseases, the impact of the investigated treatment on outcome as compared to the comparator treatment may be limited in time. For example, a new peri-operative intervention may reduce adverse events and improve quality of life in the first two months after surgery, after which the risk for events and quality of life becomes equal to that of the comparator intervention. In this case, it is sufficient (if impact on adverse events and quality of life is the main or only outcome of interest) to focus the economic evaluation on the first two months after surgery. Hence, a shorter time horizon may be justified when there is no differential mortality or long term morbidity effect between treatment options *and* with only short term differential costs. If a shorter time horizon is chosen, this should be substantiated with clear arguments. The potential consequences of not including long term costs and outcomes should in this case be discussed.

A particular issue that may be important for some drug treatments is the rapid evolution in development of new drugs. These innovative drugs may not be formally evaluated yet, but may be expected on the market in the near future, making the current drug under evaluation redundant, for instance. This cannot be an argument for shorter time horizons, but it can be mentioned in the discussion that certain innovations are expected in the near or distant future, which may change the results of the analysis. No formal analysis can be performed on the likely effect, however, as the clinical effectiveness of the innovations is still uncertain.

5.10 Guideline 10: Modelling

Modelling should be applied if the available data are insufficient to allow a full assessment of the cost-effectiveness or cost-utility of an intervention. Models should be based as much as possible on data from clinical studies with the same study intervention and comparator, on data from validated databases and/or data from literature. Modelling should always be justified. If modelling is performed, the structural hypotheses, assumptions and sources of information should be justified and presented in a clear and transparent way. Modelling inputs and outputs should be consistent with existing data and have at least face validity. Primary data and original sources of information used to define the values of input parameters as well as the original computer model should be kept at the disposal of the Expert Committee responsible for the reimbursement advice.

5.10.1 Need for modelling

Modelling may be needed for the extension of the analysis beyond observed *time periods*, e.g. because patients are no longer followed once they have reached a particular clinical endpoint. In order to know the effects of a treatment on long-term mortality or other long-term outcomes, extrapolation modelling may be necessary.

Another reason for modelling is the simulation of *final outcomes* based on observed data from intermediate outcomes. Often in clinical trials, only intermediate outcome measures are included (e.g. blood pressure reduction). Other studies may provide information on the relationship between the intermediate outcome measure and a final outcome measure (e.g. blood pressure and mortality). The relevant outcomes in economic evaluations are the gain in life-years or quality-adjusted life years.

Modelling can also be used to simulate the *real life* application of an intervention even if trial data are available. RCTs usually do not reflect real life settings. Adaptations by means of modelling may be useful to assess effectiveness instead of efficacy as presented by the RCTs. This can be done by adjusting for differences in baseline risk between the trial population and the real-world target population.[5] Adjustments for protocol-driven costs or events should also be considered.

Modelling allows the inclusion of *data from different sources*. Meta-analysis of clinical trials may increase the reliability of the clinical evidence and thereby the validity of the economic model. Administrative data may provide reliable estimates of e.g. intervention costs for the health care payers.

Sometimes, modelling is needed to take *externalities* associated with the disease or treatment into account (e.g. transmission of infections, bacterial resistance…). Externalities may not always be captured well during clinical trials, e.g. because they were not expected and therefore measurement was not included in the study protocol.

Finally, modelling can be used to compare the intervention with the relevant *comparator*. A comparisons between interventions that have never been directly compared in a clinical trial may be modelled.

The decision to model should be justified in the economic submission.

Guidelines for good general modelling practices have been developed by the modelling task force of ISPOR.[bb] Specific guidelines for infectious disease modelling have been developped by the WHO.[cc,18] These guidelines ought to be followed whenever a model is built.

5.10.2 Choice of the model design

Different types of models can be used, the major categories are decision trees and Markov models. The main principle is that a model should be kept as simple as possible. A model's internal structure should be consistent with proven or generally accepted relationships between parameters and health states. The more complex the model, the less likely it is that sufficient data are available to populate the model.

5.10.3 Precision of model structure and hypotheses

All assumptions made in the model should be explicitly documented and justified. All assumptions should be tested in the sensitivity analysis and/or scenario analysis to test the robustness of the results (see guideline 11).

If primary data or expert opinions are used, the original dataset should be provided. The population for which outcomes are modelled should be specified. This may be a hypothetical population, but should be consistent with the target population for the product and the sources used for valuing the modelling input parameters.

All variables in the model and their sources must be listed and documented in a table (Table 11):

Table 11 – Description of the variables used in a model: template

Variable	Description	Mean	Distribution & parameters (e.g. SD, 95% CI, α1, α2…)	Source

SD: Standard deviation, CI: confidence interval

bb http://www.ispor.org/workpaper/healthscience/tfmodeling.asp

cc http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.14_eng.pdf, see chapter 6

Sources used for outcome assessment, valuation of costs and assessment of probabilities should be presented and described in detail. Preference is given to peer-reviewed publications or primary data as source for the input parameters' values. Expert panels are not allowed for the assessment of probabilities or outcomes if data are available in literature. They are of the lowest level of evidence. If no published evidence is available, strict methodological criteria apply to expert panel consultation for this approach to be an acceptable source of input (see Appendix 4.3). The use of expert panels should always be well justified. Abstracts and oral presentations usually provide insufficient information to assess the quality of their contents. They should be avoided as source for input values.

Whenever input variables are based on pure assumptions, this should be explicitly mentioned as such in the table, by putting "assumption" in the column "source".

For models that extrapolate to longer time periods, i.e. for interventions with long-term sequelae, it is recommended to present different scenarios to show the impact of different extrapolation approaches on the results:[19]

- The first scenario assumes that the treatment effect disappears immediately in the extrapolated phase (stop-and-drop approach). This is the most conservative extrapolation approach.
- The second scenario assumes that the incremental treatment effect stays the same as during the observed phase.
- The third scenario assumes that the initial treatment effect fades out in the long term.

The scenarios are all part of the reference case analysis because the choice of an extrapolation approach is mainly a judgment. By presenting different, sometimes extreme, scenarios, the uncertainty related to the effectiveness of the therapy in the extended period can be assessed.

The presentation of scenarios is the most transparent option to show how robust the results are to the extrapolation approach used. Each scenario should be accompanied by appropriate sensitivity analyses on uncertain parameters as specified in guideline 11.

Models should be kept as simple as possible, but without omission of important processes. The original computer model should be put at the disposal of the Expert Committee upon request. Confidentiality will be guaranteed by the Committee. The choice of the modelling software is free.

5.10.4 Calibration, face validity and cross-validation of a model

The results of the model should be logically consistent with real-life observations and data (calibration). For example, if age-specific incidences of a disease are used in a model, the total incidence generated by the model should not considerably be higher or lower than the observed incidence in the population, unless the difference can be explained by differences in the population structure. Or life expectancy of a population with multiple severe co-morbidities should not be better after extrapolating results to a lifetime horizon in comparison to the general population. In other words, there must be a logical connection between inputs and outputs of a model.

The results of the model should be intuitively correct, that is, the model should have face validity. The model description should be transparent enough to allow an explanation of the differences with other models for the same interventions (cross-validation).

The presentation of the results of an economic model as a point estimate together with its appropriate uncertainty range is an absolute prerequisite. An economic model is by definition subject to uncertainty. The results are conditional upon the input data and the assumptions applied in the model. Both the uncertainty about the input data and the assumptions generate uncertainty in the outputs. This uncertainty should be appropriately presented, as the level of uncertainty might be an element in the decision making process. For the recommended presentation of the results, see chapter 9.

5.11 Guideline 11: Handling uncertainty and testing the robustness of the results

Irrespective of the study design, the uncertainty surrounding the cost-effectiveness/cost-utility estimates should be analysed using appropriate statistical techniques. Interval estimates should be presented for each uncertain parameter in the economic evaluation. The different types of uncertainty should be addressed, i.e. parameter, structural and methodological uncertainty. For models, probabilistic sensitivity analyses should be presented. Uncertainty around the incremental costs, incremental effects and ICERs should be provided by means of confidence or credibility intervals. A cost-effectiveness plane and cost-effectiveness acceptability curve should be presented. The most important contributors to the uncertainty of the estimated incremental cost-effectiveness/cost-utility ratio should be shown.

Uncertainty in economic evaluations of healthcare interventions is omnipresent, and should be properly described and accounted for in the submitted economic file. Uncertainty should be distinguished from variability, heterogeneity,[20] generalisability and transferability.

Variability refers to the variation or randomness observed within a homogeneous sample of patients. Variation by chance between individual patients is not the primary concern in economic evaluations that focus not on the individual but on a specific target population. Nevertheless, detailed descriptive statistics, showing the distribution and variability of costs and effects data, should be presented.

Heterogeneity refers to observed differences between patients which can, in part, be explained (e.g. differences in age, sex…).[20]

Uncertainty is usually divided into two areas:[20]

1. Parameter uncertainty: uncertainty around input parameters. This uncertainty is reflected in probability distributions based on a sample of data and is handled via probabilistic and one- or multiple-way sensitivity analyses.
2. Structural and methodological uncertainty: uncertainty coming from the analytical methods chosen to perform the evaluation (e.g. health states in the model, discount rate or extrapolation methods). This type of uncertainty is usually handled by presenting results from a methodological reference case and other scenarios handled through one-way sensitivity analyses.

Generalisability refers to applicability of the results to other populations (e.g. non-trial populations with different baseline risk). Transferability refers to the applicability of the results from other countries. These two aspects should be assessed separately. Context-specific studies are, however, preferred.

Parameter, methodological and structural uncertainty should be specifically addressed in the economic evaluation. State-of-the-art methods should be used for the estimation of the confidence interval around the incremental cost-effectiveness ratio.

In case of modelling, sensitivity analysis can help determining the importance of the different assumptions behind the model on the results. Probabilistic sensitivity analyses should be performed on all *uncertain parameters* in a model; i.e. one probabilistic sensitivity analysis where all uncertain parameters are allowed to vary according to a predefined distribution, e.g. by means of Monte Carlo simulations. Distributions used for the uncertain modelling parameters should be justified. For composite measures, such as total costs, the different components with their respective distributions should be included in the sensitivity analysis if applicable. The probabilistic sensitivity analysis should be performed on the reference case and the alternative scenarios such as the scenarios related to the assumed effectiveness of the therapy in extended time periods. It is recommended to show the most important contributors to the uncertainty of the estimated incremental cost-effectiveness/cost-utility ratio (e.g. by means of a Tornado diagram). The central estimate of the ICER results directly from the probabilistic sensitivity analysis as the mean of the simulated ICERs. This is not necessarily equal or close to the ratio of the mean incremental cost and mean incremental effect, which is the deterministic version of the ICER. A deterministic ICER can be presented if the Monte Carlo simulations fall in different quadrants of the cost-effectiveness plane.

In addition to probabilistic sensitivity analyses, a scenario or univariable sensitivity analysis could be performed on modelling parameters that are decisive for the cost-effectiveness ratio, such as the price of a pharmaceutical product. Also for *methodological uncertainty*, arising for instance from the applied discount rate or the extrapolation method used in models, scenario analyses should be used. This is comparable to one-way sensitivity analysis, where only one parameter is changed (the discount rate or the assumed effectiveness in the extended time period). For each scenario a probabilistic sensitivity analysis can be easily performed and hence results can be presented with their 95% credibility interval. Values and distributions of other parameters can be kept as in the reference case analysis for these scenarios. There is no need to present all possible combinations of all scenarios. Hence, if one scenario changes the discount rates and another scenario changes the price of the product, it is not necessary to present a scenario where both the price and the discount rates have been changed compared to the reference case.

The applicant is free to present additional univariable sensitivity or scenario analyses if these are deemed relevant. Appropriate justification of the additional analyses should be provided.

5.12 Guideline 12: Discount rate

Future costs should be discounted at a rate of 3%; future benefits at a rate of 1.5%. To assess the sensitivity of the results to the discount rate applied, different scenarios should be presented.

Incremental cost-effectiveness ratios should be presented in present values. This means that future costs and benefits should be discounted to reflect the lower value given to future costs and benefits. The formula to translate future values to their present value is: $value_t / (1 + i)^t$, with t being the time period and i being the discount rate. The choice of the discount rate for costs and benefits is mainly a normative issue. Guidelines recommended an equal rate for costs and benefits for a long time, but this approach has been debated frequently in literature. Dutch guidelines now recommend a lower discount rate for benefits than for costs.

The argument for doing so is to avoid a too strong penalization of interventions that generate most of their benefits in the future (e.g. screening and vaccination programmes). The choice of the discount rate for costs in Belgium was previously set at 3%. This rate is maintained in order to allow the comparison with previous economic evaluations. This guideline prefers consistency in the discount rate above a fluctuating one (e.g. the interest on the short-term government bonds). The change in the value of health over time is highly uncertain. Therefore, the discount rate for outcomes is uncertain. Awaiting further evidence on the most likely discount rate for outcomes in Belgium, and to remain consistent with previous guidelines, we currently recommend a rate of 1.5% for discounting outcomes in the reference case analysis.

Apart from the reference case analysis with a 3% discount rate for costs and 1.5% for effects, the company should present alternative scenarios to allow the decision maker to judge the relative importance of using different discount rates for the final result. Given the prevailing advice for the base-case analysis in many economic guidelines of other countries, a 3% discount rate for both costs and benefits can be considered. Alternative scenarios include a 0% discount rate for both costs and benefits or a 5% discount rate for both costs and benefits. For the decision maker it is important to keep in mind that, if he wishes to compare the ICER of a new product with the ICER of a product for which a decision has already been taken (based on the ICER and other elements), he should always compare the ICERs of the reference case analyses of both products.

6 GUIDELINES FOR BUDGET IMPACT ANALYSES

Economic evaluations help to assess the "value for money" of an intervention (i.e. the acceptability). Budget impact analyses assess the affordability.

The following guidelines for economic evaluations are also applicable to budget impact analyses:

- **Guideline 2 (Perspective of the evaluation),**
- **Guideline 7 (Calculation of costs),**
- **Guideline 10 (Modelling),**
- **Guideline 11 (Handling uncertainty).**

In addition, the following guidelines apply to budget impact analyses:

Target population: Besides the recommendations stated in guideline 3 for economic evaluations, budget impact analyses should estimate the potential size of the population targeted and its potential evolution over time (e.g. shifts in incidence, prevalence, disease severity). The methods used to estimate the population size should be described and justified. The degree of penetration of the intervention in the targeted population (e.g. detection rate, compliance, market share…) needs to be considered and justified.

Comparator: The budget impact analysis calculates the predicted financial impact of introducing an intervention compared to the current situation.

Costs and outcomes: In budget impact analyses, it is recommended to calculate both the global budget impact and consequences for the different health care payers separately. This implies that potential transfers of budgets between different levels of governments and/or patients should explicitly be considered. Tariffs and prices should be kept constant over the years (i.e. not inflated). The cost consequences of the treatment effect, side effects and other short- and long-term consequences (e.g. follow-up treatment) should be included in the budget impact analysis since they will have an impact on the healthcare budget.

Time horizon: The time horizon in a budget impact analysis depends on the time needed to reach a steady state. It is recommended to present the budget impact up to the steady state, with a minimum time horizon of three years.

Discount rate: Future costs and savings should not be discounted in a budget impact analysis.

6.1 Similarities and differences between economic evaluations and budget impact analyses

Economic evaluations assess the acceptability of an intervention, i.e. does it offer value for money. In contrast, budget impact analyses (BIA) help to determine if we can afford a specific intervention, i.e. do we have the budgets to implement and/or reimburse the intervention. Table 12 provides an overview of similarities and differences between guidelines for economic evaluations and BIA. More details on similarities are provided in the previous sections. In the BIA guidelines we focus mainly on the differences.

Table 12 – Similarities and differences between economic evaluations and budget impact analyses.

	CEA	BIA
Research question	Acceptability	Affordability
Perspective	Healthcare payers	
Target population	Consistent with reimbursement request	
	Closed *	Open
Comparator	On the efficiency frontier	Current situation
Costs	Direct healthcare related costs	
	No transfers	Transfers
Health outcomes	Included	Not included **
Time horizon	As long as incremental costs or outcomes are generated	Up to steady state
Modelling	Decision tree, Markov model…	
Handling uncertainty	Probabilistic and one- or multiple-way probabilistic sensitivity analyses, scenario and subgroup analyses	
Discount rate	Costs: 3%, effects: 1.5%	No discounting
Presenting results	Incremental cost, incremental effect, ICER, cost-effectiveness plane, CEA-curve, results of the sensitivity analyses	Yearly budget impact, disaggregated impact, results of the sensitivity analyses

CEA-curve: cost-effectiveness acceptability curve; ICER: incremental cost-effectiveness ratio.

** In most cases, the population in economic evaluations is closed. However, there are examples where this is not the case. For example, were there are contagion effects.*

*** Health outcomes as such are not included in the BIA. Nevertheless, the cost consequences of health outcomes (e.g. treatment cost of adverse events) are included in both the economic evaluations and BIA.*

The similarities in Table 12 show that BIA can partly rely on the economic evaluation. In case an economic evaluation has been performed, a lot of information is often already available: the cost of the initial treatment, the costs of avoided re-interventions, adverse event costs, exclusion of protocol-driven costs, adjustments to make the analysis for the real-world target population, etc. Differences should however not be neglected and several adaptations may be required to make the data from the economic evaluation useful for the BIA, such as accounting for the open population and time-dependencies required for a BIA.[21] While the BIA can be performed separately, integration of the two analyses may avoid duplication of efforts.[22]

6.2 Guideline 13: Perspective

As economic evaluations, BIA should be carried out from the healthcare payer's perspective (see 5.2). Other alternatives are also possible, such as the hospital's or patient's perspective. Nevertheless, in the context of reimbursement, the BIA calculates the impact of a policy decision on the healthcare budget. As a result, the main target of such analysis remains the healthcare payers. Complementary analysis from other perspectives should be separated from the reference case and justified.

6.3 Guideline 14: Target population

As for economic evaluations, the target population should be consistent with the population defined in the reimbursement request (see 5.3). Subgroup analysis can be performed if there is an appropriate justification. Similar as in the economic evaluation guidelines this can be due to differences in safety, treatment effect, baseline risks, or costs, which will result in different ICERs.

Furthermore, BIA entails some specific considerations:

- The *potential population size* should be specified and the estimation method described and justified.[23] Attention should be paid to the evolution of the size of the target population over time with and without the new technology.[21] If it is impossible to make a good estimate of the population size, then it is advised to perform the BIA for a number of patients that is easy to extrapolate (e.g. 100 patients). Applying this option should be justified.

- In this context, it is important to consider *shifts in incidence and prevalence*. For example, if the extension of survival is expected, it is necessary to consider the increase of the prevalence of a given illness.[24]
- *Shifts in disease severity* should be considered. For example, a screening program may detect more patients with a specific disease and may create a shift in identifying the disease at an earlier stage compared to the situation without screening.
- The *degree of implementation* needs to be considered (e.g. detection rate, the population percentage expected to use the technology,[23] compliance, the market share…). Justification for the estimates should be provided. The *market share* refers to two concepts. First, there is the market share that indicates in how far a new intervention may replace an existing alternative. For example, the introduction of a new device may replace existing treatments. This type of market share should be included in the BIA. One of the main factors that should be considered in this case is the substitution of other interventions by the new alternative.[24] On the other hand, the market share can also indicate which part of the market different competitors of a specific intervention will take. For example, if a certain intervention is reimbursed, how much of the market will be taken by company A, B, C and others that bring such a product to the market? The BIA should in the first place calculate the impact of reimbursing the intervention, and not just the companies' own product. Such additional information may be provided in a separate analysis, especially if the price of the competitors is different.
- If several relevant *subpopulations* are distinguished, both subpopulation-specific BIA and aggregated BIA for the general target population should be performed and reported.[24]
- The budget impact should be calculated for *all indications of the intervention*. This should avoid *'salami slicing'* to minimize the potential budget impact of a specific intervention. For example, a drug may be evaluated for the treatment of an orphan disease but also be used for a more common disease. This should be explicitly stated and the budget impact should be presented separately for each indication. This should be done for the indication under consideration and those for which there is already a reimbursed.
- *Off-label use* is a complex issue. Several types of off-label use should be distinguished. First, off-label use may be observed without any hard underlying evidence. This aspect of BIA may especially be of importance in a reimbursement revision or to demonstrate the importance of introducing preventive measures.[24] Next, there is off-label use because certain interventions are included in clinical practice guidelines while being off-label (e.g. in paediatrics because the drug is only licensed for adults). Finally, it may also occur that the company does not apply for marketing authorisations for a specific indication,[25] or similarly, does not apply for an alternative treatment schedule if more profitable alternatives are at their disposal. If there is evidence that these alternatives are effective and possibly more cost-effective, then the BIA should take these alternatives into account. This might support conditions for reimbursement or justify the initiation of further research.

As for all input variables, sources should be clearly described.

6.4 Guideline 15: Comparators

The budget impact analysis calculates the predicted financial impact of introducing an intervention compared to the current situation. The intervention in the BIA is the same as in the economic evaluation, but the comparator may be different since cost-effectiveness is calculated on the efficiency frontier (see 5.4 and Appendix 5).

The treatment most likely to be replaced by the new treatment can be identified through market research, surveys, database analyses or patient chart reviews. In case of an add-on treatment, the comparator is the usual daily practice without the add-on treatment.

If it is not possible to identify the treatment most likely to be replaced, the reference treatment, as defined by Belgian clinical guidelines, should be used.

Several BIAs should be performed for all relevant treatment alternatives (i.e. for those on the efficiency frontier). As such, it is not only relevant to calculate the budget impact for the intervention under consideration, but also for a more cost-effective alternative.

6.5 Guideline 16: Costs and outcomes

It is obvious that the cost of the intervention under consideration should be included in the BIA. It should be specified if the new intervention seems to replace currently used alternatives. This should be justified and the budget impact of abandoning these alternatives should also be included.[23,24]

The inclusion of cost items is directly related to the chosen perspective. Similar to the guidelines for economic evaluations, direct healthcare related costs are included in the reference case. The impact on productivity and other items outside the health-care system costs should not routinely be included in a BIA as these are not generally relevant to the budget holder.[21] Nevertheless, significant direct non-healthcare related costs (e.g. transport) or indirect non-healthcare related costs (e.g. productivity costs or costs for unpaid caregivers) could be included in BIA, provided that the relevance of these costs is considered.[24] This should be performed as a complementary analysis, clearly separated from the reference case analysis.

The cost consequences of the treatment effect, side effects and other short and long term consequences (e.g. follow-up treatment) should be included in the BIA since they will have an impact on the healthcare budget. The data source for estimating the treatment effect should be based on studies with the appropriate design (i.e. preferably RCTs). If information from the underlying studies is insufficient for determining the influence of side effects on the healthcare budget, this should be noted in the analysis.[24]

Protocol-driven costs should be excluded from the analysis.[24]

The input variables for the BIA should be presented transparently. The level of detail should be such that the reader could duplicate all the calculations in the model.[21] An overview of these input variables should be provided in a table (containing e.g. name of variable, mean cost, uncertainty, source). Assumptions should be mentioned explicitly. It is recommended to separate the measurement of resource use or volumes and the valuation or unit costs.

The valuation of cost items is related to the perspective of the BIA (see part 6.2). Researchers should strive to use Belgian real-world expenditures. Further details on cost calculations and an overview of databases is given in part 0.

It is recommended to keep the tariffs and prices stable in the BIA, unless there is a good justification for not doing so (e.g. confirmed information on pricing policy, implementation of an approved new policy rule in the near future or price changes after patent expiration).

The BIA should also include (or at least discuss) the costs related to possible conditions to introduce the intervention under consideration. This may involve the need to train the personnel or the existence of specific diagnostics or care facilities.[23,24,26] Discussion of preconditions of effective introduction should focus on those conditions that are necessary for the effective, cost-effective, and socially accepted use of the new healthcare intervention. Financial needs for establishing these preconditions should be summarised.[26]

It is recommended to calculate both the global budget impact and consequences for the different health care payers. Transfers of budgets between different governments and/or patients are not considered in economic evaluations since they are no incremental cost to the healthcare payer. This means they are included in the cost-effectiveness/utility analyses without it being clear who bears the cost. In BIA, the total budget impact is calculated in the first place. Nevertheless, introducing an intervention may have a different impact on the funds at different levels: federal, communities, regions, municipalities or other parties. Savings for one party may result in expenditures for another. For example, savings for the federal government from accelerated rehabilitation and possible shorter hospital stays may increase expenditures for communities due to increasing use of home care for patients that are sent home.[27]

Another example is the shift in expenditures when starting preventive campaigns, at the expense of communities, while this possibly creates savings at the federal level.

6.6 Guideline 17: Time horizon

The time horizon of the BIA depends on the time needed to reach a steady state. The analyst should calculate the yearly country-specific budget impact up to this steady state. Some guidelines recommend to estimate the budget impact in the short and medium term and explicitly mention a time period of 2 to 3 years,[28] a period of usually 5 years,[29] or the cumulative impact over a period of 3–5 years.[26] The ISPOR guidelines state that "BIA should be presented for the time horizons of most relevance to the budget holder. They should accord with the budgeting process of the health system of interest, which is usually annual. The framework should allow, however, for calculating shorter and longer time horizons to provide more complete information of the budgetary consequences. A particularly useful extension of the time horizon is to reflect the impact that might be expected when a steady state would be achieved. This will generally be longer than the current budget period because of costs and benefits that accrue over time."[21]

It is recommended to present the budget impact up to the steady state, with a minimum time horizon of three years. If the steady state is reached within a shorter period of time, then it is easy to extrapolate the budget impact to those 3 years. In contrast, if the budget impact would further increase after this period of time, restricting the analysis to a shorter period will not provide complete information to the decision makers in order to make well-informed decisions.

It is clear that the budget impact in the long term may be a multiple amount of the budget impact in the short term. First, the population examined in the BIA is open, which means that particular patients enter or leave the population when they meet or fail to meet the defined inclusion criteria at a given moment.[23] This contrasts to the clinical efficacy/effectiveness and the economic analysis, where the examined population usually is closed (a cohort of patients is defined at the start and all the included patients remain in the examined population within a given time horizon).[23] The Polish guidelines mention that the time horizon of the analysis should correspond to the time necessary to obtain a maximum or stable share in the market of the drug.[24] However, even if an equilibrium is reached in the market share or treated population, the budget impact may still change afterwards. For example, device replacements, re-interventions or adverse events may have an additional impact on budgets several years later. For policy makers, it is not only important to know if we can afford to fund an intervention given the current budgets, but also to know what the long term budget impact may be. Therefore, an assessment of the budget impact of a given intervention should be performed over a time period that is sufficient to reach a steady state impact on the general annual health care budget. Many factors, such as the diffusion rate, type of treatment and disease survival, long-term events, evolution of target population, etc. may thus have an impact on the appropriate time horizon for the BIA.

6.7 Guideline 18: Modelling

Similar for economic evaluations, modelling may be needed to calculate the budget impact for several reasons: make the analysis for the real-world target population, take account of the appropriate comparator, include real-world costs (e.g. excluding protocol-driven costs), extend the analysis to the appropriate time horizon, etc. In other words, bring together the best available data from different sources. For further details, we refer to part 5.10.

If an economic evaluation was performed, the BIA model should be consistent with the clinical and economic assumptions in this economic evaluation.[21] For example, assumptions on compliance should be the same in both cases. In contrast, the justified comparator in an economic evaluation (working on the efficiency frontier) may be different from the comparator in the BIA (actual financial streams compared with the current situation).

6.8 Guideline 19: Handling uncertainty

Similar to the economic evaluations, uncertainty in BIA of healthcare interventions is omnipresent, and should be properly described and accounted for.

Similar as in the economic evaluation guidelines, the probability of the appearance of particular values for a range of input variables is accounted for through probabilistic sensitivity analysis (PSA). One- or multiple-way sensitivity analysis can be performed on the most important variables such as the price of the intervention or the diffusion rate. The variability between subgroups is handled in subgroup analysis and structural or methodological uncertainty is dealt with in scenario analysis. The subgroup and scenario analyses should also be performed probabilistically. For further details, we refer to part 5.11.

6.9 Guideline 20: Discount rate

The BIA provides an estimate of financial means over time. Discounting is performed to reflect time preferences. However, the BIA calculates the (yearly) budget impact of introducing an intervention, without presenting the current value of these financial streams. Therefore, in agreement with some other guidelines,[21,23] the Belgian guidelines recommend not to discount costs in the BIA.

6.10 Guideline 21: Presenting results

Presented results should be transparent, complete and understandable. In order to do so, the budget impact should be presented for each year within the relevant time horizon. This will show the evolution of expenses over time (inclusive the steady state). Results should also be disaggregated. The contribution of different components to the budget impact should be reported separately from the general budget impact: e.g. the impact of the initial intervention, replacement costs, re-hospitalisations or re-interventions, adverse events, follow-up costs, etc.

In the base case, the BIA separately presents the direct healthcare related costs. Where it is likely to have an impact on the results of the analysis, the impact of the intervention on direct non-healthcare related costs (e.g. transport) or indirect costs (e.g. productivity loss) can be quantified in a separate analysis.

Depending on the approach used, and if considered relevant, disaggregation is possible for several other aspects:

- Outcomes can be presented separately for the different healthcare payers. A distinction is not only possible between government and patients, but also between e.g. the federal government and the communities.
- Outcomes can be presented in natural (e.g. number of unpaid working days) and monetary units.[21, 24]
- Impact on the pharmaceutical budget must be presented separately from the impact on other budgets

Results of the probabilistic sensitivity analysis should show the mean budget impact, as well as the 95% credibility interval. The mean and 95% credibility interval can also be presented for the different components. A critical description of the obtained results and conclusions is necessary. Presentation of the (dis)aggregated budget impact in table format or in a graph are encouraged. Similar as for the economic evaluation, results of the sensitivity and/or scenario analyses can be presented in table format or graph. The factors that determine the budget impact should be described.[2]

7 DISCUSSION

These methodological and reporting guidelines are developed as a tool to make economic evaluations and budget impact analyses in Belgium more relevant, transparent and consistent.

The ultimate decision to reimburse or not reimburse a medical intervention will depend on the quality of the submitted reimbursement request file and the therapeutic value of the intervention but also on other aspects that may not be considered explicitly in the submission, e.g. equity implications, severity of disease, patient characteristics and organisational issues. As such, the economic evaluation and/or the BIA will be but one input in the decision making process.[9] Other information or additional analyses that may provide relevant information to the policy maker may be presented but should be clearly separated from the original economic evaluation and BIA. An intervention with a relatively high incremental cost-effectiveness ratio may still be worthwhile if other elements weighted heavily in the decision process. Nevertheless, the economic evaluation and the BIA are very important elements for the decision maker, as they give clues about the efficient allocation of scarce resources and the affordability of specific interventions. Quality and consistency in health economic submissions might improve the extent to which such evaluations can reliably and consistently be used in the reimbursement decision making process.

8 POLICY RECOMMENDATIONS

A number of issues have been identified during the development process of these guidelines, giving rise to some policy recommendations.

First, access to data is a major problem in Belgium. It should be noted, however, that since the publication of the first guidelines for pharmacoeconomic evaluations in Belgium, several initiatives have been taken to improve access to these data. For example, the per diem price per hospital is now publicly available. These data are made available in compliance with the privacy regulation by provision of aggregated rather than individual data.

Second, the Royal Decree of December 21, 2001 would benefit from an integration of guideline 2 concerning the perspective of the cost calculation in an economic evaluation. The Decree stipulates that the advice formulated by the Drug Reimbursement Committee should take the relative costs to the health insurance (RIZIV–INAMI) and the relative effects into account. However, as demonstrated in guideline 2, using the costs for the health insurance in a full economic evaluation may have a perverse effect in the Belgian health care reimbursement system towards other health care payers, such as the patients. It would be more appropriate to state that the costs should be calculated from the perspective of the health care payers, including the government and the patient. Also, in general, the recommendations from this report should be integrated in the legislation about the reimbursement of drugs, medical devices and medical interventions.

Third, new evidence or reliable data may become available after a reimbursement decision has been made, that invalidate the results of the economic evaluation or the budget impact analysis. In that case health care payers should be allowed to ask for a revision of the reimbursement conditions of that intervention and should more often use this possibility.

Fourth, the problem of access to complete data from *all* RCTs, including *all* outcomes according to the trial protocol, to governmental agencies and other research groups remains, however, a problem. Initiatives have been taken on the European level, to register all clinical trials set up in Europe in a central public database; In addition, a collaboration between EMA and HTA agencies has been set up to improve the relevance and completeness of the European Public Assessment Reports for national reimbursement commissions. While this is an important step in the right direction for pharmaceutical products, data requirements and data availability for medical devices lag behind.

Fifth, input data required to performed an economic evaluation or a budget impact analyses are numerous and specific. The need for such data should be taken into account when setting up clinical trials, before market authorization and before revision requests.

Sixth, the analysis, reporting, evaluation and interpretation of economic evaluations and budget impact analyses are of utmost importance in the context of advising reimbursement committees. Applicants and policy makers should take care that sufficient resources are available to take up this responsibility. The systematic use of the economic guidelines will increase the credibility of the evaluations and consequently their usefulness for drug reimbursement decisions.

Finally, Belgium lacks baseline reference data on the health status of the Belgian citizen in each age and sex group, collected with a generic utility instrument that can be used to calculate QALYs. As a consequence, economic evaluations have to rely on baseline reference data from other countries, introducing additional uncertainty in the economic evaluation as we cannot be sure whether the reference health states from abroad are applicable to the Belgian population. There is an urgent need for data collected in a representative sample of the general population, allowing to judge the relative gain and/or loss in health from an intervention and/or a disease.

Key points

To the Minister of Social Affairs and Public Health:

- **Access to and provision of Belgian data for the measurement and valuation of resource use should be further facilitated for economic evaluations and budget impact analyses.**
- **The recommendations from this report should be integrated in the legislation about the reimbursement of drugs, medical devices and medical interventions.**
- **If new evidence or reliable data invalidate the results of an economic evaluation or a budget impact analysis, also health care payers should be allowed to ask for a revision of the reimbursement conditions and more often use this possibility.**

To the health care industry and the competent national and international bodies:

- **Access to data from RCTs available at the companies should be facilitated for governmental agencies.**

To the health care industry:

- **Data requirements for economic evaluations and budget impact analyses should be taken into account when setting up clinical trials, before market authorization as well as for revisions.**

To the healthcare industry and the Experts Committees:

- **To increase the credibility and usefulness of economic evaluations and budget impact analyses for reimbursement decisions, both the applicants and the RIZIV–INAMI should systematically apply these guidelines for drugs and medical devices. The extent to which those guidelines can be integrated in the current appraisal procedure should be assessed. For other medical interventions, the operational implementation of these guidelines will be made progressively and will be evaluated after 2 to 3 years.**

To the sponsors of the Belgian Health Interview Survey and the WIV–ISP:

- **Baseline reference data on the health state of the Belgian citizen in all age and sex groups should be collected, using a generic utility instrument (i.e. EQ-5D) to allow more valid estimates of the level and the natural evolution of the health-related quality of life.**

9 REPORTING GUIDELINES

The recommended structure of an economic evaluation report is presented below. This structure is based on the reporting guidelines developed by the Pharmacoeconomic Committee of the Belgian Society for Pharmacoepidemiology (BESPE).[30] Some specific reporting guidelines for models are presented in Chapter 10.

9.1 Executive Summary

Includes:

- Objectives: specifying study intervention, comparator, target population.
- Methods: design, analytic technique, sources for effectiveness evaluation, cost calculation methods, time horizon, sensitivity analysis, discount rate.
- Results: incremental costs, incremental effects, incremental cost-effectiveness/cost-utility ratio, sensitivity, additional results.
- Conclusions.

9.2 Introduction

Information about the illness or health problem:

- Disease area (pathology/problem).
- Epidemiology (incidence and prevalence, in absolute and relative figures (e.g. per 100 000 inhabitants).
- Natural evolution of the illness, morbidity and mortality.
- Current clinical practice.

9.3 Objectives

- Study intervention: therapeutic group, product name (+ generic name) and galenic type if applicable, route of administration, treatment plan, approved indications.
- Comparator (describe treatment and options if treatment fails) + justification in a Belgian context.
- Target population and possible subgroups + justification for choice of patients and subgroups in a Belgian context.
- Based on this information: formulate a clear question in answerable form.

9.4 Literature review

9.4.1 Clinical literature review

9.4.1.1 Methods

- Review questions.
- Search strategy, including search terms and databases used.
- Selection procedures and criteria.
- Quality assessment tools and procedures.
- Data extraction strategy.

9.4.1.2 Results

- Flow diagram.
- Evidence tables.
- Synthesis of the extracted evidence.

Data need to be accompanied by relevant measures of variability.

9.4.1.3 Discussion and Conclusions of the clinical literature review

9.4.2 Economic literature review

9.4.2.1 Methods

- Review questions.
- Search strategy, including search terms and databases use.
- Selection procedures and criteria.
- Quality assessment tools and procedures.
- Data extraction strategy.

9.4.2.2 Results

- Flow diagram.
- Evidence tables.
- Synthesis of the extracted evidence.

Data need to be accompanied by relevant measures of variability.

9.4.2.3 Discussion and Conclusions of the economic literature review

Data extraction sheets are provided in Appendix 3.

9.5 Basic elements of the economic evaluation

9.5.1 Analytic technique

- Analytic technique used (CEA or CUA) + reasons for this choice.

9.5.2 Study design

- Study design used (Trial-based pharmacoeconomic evaluation or model) + justification for this design.
- If modelling is used, describe the model's structure, including the assumptions used.

9.5.3 Methods used for valuation of costs

- Methods used for the identification, measurement and valuation of costs.
- Methods used to validate the data, documentation on the quality control of the data.

9.5.4 Methods used for outcome assessment

- Methods used for the measurement and valuation of outcomes.
- Methods used to validate the data, documentation on the quality control of the data.

9.5.5 Method of analysis of the data

- Statistical analysis techniques, handling missing data, statistical techniques for the sensitivity analysis.

9.5.6 Time horizon and discount rate

- Choice of, and rationale for, the time horizon and the discount ratefor the analysis.
- Reasons for an extension of the analytical horizon in relation to the primary data (e.g. from clinical trials).

9.5.7 Sensitivity analysis

- Parameters on which a sensitivity analysis is performed.
- Distributions used for uncertain parameters.
- Sources for distributions.

9.6 Research Methods

9.6.1 Identification, measurement and valuation of costs

- Which cost items were taken into account and why.
- What natural units were used to express the selected cost items before they were converted into monetary units.
- Sources consulted for the measurement of resource use.
- If a number of data elements were difficult to measure, show how the problem was solved.
- Provide a table with quantities of resource use per cost item and unit costs attached to the items.
- The cost calculation must be reproducible.

9.6.2 Identification, measurement and valuation of health-related outcomes

- Which health-related outcomes were, or were not taken into consideration and why (e.g. side effects, morbidity, mortality).
- Summary of the assumptions made regarding the identification, measurement and valuation of health outcomes.
- Possible differences in effectiveness between patient subgroups.
- Possible differences between the efficacy measured on the one hand and the effectiveness on the other.

- Methods used to described health status (instruments used).
- Methods used to measure health-related quality of life.

9.7 Results

9.7.1 Basic results

- Undiscounted life expectancy should be presented for both the interventional and comparator group. This allows to check how realistic results are. In cost-utility analyses, the outcomes both with and without QoL adjustments should be presented.
- Results should be presented in a tabular form. Undiscounted outcomes should be presented separately for the study intervention and the comparator(s). Point estimates subject to variability should always be presented with relevant measures of this variability (e.g. 95% confidence or credibility intervals). The table should therefore contain incremental costs and incremental outcomes with the 95% confidence or credibility interval. Incremental cost-effectiveness ratios should be presented if the treatment is not dominant (lower costs and better effectiveness) or dominated (higher costs and lower effectiveness).

Table 13 – Presentation of the results of an economic evaluation: template

Reference case	Mean	Lower limit of the 95% CrI	Upper limit of the 95% CrI
Incremental costs			
Incremental effects			
ICER* (€/LYG or €/QALY gained)			

** If relevant, i.e. if the intervention is not dominated or dominant. In such cases, incremental costs and incremental effects should still be reported separately. CrI: credibility interval.*

9.7.2 Uncertainty analysis

- Present 95% confidence or credibility interval around the incremental costs, the incremental effects and the incremental cost-effectiveness ratio.
- Present cost-effectiveness or cost-utility plane.
- Cost-effectiveness acceptability curve (see Appendix 5).

9.8 Discussion

- Weaknesses of the study.
- Comparison with other studies, if available .

9.9 Conclusion

9.10 Transparency of financial support

- Disclose financing and contractual arrangements. Declaration of interests.
- Autonomy and publication rights of the researchers.

9.11 References

9.12 Addenda

- Detailed data tables.
- Interim results.
- Work sheets and registration forms used for data collection, questionnaires, measuring tools, etc.
- A detailed description of the measuring tools, data and analysis.

10 PRESENTATION OF A MODEL

10.1 Data

The data used in a model should be presented in tabular form, with references, as presented in Table 11 above.

Distributions of modelling input variables should be presented with the relevant parameters of their distribution, e.g. Beta distributions should be presented with alpha1 and alpha2.

Continuous variables should be characterized by their mean and 95% confidence interval. Measures of precision should be presented. Uncertainty around input parameters and distributions for (probabilistic) sensitivity analyses should be presented.

For each health state used in a Markov model, the nature of the health state should be specified (temporary, absorbing). The choice of the health states (and the omission to avoid complexity) should be justified. Transition probabilities should be presented, e.g. in a matrix form. It should be indicated whether a transition probability is constant or variable. The choice of the cycle length should be justified.

10.2 Results

10.2.1 Reference case analysis

See 9.7.1.

10.2.2 Uncertainty analysis

Parameter uncertainty should be examined using probabilistic sensitivity analysis. Cost-effectiveness estimates should be presented on a cost-effectiveness plane and cost-effectiveness acceptability curve. The *cost-effectiveness plane*, with the results of the Monte Carlo simulations or bootstrapping, should always be presented for the cost-per-QALY gained and/or for the cost-per-LY gained. In addition, if simulations are spread over different quadrants of the cost-effectiveness plane, the percentage of simulations in each quadrant should be reported. A *cost-effectiveness acceptability curve* should be presented in order to show the probability that the treatment is cost-effective, given varying theoretical threshold values for the cost-effectiveness ratio.

The contribution of each uncertain parameter to the uncertainty in the ICER can also be presented in case of probabilistic sensitivity analysis.

If there are additional sources of uncertainty, e.g. regarding the model structure, source of input data, assumptions, separate analyses can be presented.

A *Tornado diagram* should be presented to highlight the modelling parameters with the largest impact on the results. Uncertainty around the incremental costs (IC), incremental effects (IE) and ICERs in scenario analyses can be presented in an analogous table format as the reference case.

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Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. Value Health. 2007;10(5):336-47.

APPENDICES

APPENDIX 1. CLASSIFICATION OF ECONOMIC STUDIES

Figure 1 – Classification of economic studies

		Are both costs (inputs) and consequences (outputs) of the alternatives examined?		
		No		Yes
		Consequences only	Costs only	
Is there a comparison of at least two alternatives?	No	*Partial evaluation*		*Partial evaluation*
		Outcome description	Cost description	Cost-consequence analysis
	Yes	*Partial evaluation*		*Full economic evaluation*
		Efficacy or effectiveness evaluation	Cost comparison	Cost-utility analysis (CUA) Cost-benefit analysis (CBA) Cost-effectiveness analysis (CEA) Cost-minimisation analysis (CMA)

Adapted from Drummond M et al.[31]

APPENDIX 2. CHECKLIST FOR ASSESSING ECONOMIC EVALUATIONS

This section is adapted from Drummond et al.[32] It should be noted that for some questions in this checklist, the assessor will have to make value judgments. Applying this checklist will therefore not preclude critical appraisal of the study quality by the researcher.

- Is there a well defined question?
- Is there comprehensive description of alternatives?
- Are all important and relevant costs and outcomes for each alternative identified?
- Has clinical effectiveness been established?
- Are costs and outcomes measured accurately?
- Are costs and outcomes valued credibly?
- Are costs and outcomes adjusted for differential timing?
- Is there an incremental analysis of costs and consequences?
- Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?
- How far do study results include all issues of concern to users?
- Are the results generalisable to the setting of interest in the review?

APPENDIX 3. DATA EXTRACTION SHEET FOR ECONOMIC EVALUATIONS

Table 14 – Data extraction sheet for economic evaluations: template

Reference	
Sponsor(s) of the study	
Country, currency, price year	
Research question	
Analytic technique	
Study Design	
Perspective	
Time horizon	
Interventions compared	
Population	
Assumptions	
Data sources for costs	
Data sources for outcomes	
Cost items included	
Outcomes parameter	
Discounting (Yes/No + rate)	
Results:	
Costs	
Outcomes	
Cost-effectiveness	
Sensitivity analysis	
Conclusions	
Remarks	Specify weaknesses of the study

APPENDIX 4. TECHNICAL NOTES

This section presents some technical aspects of the methods that have been mentioned in the guidelines.

Appendix 4.1. Assessment of external validity

This list of issues for external validity has been derived from a paper published by Rothwell.[8]

Appendix 4.1.1. Setting of the trial

- Healthcare system
- Country
- Recruitment from primary, secondary or tertiary care
- Selection of participating centres
- Selection of participating clinicians

Appendix 4.1.2. Selection of patients

- Methods of prerandomisation diagnosis and investigation
- Eligibility criteria
- Exclusion criteria
- Placebo run-in period
- Treatment run-in period
- Enrichment strategies
- Ratio of randomised patients to eligible non-randomised patients in participating centres
- Proportion of patients who declined randomisation

Appendix 4.1.3. Characteristics of randomised patients

- Baseline clinical characteristics
- Racial group
- Uniformity of underlying pathology
- Stage in the natural history of their disease
- Severity of disease
- Comorbidity
- Absolute risks of a poor outcome in the control group

Appendix 4.1.4. Differences between the trial protocol and routine practice

- Trial intervention
- Timing of treatment
- Appropriateness/relevance of control intervention
- Adequacy of non-trial treatment – both intended and actual
- Prohibition of certain non-trial treatments
- Therapeutic or diagnostic advances since trial was done

Appendix 4.1.5. Outcome measures and follow-up

- Clinical relevance of surrogate outcomes
- Clinical relevance, validity and reproducibility of complex scales
- Effect of intervention on most relevant components of composite outcomes
- Who measured outcome
- Use of patient-centred outcomes
- Frequency of follow-up
- Adequacy of the length of follow-up

Appendix 4.1.6. Adverse effects of treatment

- Completeness of reporting of relevant adverse effects
- Rates of discontinuation of treatment
- Selection of trial centres and/or clinicians on the basis of skill or experience
- Exclusion of patients at risk of complications
- Exclusion of patients who experienced adverse effects during a run-in period
- Intensity of trial safety procedures

Appendix 4.2. Outcome valuation

Appendix 4.2.1. Health-related quality of life

Outcomes can be expressed in physical units (life years gained) or in 'utility' terms. The most frequently used utility outcomes are QALYs. For the valuation of the quality weights of life years gained, different methods and instruments can be used. Different possibilities exist for the assessment of health-related quality of life, but not all are useful for economic evaluations. There are disease specific and generic health-related quality-of-life measures, profile measures or single index measures, health-related quality of life can be assessed by patients themselves or by health care providers or family and valuation of a health state can be done by means of a Time-Trade-Off, Standard Gamble or Rating Scale.

Disease-specific quality-of-life measures are useful to get an insight into the domains of life that are affected by a disease or treatment. They are considered to be more sensitive to small changes in health-related quality of life in a specific disease than generic measures. However, from a societal point of view, it is also necessary to include a generic outcome measure in the analysis. Decisions about the reimbursement if an intervention involves budget allocation decisions. Therefore it is useful to be able to compare different budget allocations in terms of the incremental cost per QALY they involve. Only with a generic utility outcome measure, broad comparisons across diseases are possible.

Profile measures are less useful for economic evaluations unless they allow translation into one single utility index that can then serve as a weight for life years gained. However, apart from the EQ-5D, HUI 2/3 and the SF-6D, there are very few profile measures for health-related quality of life that can be translated into such a utility index.

The values for health-related quality of life attached to different health states can be derived from patients, the general public, health care providers or family. Including patients' preferences in the outcome assessment seems the most logical approach. However, some caveats should be kept in mind. If patients are asked to value their health-related quality of life directly on a visual analogue scale and these raw data are directly used for analysis, there will be a problem of comparability and aggregation. The values of one patient are not necessarily comparable to the values of another patient, which makes aggregation and calculation of means, medians and spread of little relevance. For a wide application of the utility data and for reasons of comparability across patient groups, it is important to use public preferences values for health states described by patients (indirect method) (see Appendix 7).

There are three major direct methods for measuring health state preferences: the time trade-off, the standard gamble and the visual analogue scale. Each method has advantages and disadvantages. The time trade-off risks to be biased by time preference of the respondents, the standard gamble by the risk attitude of the respondents and the visual analogue scale by the definition of the endpoints.

In order to ensure that the patient's perspective is represented, it is crucial that the health states are first described by the patients, using a generic descriptive system for health-related quality of life (e.g. the EQ-5D, the SF-6D). The utilities corresponding to these descriptions should be derived from preferences for health states expressed by the general public.

Appendix 4.3. Use of expert panels

Use of expert panels should be avoided as much as possible. Sometimes, however, insufficient empirical data are available to estimate variables needed for the economic evaluation. This relates specifically to resource use. Expert panels can help to predict which resources will be used and how often each will be used to manage outcomes reported but not followed-up in clinical trials.

If expert opinion is used in a submission, the need for expert opinion should be justified. The methods used to obtain and collate the opinions should be described in detail. The following elements should be addressed:

- the criteria for selecting the experts,
- the number of experts approached,
- the number and identity of experts who participated,
- whether a declaration of potential conflict(s) of interest was sought from all experts or medical specialty groups whose opinions were sought,
- whether the participants were blinded to the purpose of the study,
- whether the experts were remunerated for their participation and how,
- the background information provided and its consistency with the totality of the evidence provided in the submission,
- the detailed method that was followed to collect the opinions,
- the medium used to collect the opinions (direct interview, telephone interview or self-administered questionnaire…),
- the questions asked (with a copy of the questionnaire or an outline of the interview),
- whether iteration was used in the collation of opinions and, if so, how it was used,
- the number of responses received for each question,
- whether all experts agreed with each response, and, if not:
    - the approach used to finalize the estimates. For example, a Delphi technique could be applied; or the majority opinion, the median, or the mean could be presented,
    - the approach used to present the variability in the opinions (range, variance).

It may be useful to ask each expert to explain the reasoning behind the expert opinion offered.

The expert opinions should be summarised and the variability in opinions presented. It should be clearly indicated how the opinions have been used in the economic evaluation and how is dealt with the uncertainty around the expert opinions.

Appendix 4.4. Hospital per diem prices

The financing of non-medical hospital activities (i.e. capital expenditures for housing and medico-technical facilities, hotel function, nursing care, etc.) is based on the reforms introduced in 2002. Since 2002, Belgian hospitals receive an annual budget (so called “budget of financial means”) which covers their activities for the period July to June the 30th of the next year. The budget is adapted on January, it is computed by the FPS public health and its amount is different for each hospital. The budget is composed of three major parts (A-Capital costs, B-Operational costs and C-Corrective measures), which are further divided into subparts. The share of each (sub-)part in the total budget is given in parentheses in the table below.

Table 15 – Components of the hospital budget of financial means

Categories		Description
A (8%)	A1	Investment charges
	A2	Short-term credit burdens
	A3	Investment charges for some medico-technical services which are exclusively financed via the hospital budget (not via fees)
B (>90%)	B1	Common operational costs (administration, maintenance, laundry) (30%)
	B2	Clinical costs (personnel and medical equipment) (40–50%)
	B3	Medico-technical departments (radiotherapy, MRI and PET scans) (1%)
	B4	Some specific (mostly) lump sum costs (as a result of legal obligations), e.g. hospital hygiene, quality assessment, palliative care and recording of hospital data
	B5	Pharmacy costs (2%)
	B6	Costs for carrying out the social agreements for personnel not included in the budget of financial means (2%)
	B7	Extra costs for teaching hospitals or university function of the hospital (applied scientific research, the development of new technologies and the training of specialists) (3%)
	B8	Specific costs for patients with a weaker socioeconomic profile or social function of the hospital (0.5%)
	B9	Extra-legal financial benefits
C		Corrective measures

How is this budget paid to the hospitals? The payment of the budget of financial means to a hospital contains two parts: a fixed part and a variable part. The *fixed part* is paid by the sickness funds on the basis of monthly advances (the so-called provisional twelfths). This part includes (theoretically) 80% of subparts B1 and B2, and 100% of all other parts. The *variable part*, including 20% of subparts B1 and B2, is paid, via an invoice, according to the number of admissions (10% of the budget) and the number of nursing days (10% of the budget) for the general hospitals, and exclusively according to the number of days (20% of the budget) for the other hospitals. The invoice is submitted by the hospitals to the sickness funds for all patients enrolled in a sickness fund.[dd] Specific RIZIV–INAMI tariff codes (from the nomenclatuur–nomenclature) have been created to this effect). The amounts per admission and per nursing day are hospital-specific and also depend on the type of hospital stay (e.g. acute, burned, elderly, psychiatric, palliative and chronic disease care). They are adapted twice a year.

Note that these codes are the only ones recorded in the MFG–RFM administrative database. It is therefore not suitable to use this database for economic evaluations since it only records the variable part (i.e. 20%) of the hospital stay costs while the fixed part (80%) of this budget is not recorded in this database.

The amounts per admission and per nursing day are published as excel files on the RIZIV–INAMI website, together with the 100% per diem prices (in which admission and nursing day amounts are imputed).[ee] The per diem prices are reported per hospital and per type of hospital stay.

dd For patients not enrolled in a sickness fund, the invoice (with the full day-price covering categories A, B and C) is sent to the paying authorities (i.e. OCMW/CPAS, a private health insurance or a work accident insurance).

ee http://www.riziv.fgov.be/care/fr/hospitals/specific-information/prices-day/index.htm

Based on this list of 100% prices, it could be tempting then to compute a *mathematical* average across all hospitals to derive Belgian average per diem prices per type of hospital stay. This method however does not account for the volume effect of each hospital such that big hospitals with higher hospitalization days and per diem prices have the same weight as smaller hospitals with lower per diem prices. The simple mathematical average of the 100% per diem should therefore not be used.

Rather the *weighted* average 100% per diem price that accounts for disparities in the case-mix (different levels of activities) of the hospitals should be used. These weighted averages are to be found in section 5.7.3.5 of these guidelines.

Appendix 4.5. Indirect comparisons

- Results from direct comparisons in RCTs are the preferred method to estimate treatment effects. If no direct comparisons are available, indirect comparisons from RCTs can be performed.
- Results from the naïve approach, i.e. comparing simply the treatment arm of the RCTs as if they were one single trial, are completely untrustworthy.
- Indirect comparisons should be based on "adjusted" methods, which use the common control arm of RCTs as a way to "standardize" the comparison. Different methods of increasing complexity are available.

The randomized controlled trial (RCT) is the most valid design for evaluating the relative efficacy of competing treatments. However, in many cases, there is no trial available comparing directly the treatments, interventions or technologies of interest. A common example is within a class of several drugs (A and B), each of which has been studied in placebo-controlled RCT (often needed to get approval of the drug), but there are very few trials in which the drugs have been compared directly with each other. Another example is within the setting of an active-controlled trial, where the purpose is to demonstrate that a new treatment (A) is equivalent (not better nor worse by a certain amount) to a standard treatment (C), which itself has previously been shown to be superior to a placebo. The active-controlled trial comparing A versus C implicitly assumes, based on an indirect comparison, that the new treatment A is better than a placebo (i.e. is effective).

Although indirect comparison can arise in different contexts and can have different purposes, the statistical options are the same whichever scenario applies. The simplest case is when results of 2 RCTs are available, RCT 1 comparing treatment B with treatment A (B vs. A) and RCT 2 comparing treatment C versus treatment A (C vs. A), and the purpose is to compare B and C (B vs. C), indirectly. Different statistical methods have recently been proposed for this purpose, and there is still a lot of research performed on this topic. Glenny et al.[16] have done an excellent overview of the literature, with some additional research to compare the different methods. A summary of their findings follows, focusing on the main methods.

Method 1: The naïve method (Unadjusted Comparison). In the naïve method, results from treatment arms are simply compared between each other as if they would come from a single trial (so the results in the treatment B arm are directly compared to the results in the treatment C arm), ignoring the fact that studies are RCTs and discarding information from control arms (A arm). Based on theoretical and empirical evidence, Glenny et al conclude that "the results of such analysis are completely untrustworthy, and naïve comparisons should never be made".

The other methods are called "adjusted", in the sense that the indirect comparison is adjusted by the results of their direct common control group within each RCT (treatment A), which is used as a way to "standardize" the results of the treatment arms.

Method 2: Adjusted Indirect Comparison. This method has been discussed by Bucher et al,[13] for the case of binary data, but it can be generalized to any kind of data (continuous, time to event..). First, from the 2 RCTs, estimates for treatment effects and their standard error are known. These treatment effects relate to the scale on which the data would be analyzed: means for continuous data, log odds ratio for binary data, log hazard ratio for time to event data… The effect B vs. C is then estimated by the difference between the effects observed in the 2 trials, and the variances are summed.

Other methods of increasing complexity exist (meta-regression methods, generalized linear model, Bayesian methods) and are described in the HTA review.[16]

Main Assumptions. The key assumption of the indirect comparison using the results of trials A vs. B and A vs. C is that there should be no important difference between the 2 sets of trials with respect to aspects that could influence (bias) the estimated treatment effect of B vs. C. In other words, there must be no confounding of the comparison by some trial characteristics. Example of confounding is that when the treatment effect is influenced by some factors that itself varies across the different treatment comparisons, such as clinical setting or length of follow up. This situation has been illustrated graphically by Baker et al.[33]

APPENDIX 5. THE COST-EFFECTIVENESS PLANE, COST-EFFECTIVENESS ACCEPTABILITY CURVE, AND EFFICIENCY FRONTIER

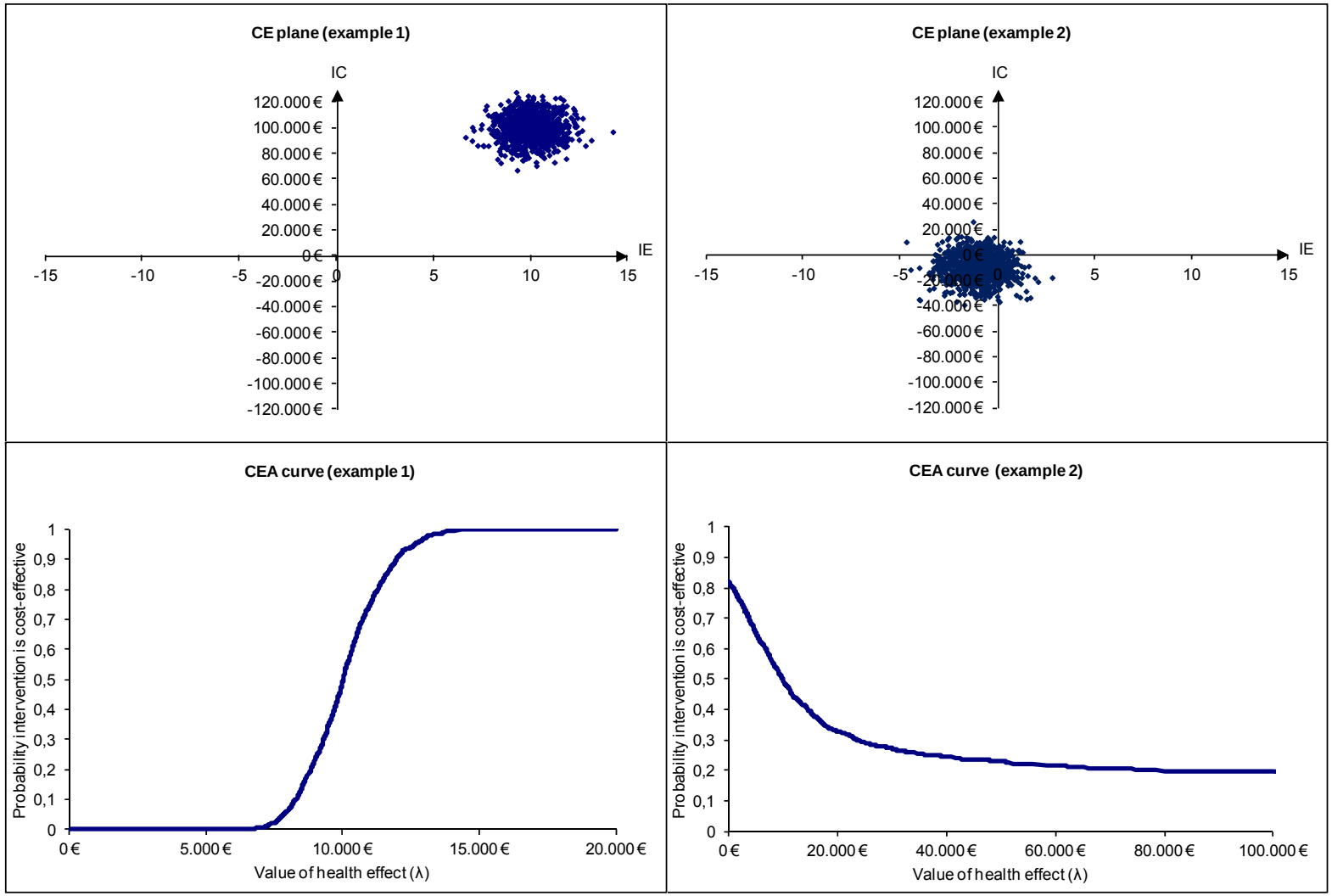
The *cost-effectiveness plane* is used to present the results of a cost-effectiveness or cost-utility analysis. Incremental effects (life-years or quality-adjusted life years (QALYs)) are presented on the x-axis. The y-axis shows the incremental costs. The centre of the figure shows the comparator. As such, there are four quadrants comparing the intervention with the comparator:

1. The intervention is more effective and more costly,
2. The intervention is more effective and less costly,
3. The intervention is less effective and less costly, and
4. The intervention is less effective and more costly than the comparator.

Interventions is the 2nd quadrant dominate the comparator, while those in the 4th quadrant are being dominated by the comparator.

The *cost-effectiveness acceptability (CEA-)curve* presents the probability that a given intervention is considered cost-effective on the basis of the value assigned to an additional life year or QALY. The shape of this curve depends on the location and proportion of incremental costs and effects over the four quadrants of the cost-effectiveness plane. In Figure 2, two examples are shown. For more information we refer to Fenwick et al.[34]

Figure 2 – The cost-effectiveness plane and cost-effectiveness acceptability curve

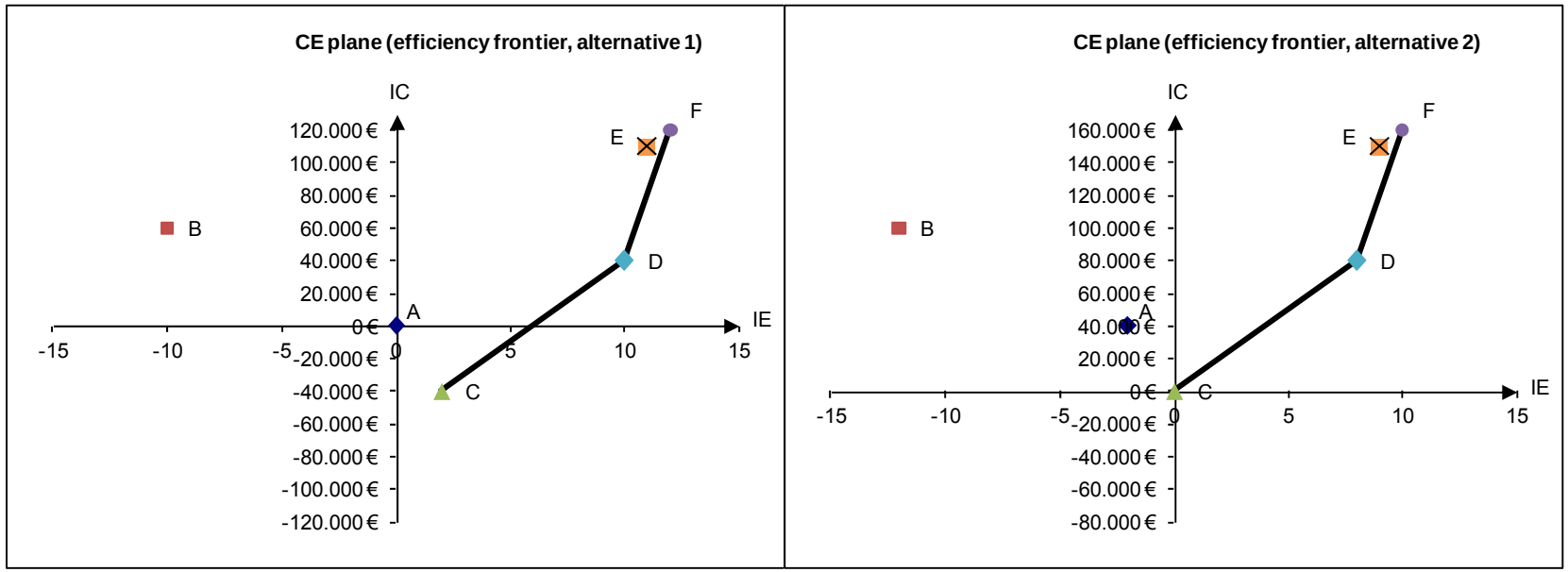


CE: cost-effectiveness; IC: incremental cost; IE: incremental effect

The *efficiency frontier* is the curve on the cost-effectiveness plane formed by the incremental cost-effectiveness or cost-utility ratios of the non-dominated comparators.

Figure 3 provides an example. In this example, interventions A, B, C, D, E and F are all alternative interventions for a specific population with a certain disease. Intervention B (quadrant IV) is dominated by intervention A. Intervention A is dominated by C (quadrant II). Therefore, C becomes a justified comparator for intervention D. E is excluded due to extended dominance, i.e. there is a linear combination of other strategies (D and F) that can produce the same (or greater) benefit at lower (or the same) cost. As such, the comparator of intervention F becomes alternative D. Working on the efficiency frontier can have a large impact on results, conclusions and policy recommendations.[10] In this deterministic example, F would have an ICER of €10 000 per QALY if compared with (the non-efficient) alternative A. However, taking into account alternative D, this becomes €40 000 per QALY.

Figure 3 – The efficiency frontier



CE: cost-effectiveness; IC: incremental cost; IE: incremental effect.
Alternative 1 and 2 present the same interventions and ICERs. The only difference is that in alternative 2, the first non-dominated intervention is put in the centre of the cost-effectiveness plane

APPENDIX 6. LIST OF BELGIAN DATABASES FOR THE MEASUREMENT AND VALUATION OF RESOURCE USE

Table 16 – Belgian databases for the measurement and valuation of resource use

Owner	Database and Information collected	Start	Access
FEDERAL LEVEL			
Cellule Technique pour la gestion des données RCM-RFM Technische cel voor het beheer van de MKG-MFG data	Aggregated data (coupled MKG and MFG data). Classification according to the ICD9-CM and INAMI–RIZIV nomenclature codes: • Mean length of hospital stay per APR-DRG / Severity of illness • Distributional parameters per APR-DRG / Severity of illness • Average cost per hospital stay per APR-DRG / Severity of illness	1996	https://tct.fgov.be/etct/index.html Public access NB: Costs from the TCT do not account for the extrapolation in lump sums for hospital drugs, medical imaging and laboratory testing. They may nonetheless be used as such.
Bases de données Agence Intermutualiste (AIM) Databanken Intermutualistisch Agentschap (IMA–AIM)	Individual data on health care consumption and reimbursement (health insurance and patients' share) for al insured patients. Both ambulatory and hospitalized patients.	2002	http://www.nic-ima.be/ No public access
INAMI–RIZIV	Unit prices / costs for ambulatory and hospital health care services Search engine 'NomenSoft', available at:	-	http://www.riziv.be/care/fr/nomenclature/index.htm https://www.riziv.fgov.be/webprd/appl/pnomen/Search.aspx?lg=N
INAMI–RIZIV	Unit prices for reimbursed drugs (reimbursement basis and the patients' share including any supplement due to the reference pricing system).	-	http://www.riziv.fgov.be/drug/fr/index.htm
INAMI–RIZIV	Farmanet–Pharmanet: consumption of reimbursed drugs delivered to non-hospitalised patients	2004	No public access
INAMI–RIZIV	Prices (reimbursement basis and patients' share) of reimbursed implants and invasive medical devices	-	https://www.riziv.fgov.be/insurer/fr/rate/index.htm (Articles 28, 35 and 35bis of the RIZIV–INAMI nomenclature)

Owner	Database and Information collected	Start	Access
INAMI–RIZIV	Per diem prices for Belgian hospitals: per hospital and per type of hospital stay (acute, burns, geriatrics, palliative, psychiatric and specialized stays). Remark: the weighted averages are reported in this guideline.	-	http://www.riziv.fgov.be/care/nl/hospitals/specific-information/prices-day/index.htm
INAMI–RIZIV	List of pharmaceuticals excluded from the hospital lump sum and reimbursed by a retrospective fee-for-service system.	-	http://www.riziv.fgov.be/care/fr/hospitals/specific-information/forfaitarisation/index.htm
INAMI–RIZIV	Fee-for-service charges per laboratory test (25% and 100% of the honorarium fee). Laboratory tests lump sums per inpatient day and per hospital. Laboratory tests lump sums per admission.	-	https://www.riziv.fgov.be/insurer/fr/rate/index.htm http://www.inami.fgov.be/care/fr/hospitals/specific-information/pseudo/index.htm https://www.riziv.fgov.be/insurer/fr/rate/index.htm
INAMI–RIZIV	Fee-for-service charges per medical imaging act consultancy lump sums. Medical imaging act lump sum per admission	-	http://www.inami.fgov.be/insurer/fr/rate/index.htm http://www.inami.fgov.be/care/fr/hospitals/specific-information/pseudo/index.htm
BCFI–CBIP	Unit prices for reimbursed and non-reimbursed (e.g. over the counter) drugs	-	http://www.cbip.be/ Public access
SPF Santé publique FOD Volksgezondheid	RCM–MKG: Health care consumption (INAMI–RIZIV nomenclature codes) per general hospital stay. Classification according to the ICD-9-CM codes,	1995	No public access
	RIM–MVG: Nursing care consumption per general (non psychiatric) hospital stay	1988	No public access
	RPM–MPG: Health care consumption per psychiatric hospital stay. Classification according to the DSM IV and ICD-9-CM codes	1996	No public access
ISP–WIV	Sentinel general practitioners: Health care consumption in ambulant sector	1979	https://www.wiv-isp.be/ Public access

Owner	Database and Information collected	Start	Access
COMMUNITY LEVEL			
Registre du cancer Kanker register	Aggregated data on specialized health care consumption for hospitalized cancer patients. Coverage: Flanders	1997	http://www.kankerregister.org/ Public access
Kind & Gezin	IKAROS (geIntegreerd Kind Activiteiten Regio OndersteuningsSysteem): Health care consumption (ambulant and hospitalized) for children up to 3 years. Coverage: Flanders	1999	http://www.kindengezin.be Public access
ONE	BDMS (Banque de données medico-sociales): Health care consumption (ambulant and hospitalized) for children up to 3 years and for pregnant women. Coverage: Wallonia	1994	http://www.one.be/index.php?id=banque-de-donnees-medico-sociale Public access
Department of general practice, KU Leuven	INTEGO (Integrated computerized network). Health care consumption in first line treatment (GPs) and ambulant care. Coverage: Flanders	1994	http://www.intego.be/

Note: a thorough description of most of the databases presented here can be found in Van de Sande et al.35

APPENDIX 7. FLEMISH EQ-5D INDEX VALUES

Table 17 – Flemish EQ-5D index values

State	Score	State	Score	State	Score	State	Score	State	Score	State	Score	State	Score	State	Score	State	Score
11111	1.0000	**12113**	0.3020	**13122**	0.2391	**21131**	0.3497	**22133**	0.0602	**23222**	0.1339	**31231**	0.2444	**32231**	0.1618	**33233**	-0.1277
11112	0.7444	**12121**	0.6815	**13123**	0.1357	**21132**	0.2463	**22211**	0.6599	**23223**	0.0305	**31232**	0.1410	**32232**	0.0584	**33311**	0.2157
11113	0.3847	**12122**	0.5781	**13131**	0.2588	**21133**	0.1429	**22212**	0.5565	**23231**	0.1536	**31233**	0.0376	**32233**	-0.0450	**33312**	0.1123
11121	0.7641	**12123**	0.2184	**13132**	0.1554	**21211**	0.7426	**22213**	0.1968	**23232**	0.0502	**31311**	0.3810	**32311**	0.2984	**33313**	0.0089
11122	0.6607	**12131**	0.3415	**13133**	0.0520	**21212**	0.6392	**22221**	0.5762	**23233**	-0.0532	**31312**	0.2776	**32312**	0.1950	**33321**	0.1320
11123	0.3010	**12132**	0.2381	**13211**	0.3954	**21213**	0.2795	**22222**	0.4728	**23311**	0.2902	**31313**	0.1742	**32313**	0.0916	**33322**	0.0286
11131	0.4241	**12133**	0.1347	**13212**	0.2920	**21221**	0.6589	**22223**	0.1131	**23312**	0.1868	**31321**	0.2974	**32321**	0.2147	**33323**	-0.0748
11132	0.3207	**12211**	0.7344	**13213**	0.1886	**21222**	0.5555	**22231**	0.2362	**23313**	0.0834	**31322**	0.1940	**32322**	0.1113	**33331**	0.0484
11133	0.2173	**12212**	0.6310	**13221**	0.3117	**21223**	0.1958	**22232**	0.1328	**23321**	0.2065	**31323**	0.0906	**32323**	0.0079	**33332**	-0.0550
11211	0.8170	**12213**	0.2713	**13222**	0.2083	**21231**	0.3189	**22233**	0.0294	**23322**	0.1031	**31331**	0.2137	**32331**	0.1310	**33333**	-0.1584
11212	0.7136	**12221**	0.6507	**13223**	0.1049	**21232**	0.2155	**22311**	0.3728	**23323**	-0.0003	**31332**	0.1103	**32332**	0.0276	**Dead**	0
11213	0.3539	**12222**	0.5473	**13231**	0.2280	**21233**	0.1121	**22312**	0.2694	**23331**	0.1228	**31333**	0.0069	**32333**	-0.0758	**Unconscious**	-0.0163
11221	0.7333	**12223**	0.1876	**13232**	0.1246	**21311**	0.4555	**22313**	0.1660	**23332**	0.0194	**32111**	0.3599	**33111**	0.2773		
11222	0.6299	**12231**	0.3108	**13233**	0.0212	**21312**	0.3521	**22321**	0.2892	**23333**	-0.0840	**32112**	0.2565	**33112**	0.1739		
11223	0.2702	**12232**	0.2073	**13311**	0.3646	**21313**	0.2487	**22322**	0.1858	**31111**	0.4426	**32112**	0.2565	**33113**	0.0705		
11231	0.3934	**12233**	0.1039	**13312**	0.2612	**21321**	0.3718	**22323**	0.0824	**31112**	0.3392	**32113**	0.1531	**33121**	0.1936		
11232	0.2900	**12311**	0.4473	**13313**	0.1578	**21322**	0.2684	**22331**	0.2055	**31113**	0.2358	**32121**	0.2762	**33122**	0.0902		
11233	0.1866	**12312**	0.3439	**13321**	0.2810	**21323**	0.1650	**22332**	0.1021	**31121**	0.3589	**32121**	0.2762	**33123**	-0.0132		
11311	0.5300	**12313**	0.2405	**13322**	0.1776	**21331**	0.2881	**22333**	-0.0013	**31122**	0.2555	**32122**	0.1728	**33131**	0.1099		
11312	0.4266	**12321**	0.3636	**13323**	0.0742	**21332**	0.1847	**23111**	0.3517	**31123**	0.1521	**32123**	0.0694	**33132**	0.0065		
11313	0.3232	**12322**	0.2602	**13331**	0.1973	**21333**	0.0813	**23122**	0.1646	**31131**	0.2752	**32131**	0.1926	**33133**	-0.0969		
11321	0.4463	**12323**	0.1568	**13332**	0.0939	**22111**	0.6907	**23123**	0.0612	**31132**	0.1718	**32132**	0.0892	**33211**	0.2465		
11322	0.3429	**12331**	0.2799	**13333**	-0.0095	**22112**	0.5873	**23131**	0.1844	**31133**	0.0684	**32133**	-0.0142	**33212**	0.1431		
11323	0.2395	**12332**	0.1765	**21111**	0.7733	**22113**	0.2276	**23132**	0.0810	**31211**	0.4118	**32211**	0.3291	**33213**	0.0397		
11331	0.3626	**12333**	0.0731	**21112**	0.6699	**22121**	0.6070	**23133**	-0.0224	**31212**	0.3084	**32212**	0.2257	**33221**	0.1628		
11332	0.2592	**13111**	0.4262	**21113**	0.3102	**22122**	0.5036	**23211**	0.3209	**31213**	0.2050	**32213**	0.1223	**33222**	0.0594		
11333	0.1558	**13112**	0.3228	**21121**	0.6897	**22123**	0.1439	**23212**	0.2175	**31221**	0.3281	**32221**	0.2455	**33223**	-0.0440		
12111	0.7651	**13113**	0.2194	**21122**	0.5863	**22131**	0.2670	**23213**	0.1141	**31222**	0.2247	**32222**	0.1421	**33231**	0.0791	Source: Cleemput et al. 2010.[36]	
12112	0.6617	**13121**	0.3425	**21123**	0.2266	**22132**	0.1636	**23221**	0.2373	**31223**	0.1213	**32223**	0.0387	**33232**	-0.0243		

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