Belgian Methodological Guidelines for Pharmacoeconomic Evaluations: Toward Standardization of Drug Reimbursement Requests

Irina Cleemput, PhD, Philippe van Wilder, Pharm, MSc, Michel Huybrechts, MD, France Vrijens, MSc
Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium

ABSTRACT

Objective: To develop methodological guidelines for pharmacoeconomic evaluation (PE) submitted to the Belgian Drug Reimbursement Committee as part of a drug reimbursement request.

Methods: In 2006, preliminary pharmacoeconomic guidelines were developed by a multidisciplinary research team. Their feasibility was tested and discussed with all stakeholders. The guidelines were adapted and finalized in 2008.

Results: The literature review should be transparent and reproducible. PE should be performed from the perspective of the health-care payer, including the governmental payer and the patient. The target population should reflect the population identified for routine use. The comparator to be considered in the evaluation is the treatment most likely to be replaced. Cost-effectiveness and cost-utility analyses are accepted as reference case techniques, under specific conditions. A final end point—as opposed to a surrogate end point—should be used in the incremental cost-effectiveness ratio (ICER). For the calculation of quality-adjusted life-years (QALYs), a generic quality-of-life measure should be used. PE should in principle apply a lifetime horizon. Application of shorter time horizons requires appropriate justification. Uncertainty around the ICER should always be assessed. Costs and outcomes should be discounted at 3% and 1.5%, respectively.

Conclusion: The current guidelines are the result of a constructive collaboration between the Belgian Health Care Knowledge Centre, the National Institute for Health and Disability Insurance and the pharmaceutical industry. A point of special attention is the accessibility of existing Belgian resource use data for PE. As PE should serve Belgian health-care policy, they should preferably be based on the best available data.

Keywords: guidelines, health policy, pharmacoeconomic evaluation, reimbursement.

Introduction

Pharmaceutical products are reimbursed in Belgium on the basis of their therapeutic value, and are categorized into three classes accordingly. Class 1 drugs have a therapeutic added value compared to existing therapeutic alternatives; class 2 drugs have a comparable therapeutic value; and class 3 drugs are mainly generics. Since 2002, a request for reimbursement of a pharmaceutical product of Class 1 by a pharmaceutical company has to be accompanied by a pharmacoeconomic evaluation (PE). These reimbursement requests are evaluated by the Drug Reimbursement Committee (CTG/CRM), a division of the National Institute for Health and Disability Insurance (NIHDI). The decision to list and reimburse the level of reimbursement of a Class 1 drug is based on five criteria, as detailed in the Royal Decree [1]:

1. the therapeutic value, taking into account the efficacy, effectiveness, side effects, applicability and user-friendliness of the product;
2. the market price of the drug and the requested reimbursement price;
3. the clinical effectiveness and likely impact of the product, taking into account therapeutic and social needs;
4. the budget impact for the National Health Insurance; and
5. the cost-effectiveness of the product from the perspective of the National Health Insurance.

The definition of therapeutic value used in the Royal Decree is broader 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. 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 [2].

Based on an evaluation 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 appropriateness of reimbursement, the reimbursement rate, the conditions for reimbursement and the class of the product.

The evaluation of the pharmacoeconomic analyses has been hampered by the absence of formal guidelines for conducting and reporting PE. A pilot assessment of 10 submitted files for reimbursement requests revealed a large variability in methodological quality and reporting formats, which leads to more time consuming evaluation processes. The 10 files related to 10 different Class 1 products for which the reimbursement request was submitted between 2002 and 2004. The aim of the assessment was exploratory. The focus was on identifying the perceived methodological problems in the submissions and in the assessments made. Problem items appearing during the assessment were noted in sequential order for each submission. Methodological aspects were reviewed and classified according to the QHES instrument [3], while for statistical problems free text notes were taken of the type of problems encountered. No scoring system of the submissions was performed as the
research was exploratory in nature, aiming to identify the strengths and weaknesses of the submissions rather than to score the submissions. For the 10 reviewed pharmacoeconomic studies, the major areas of concern were, in decreasing order of occurrence:

1. methods and definitions of costs and cost measurement;
2. description of model validation, reliability and limitations, and presentation of the model;
3. comparator choice;
4. definition and estimation of clinical effectiveness or efficacy; and
5. general shortcomings in uncertainty and sensitivity analysis.

These findings underscored the need for clear guidelines on PE.

Objectives

The objective of this study was to develop methodological and reporting guidelines for PE submitted to the Drug Reimbursement Committee as part of a drug reimbursement request in Belgium. The guidelines aim to increase the methodological quality, transparency, and uniformity of the pharmacoeconomic submissions. This will help to increase consistency across the reimbursement files, both in the file submitted by applicants and in the evaluation reports made by the Drug Reimbursement Committee.

Methods

Existing guidelines from other countries were reviewed (Dutch [4], French [5], Australian [6], and British [7] guidelines). Only guidelines issued or updated after July 2003 were considered because the field of pharmacoeconomics is continually evolving and regular updates are necessary. For most methodological aspects, different approaches exist. To improve consistency in the files, a “reference case” was presented, including the essential elements for each PE together with the most appropriate methodology given the objectives of the reimbursement committee, i.e., maximizing health gain within resource constraints. Additional analyses using other approaches were allowed, but had to be distinguished from the reference case analysis and justified.

The development of the guidelines was done in two phases. Phase one consisted of the development of a set of draft guidelines. These provisional guidelines were developed by the Belgian Health Care Knowledge Centre (KCE) in collaboration with the NIHDI. The formal procedures for KCE studies were followed. A group of external experts was invited to review draft documents on a regular basis and give feedback during formal meetings. In case no consensus was found on specific issues, the principal investigators from KCE/NHIDI (authors of this paper) took the final decision. Therefore, the guidelines do not necessarily reflect the personal opinions of the external experts. The final document was validated by three external validators that had not been involved in the previous review process. They assessed the scientific validity of the guidelines and were not allowed to impose changes that purely reflected a personal opinion. The external expert and validators group consisted of eight health economists from Belgium and abroad, two pharmacists, one medical doctor with training in health economics, and one statistician. Phase two consisted of a practical implementation of these guidelines during a 12-month period to test the guideline’s feasibility. Participation in the pilot test was voluntary. One company submitted an adaptation according to the draft guidelines of an earlier submitted PE of a product for which the reimbursement decision was already taken. This approach was used to strictly separate the evaluation 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 [8]. The companies’ comments were sometimes a request for clarification, sometimes punctual and sometimes critical. One of the major concerns expressed by the pharmaceutical companies is the lack of access to specific data that are nevertheless available at the governmental level. This concern could not be solved within the pharmacoeconomic guidelines but the message was nevertheless transferred to the Belgian policymakers. When the companies considered the interpretation of a guideline in a specific situation unclear, the guideline was adapted to improve clarity and general applicability of the guidelines. Concerns about legal issues, such as ownership of data, or potential misuse of transferred data or models were solved through discussion between the CTG/CRM and the companies.

Pharmacoeconomic Guidelines

The reference case defines the elements of a PE and the recommended methodology for each component (Table 1).

Guideline 1: Literature review

A thorough and systematic literature review of clinical effectiveness and cost-effectiveness of the product is the starting point of the PE, as its value crucially depends on the value of the evidence it is based upon. This should be the best available up-to-date evidence on the intervention and the comparator. Besides published literature, an overview of ongoing studies should be provided. Off-label medical treatments are not acceptable as comparators in the formal economic evaluation because reimbursement is legally limited to the official indication in the Summary of Product Characteristics (SPC). Nevertheless, the evidence on their (cost-)effectiveness can be described in the literature review. This increases transparency of the dossier, and for the Drug Reimbursement Committee, the existence and current use of an off-label used product can sometimes be a consideration in the advice to the minister.

The basic principle of the literature search is transparency in selection criteria and reproducibility of the search. The best available up-to-date evidence can be found after the methodology of systematic literature reviews, e.g., according to the guidelines of the Centre for Reviews and Dissemination [9].

The review should start with identification of the review questions. This includes specification of the population, the intervention, the comparator, the outcomes, and the study designs selected. 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.

Databases searched should include at least MEDLINE, Embase, the Cochrane Controlled Trials Register, the Cochrane Database of Systematic reviews and the National Health Service Centre for Reviews and Dissemination (NHS CRD) review databases. The report of the literature review should include the search strategy for each database, the study selection criteria, selection procedures and results of the selection, the quality assessment tools [10–13] and quality assessment results, and the data extraction sheets. A synthesis of the evidence should be provided.
Study design • Pharmacoeconomic evaluations should always be based to some extent on data from RCTs or noninterventional studies comparing effectiveness of the product and its cost-effectiveness relative to its comparator(s), ongoing studies should be mentioned

Perspective of the evaluation Only direct health-care costs from the perspective of the health-care payer; this includes payments out of the government’s health-care budget as well as patients’ copayments

Target population • Health outcomes measured in patients and valued from a societal perspective

Comparator • Consistent with the patient population defined in registration documents

Analytic technique • Cost-effectiveness analysis if improving life expectancy is the main objective of the treatment and the most important outcome

Calculation of costs The identification, measurement and valuation of costs should be consistent with the perspective of the Belgian health-care payer.

Time horizon Chronic diseases and acute diseases with long-term sequelae: shorter time horizon with appropriate justification

Modeling • Applied if available data are insufficient to allow a full assessment of the cost-effectiveness or cost–utility of a product

Handling uncertainty • Uncertainty around cost-effectiveness/cost–utility estimates should always be analyzed

Discount rate • Costs at 3%

### Table I Reference case methods

<table>
<thead>
<tr>
<th>Component of PE evaluation</th>
<th>Reference case</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature review</td>
<td>• Description of the disease and the interventions studied</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>• Systematic review of the existing clinical and economic studies on the intervention: best available up-to-date evidence for clinical effectiveness of the product and its cost-effectiveness relative to its comparator(s), ongoing studies should be mentioned</td>
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<tr>
<td></td>
<td>• Reproducible search strategy</td>
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<td></td>
<td>• Transparent selection criteria and selection procedures</td>
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<td></td>
<td>• Critical appraisal of the evidence</td>
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<td></td>
<td>• Quality assessment of the evidence</td>
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<tr>
<td></td>
<td>• Data extraction sheets</td>
<td></td>
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<tr>
<td></td>
<td>• Clear and concise synthesis, substantiated with references</td>
<td></td>
</tr>
<tr>
<td>Perspective of the evaluation</td>
<td>• Only direct health-care costs from the perspective of the health-care payer; this includes payments out of the government’s health-care budget as well as patients’ copayments</td>
<td>2</td>
</tr>
<tr>
<td>Target population</td>
<td>• Health outcomes measured in patients and valued from a societal perspective</td>
<td></td>
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<tr>
<td>Comparator</td>
<td>• Consistent with the patient population defined in registration documents</td>
<td>3</td>
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<tr>
<td></td>
<td>• Subgroup analyses if appropriate (statistical) justification for subgroup analysis is provided</td>
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<td></td>
<td>• Post hoc subgroup analyses only if costs between the subgroups are proven to be different based on appropriate statistical analyses. (relative effectiveness must be assumed equal across subgroups in this case);</td>
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<td></td>
<td>• Epidemiological data for Belgium presented for the entire target population and relevant subgroups.</td>
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<td></td>
<td>• Comparison with either the treatment that is most likely to be replaced by the new treatment or, in case of add-on treatments, the current treatment without the add-on product</td>
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<tr>
<td></td>
<td>• If most appropriate comparator unknown: recommended treatment according to the Belgian clinical guidelines</td>
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<tr>
<td></td>
<td>• Multiple comparators possible</td>
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<td></td>
<td>• Medical and/or nonmedical treatment(s)</td>
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<td></td>
<td>• No comparison with off-label used products in reference case analysis</td>
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<td></td>
<td>• Justification of the choice of the comparator(s)</td>
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<td></td>
<td>• Indirect comparisons only allowed under specific conditions</td>
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<tr>
<td>Analytic technique</td>
<td>• Cost-effectiveness analysis if improving life expectancy is the main objective of the treatment and the most important outcome from the patient point of view or if there is a clearly identified dominant clinical outcome parameter that is relevant to the patient (e.g., avoiding complications) and there are no other patient-relevant outcome parameters (e.g., side effects) expressed in different units</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>• Cost–utility analysis 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</td>
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<tr>
<td></td>
<td>• Cost–benefit analyses are not accepted as a reference case</td>
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<td></td>
<td>• Results expressed as incremental cost-effectiveness or cost–utility ratios with their associated distribution</td>
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<td></td>
<td>• If a cost–utility ratio presented as reference case result, corresponding cost per life-year gained should also be presented</td>
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<tr>
<td>Study design</td>
<td>• Pharmacoeconomic evaluations should always be based to some extent on data from RCTs or noninterventional studies comparing the study product and a relevant comparator</td>
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<td></td>
<td>• Economic evaluations based on active control studies are preferred</td>
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<td></td>
<td>• If modeling 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</td>
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<tr>
<td>Calculation of costs</td>
<td>• The identification, measurement and valuation of costs should be consistent with the perspective of the Belgian health-care payer.</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>• Non–health-care costs or unrelated health-care costs should not be included in the reference case analysis. Validated sources should be used for the unit costs.</td>
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<td></td>
<td>• In the absence of market prices for specific resources, standardised proxies for unit costs can be used, unless the intervention is expected to have a high impact on the value of the proxy. Data from private databases can be used provided that these databases comply with legal requirements related to privacy issues.</td>
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<td></td>
<td>• Where generic pharmaceutical products exist, the reference price for these products should be used in the pharmacoeconomic evaluation, even if the generics are not frequently used in Belgium.</td>
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<td></td>
<td>• For copayments, the general rule is to use the copayments paid by regularly insured patients falling outside any of the specific categories that benefit from increased reimbursement. Deviations from this rule should be justified.</td>
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<tr>
<td>Valuation of outcomes</td>
<td>• Final end points, preferably clearly defined outcome measures, for which there is little debate about the measurement methods</td>
<td>8</td>
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<tr>
<td></td>
<td>• Cost–effectiveness analyses: life years gained for chronic conditions and acute conditions with long term sequelae or a relevant short term outcome for acute conditions with no long term consequences</td>
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<tr>
<td></td>
<td>• Cost–utility analyses: QALYs gained</td>
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<td></td>
<td>• Life expectancy estimates based on Belgian age-specific life tables</td>
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<td></td>
<td>• Health-related quality of life weights based on empirical data, obtained with a descriptive system for health status for which corresponding preference values exist from the general public.</td>
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<tr>
<td></td>
<td>• Quality of life weights derived with generic instrument</td>
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<tr>
<td>Time horizon</td>
<td>Chronic diseases and acute diseases with long-term sequelae: lifetime horizon</td>
<td>9</td>
</tr>
<tr>
<td>Modeling</td>
<td>• Applied if available data are insufficient to allow a full assessment of the cost-effectiveness or cost–utility of a product</td>
<td>10</td>
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<tr>
<td></td>
<td>• Based as much as possible on data from clinical studies comparing the study medication and the comparator, on data from validated databases and/or data from literature.</td>
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<tr>
<td></td>
<td>• Justification for modeling</td>
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<tr>
<td></td>
<td>• Structural hypotheses, assumptions and sources of information presented in clear and transparent way.</td>
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<tr>
<td></td>
<td>• Model inputs and outputs consistent with existing data and have face validity.</td>
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<tr>
<td></td>
<td>• Primary data and original sources of information used to define the values of input parameters as well as the original computer model are kept at the disposal of the Drug Reimbursement Committee.</td>
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<tr>
<td>Handling uncertainty</td>
<td>• Uncertainty around cost-effectiveness/cost–utility estimates should always be analyzed</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>• Methodological uncertainty</td>
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<td>• Data uncertainty</td>
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<td></td>
<td>• For models, probabilistic sensitivity analyses</td>
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<td></td>
<td>• Presentation of cost-effectiveness plane and cost-effectiveness acceptability curve or—for dominant interventions—the net monetary benefit function.</td>
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<td></td>
<td>• Assessment of the most important contributors to the variability of the estimated incremental cost-effectiveness/cost–utility ratio.</td>
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<tr>
<td>Discount rate</td>
<td>• Costs at 3%</td>
<td>12</td>
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<tr>
<td></td>
<td>• Benefits at 1.5%</td>
<td></td>
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<tr>
<td></td>
<td>• Other scenarios can be presented to test sensitivity of results to discount rates applied</td>
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</table>
If modeling is used for the PE, all (clinical) studies that served as a basis for the modeling input parameters' valuation should be described, including their methodology, assumptions and results. Relevance and appropriateness should be discussed. If unpublished material is used in the economic evaluation, a sufficiently detailed description of the material should be provided.

The external validity of study results included in the review should be assessed [14], especially if these results are used in the economic evaluation afterward. The external validity assessment is mainly descriptive in nature.

Guideline 2: Perspective of the Evaluation
The health-care decision-maker is usually interested in the costs of a treatment from the point of view of the health-care sector and in the health gains for society. Health-care costs include costs paid out of the health-care budget and patients' copayments. To be of interest to the decision-maker, the incremental costs should reflect the incremental costs for the health-care payers, i.e., the patients and the government who allocates the health-care budget.

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 the values of health-related quality of life should be values allocated to these states by the general public.

This recommendation does not mean that broader consequences of a treatment cannot or will not be taken into account in resource allocation decisions. The decision-maker may take other consequences into account in determining the value of a therapy: reductions in the absence from work; implications for equity; organizational issues; population characteristics; budget impact; etc. If these consequences are expected to be important for a specific treatment, additional analyses can be presented but these should be clearly distinguished from the reference case.

Guideline 3: Target Population
The target population described in the pharmacoeconomic file should be consistent with the target population identified for routine use of the product. The definition of the target population for routine use of a product 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). If the implications of a product on the costs or effects of treatment are proven to be different between subgroups in the product registration file, subgroup analyses should be performed in the PE. Even if subgroups are not analyzed in clinical studies, however, there might still be room for subgroup analyses in the economic evaluation, i.e., when the variables affecting the cost-effectiveness are different from the variables affecting the clinical efficacy. Such analyses are post hoc subgroup analyses. A number of conditions apply to post-hoc subgroup analyses [8]. Care should be taken in using appropriate statistical methods dealing with effect estimation in case of heterogeneity among subgroups [15] and not just multiply the number of analyses which may generate spurious findings.

Guideline 4: Comparators
The drug should be compared with a treatment with proven efficacy (in RCTs) that is considered the recommended treatment in daily practice in Belgium for the target indication. It is the treatment that most prescribers would replace with the new treatment if it becomes available and reimbursed. This can be a medical or nonmedical treatment. Multiple comparators can be considered if relevant in the Belgian context. Effective comparators used in other countries but not (yet) in Belgium—although potentially relevant for Belgium—should be described in the literature review.

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. Guidelines or patterns of care from other countries should be treated with caution, as they are not necessarily relevant to Belgium.

The comparator can be another medical treatment, best supportive care, watchful waiting or doing nothing. If the comparator commonly used in clinical trials is no longer relevant, e.g., due to changes in prescription behavior or therapeutic insights over time, indirect comparisons and/or modeling may be required. Indirect comparisons are only acceptable if no single trial of appropriate quality has been performed. Appropriate statistical techniques must be used for indirect comparisons [16–18].

If no direct comparisons between the standard treatment and the study treatment are available and if indirect comparisons are not possible, a PE cannot be performed.

Guideline 5: Analytic Technique
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-effectiveness analysis. In cost-effectiveness analyses, the outcome should be expressed in terms of life years gained, unless there are strong arguments to use another physical or clinical outcome variable (e.g., in case of acute diseases without long-term sequelae or in case of major clinical outcome parameter and a number of minor outcome parameters moving in the same direction). The incremental cost-effectiveness ratio (ICER) should be presented unless the effectiveness of a drug is better and the costs lower than the comparators' (dominance), in which case the cost savings and incremental effects are presented as separate values rather than as a ratio.

Cost–utility analysis. A cost–utility analysis should be seen as a complement to a cost-effectiveness analysis. If cost–utility analysis is added to the reference case analysis, the report should also contain the cost per life year gained to provide the most complete information to the decision-maker.

Cost–utility analysis can be considered 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 vs. survival).

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

Cost-minimization analysis. Cost-minimization analyses are used if the effects of two treatments are identical. Hence, cost-minimization analysis can only be justified by proof of equal outcome.
Cost–benefit analysis. Given the methodological difficulties and controversies associated with the valuation of health outcomes in monetary terms, 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 nonhealth impacts.

Guideline 6: Study Design

Cost-effectiveness or cost-utility analysis can be performed alongside a clinical study or can be based on a model. 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 deal with these limitations.

Pharmacoeconomic evaluations alongside clinical studies. There are basically two types of PE alongside clinical studies: piggy-back studies, i.e., an evaluation alongside a randomized controlled trial (RCT); and economic evaluations alongside noninterventional studies.

The weaknesses of piggy-back studies are directly related to the purpose of RCTs, where the primary objective is to evaluate the efficacy of a therapy. For economic evaluations, information is needed on the effectiveness in routine practice. Other weaknesses of RCTs for the purpose of PE are potentially inappropriate comparator, inadequate sample size, limited time horizon, protocol-driven costs or outcomes, and inappropriate outcome measures for economic evaluation purposes and patient selection. Moreover, when performed in other countries, the treatment protocol of the RCT 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 modeling.

On the other hand, RCTs have 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 the efficacy of a product. Piggy-back studies are useful if the weaknesses are made explicit and whenever possible tackled in advance, either a priori by including the economic evaluation in the study protocol of the RCT or ex post by taking appropriate measures to tackle the weaknesses.

Noninterventional studies avoid some of the weaknesses of RCTs but may nevertheless be insufficient to demonstrate long-term cost-effectiveness of a product. Noninterventional studies are especially useful to demonstrate the effectiveness (in contrast to efficacy), which is useful for the post-registration evaluation of the real cost-effectiveness of the product after 1.5 to 3 years. At the time of the reimbursement request, noninterventional studies will usually not be available yet. As for interventional studies, the design should take the specific elements needed for the economic evaluation into account.

For PE alongside RCTs or noninterventional studies, original data should be made available to the Drug Reimbursement Committee upon request.

Modeling. Even if a trial-based PE exists, some modeling 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 in the analysis of an economic evaluation based on a clinical study, certain assumptions will be made (e.g., assuming that the study population and observed resource use are representative for Belgium), which turns it de facto into a model. A separate guideline is devoted to modeling (see guideline 10).

Guideline 7: Calculation of Costs

Valuation of resource use in monetary units must be consistent with the perspective of the analysis, i.e., the health-care payer’s. For the health-care policymakers’ information, costs for the different categories of health-care payers should also be presented separately, i.e., as costs borne by the different categories of payers.

Cost categories. Table 2 specifies the cost categories that should be included or excluded from the cost analysis in the reference case.

<table>
<thead>
<tr>
<th>Cost categories</th>
<th>Included in the model</th>
<th>Excluded in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td>Included, e.g., health services, medications, hospitalizations . . .</td>
<td>Not included, e.g., travel expenses to and from hospital, informal care, home care</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>Not included, e.g., health-care costs in life years gained (unrelated health-care costs)</td>
<td>Not included, e.g., productivity losses</td>
</tr>
</tbody>
</table>

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 within the national context. Different sources can be used to obtain observational data: clinical trials, prospective observational studies, databases, and patient charts. Expert panels should only be used as a complementary source of information. The use of expert panel data is subject to specific conditions: methods used to obtain resource use estimates from experts should be transparent, questionnaires should be attached to the report, and descriptive statistics—and in case of small samples (<10 experts) individual responses—should be presented. 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.

Official governmental data sources should be used whenever possible [19]. Private databases can be used if they comply with legal requirements about privacy. Each database has its weaknesses, such as for instance the cross-sectional nature of the data, overestimation of the length of stay, imperfect registration, etc. These weaknesses can generally not be remedied without major assumptions. Therefore it is recommended to make explicit the underlying assumptions and discuss their weaknesses and potential impact on the cost estimates in the text rather than to try to solve them by means of ad hoc manipulations of the data.

Valuation of resource use. 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 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 microcosting approaches, can be presented in alternative scenarios, and supported with arguments of why the analyst thinks these alternative cost estimates are more appropriate.

Where generic pharmaceutical products exist, the reference price for these products should be used in the PE, even if the generics are not frequently used in the target population in Belgium. The rationale of this approach is that the limited use of the generics is a policy issue that is outside the scope of the PE. The aim of the PE is to assess the ICER relative to the appropriate (cost-effective) 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.

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

**Guideline 8: Estimation and Valuation of Outcomes**

The valuation of outcomes depends on the analytic technique used.

*Effectiveness evaluation in cost-effectiveness analysis.* In cost-effectiveness analyses outcomes should be expressed in terms of “number of life years gained”, unless there are strong arguments in favor of another outcome parameter, e.g., in case of acute diseases without long term sequelae. Age-specific life tables for Belgium should be used to estimate life expectancy.

The estimated number of life years gained should consider the impact of the treatment on all-cause mortality in the reference case analysis. Effectiveness estimates based on disease-specific mortality can be presented in complementary analyses. Unless the disease has a major impact on overall mortality in the population examined, it is not necessary to correct all-cause mortality figures for the fact that they include disease-specific mortality [20]. All-cause mortality should be modeled nonparametrically based on life table data. The functional form of the chosen disease-specific mortality function should be explained and justified.

*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. QALYs should not be weighted in the pharmacoeconomic analysis to reflect distributional preferences of the general public as there is too little evidence on the precise distributional preference function. This means that in submitted PE, 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, requires two steps: health state description and health state valuation.

*Health state description.* Health states should be described on a generic descriptive system such as the EQ-5D or SF-36. Health state descriptions in similar patient populations in other countries may be used.

If it is thought that the generic instruments are insufficiently sensitive to relevant changes in health in a specific disease, additional (disease-specific) quality of life results can be described in separate analyses.

The use of expert panels to describe patients’ health states is only accepted if patients cannot describe their health state themselves (e.g., mentally ill patients, children, unconscious patients). The reason for using expert panels for the description of health states should always be justified.

*Health state valuation.* Health states should be valued on a 0 (= value for dead) to 1 (= value for perfect health) scale. Values assigned to the health state descriptions should come from (a representative sample of) the general public, preferably from Belgium. 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 is only allowed if mapping functions are based on and validated with empirical data. Hence, when mapping is done, the state-of-the-art methodology for mapping should be used.

If no original Belgian data are available 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. If evidence exists that preference values are stable across countries, this should be described.

Disease-specific health state descriptions, obtained with a sufficiently validated instrument for which references are provided, should also be valued by the general public. If no complete valuation set for all health states that can be described with the instrument can be inferred from a subset of valuations derived from the general public, either Time Trade-Off (TTO) or Standard Gamble (SG) should be used for this valuation by the general public. Selection of people from the general public, representativeness and methods for surveying the subjects should be described.

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 PE. Consistency in methodology for the valuation of utilities of different health states in the PE should be pursued.

**Guideline 9: Time Horizon**

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 drug treatment and the 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. Sometimes a shorter time horizon may be justified, e.g., for very acute diseases with 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.

The expected appearance of an innovative drug in the near or distant future is no argument for applying a shorter time horizon. As long as the clinical effectiveness of these innovations is not studied, it is impossible to perform a formal analysis of its likely impact.
**Guideline 10: Modeling**

**Need for modeling.** Models are used for different reasons: extension of time horizons, extrapolation of intermediate outcome parameters to final outcome parameters, simulation of effectiveness as compared to efficacy, consideration ofexternalities associated with a treatment, indirect comparisons, translation of foreign data to the Belgian context, etc. The strength of a modeling approach is that pooled data, e.g., from meta-analyses of different clinical trials, can be used for the economic evaluation. The major weakness of models is that often major assumptions have to be made (e.g., about the comparability of the data derived from different sources, resource use in Belgium, etc.). The arguments for using a modeling approach should be set out clearly and sources for hypotheses should be presented.

Modeling is optional. If good quality Belgian data from clinical studies are available over a relevant time period, including all appropriate outcome measures and reflecting the methodological standards for trial-based PE (guideline 6), modeling is not needed.

The guidelines for good modeling practices developed by the modeling task force of ISPOR [20] should be followed.

**Precision of model structure and hypotheses.** The main principle should be to keep the model as simple as possible. The more complex the model, the more uncertain the results and the less likely that one is able to populate the model with valid data.

All assumptions made in the model, be it for outcome assessment, valuation of costs, and assessment of probabilities, should be documented and justified. 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 and use of expert panels cannot be avoided, strict methodological criteria apply. The use of expert panels is generally discouraged but should—if used—always be well justified.

All assumptions should be tested in the sensitivity analysis and/or scenario analysis to test the robustness of the results.

For models that extrapolate to longer time periods, i.e., for chronic conditions or treatments/diseases with long-term sequelae, it is recommended to present different scenarios to show the impact of different extrapolation approaches on the results [21].

- 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. 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.

The original computer model should be put at the disposal of the Drug Reimbursement Committee upon request. The choice of the modeling software is free.

**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) [20]. 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. 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) [20].

**Guideline 11: Handling Uncertainty and Testing Robustness of Results**

Uncertainty is usually divided into three broad areas: 1) methodological uncertainty coming from the analytical methods chosen to perform the evaluation (e.g., discount rate or extrapolation methods; this is usually handled by presenting results from the reference case and a number of alternative scenarios); 2) data uncertainty coming from variability in sample data (handled via statistical analyses) or from uncertainty ranges chosen for non-sample data (handled via sensitivity analyses); and 3) uncertain generalizability of the study results to other populations and/or other contexts (handled via descriptive external validity assessment). Each of these three areas of uncertainty should be specifically addressed in the sensitivity analysis [22].

In case of modeling, probabilistic sensitivity analyses should be performed on all uncertain parameters in a model, e.g., by means of Monte Carlo simulation. Distributions used for the uncertain modeling parameters should be justified. 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 modeling parameters that are decisive for the cost-effectiveness ratio such as the price of the product or the discount rate for costs and outcomes. 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. 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.

In the case of observed cost and effects data in a trial based pharmacoeconomic study, state-of-the-art methods should be used for the estimation of the confidence interval around the incremental cost-effectiveness ratio (e.g., bootstrapping).

The cost-effectiveness plane, with the results of the Monte Carlo simulations or bootstrapping, should be presented, both for the cost per QALY gained and for the cost per life year gained. In addition, a cost-effectiveness acceptability curve should be presented to show the probability that the treatment is cost-effective, given varying threshold values for the ICER.

If the results of the probabilistic sensitivity analysis shows a negative lower bound for the ICER, the incremental costs (or savings) and incremental effects (or harms) should be reported
separately for the lower bound of the 95% credibility interval, the point estimate and the upper bound of the 95% credibility interval. In addition, the percentage of the simulations where a negative ICER was found should be reported (if the simulated results fall in different quadrants of the cost-effectiveness plane, a separate percentage for each quadrant should be reported).

**Guideline 12: Discount Rate**

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 “right” choice for the discount rate of costs and benefits is still a matter of debate [23–26]. The choice of the discount rate for costs is based on the return on risk-free government bonds, currently about 3% in Belgium. The choice of the discount rate for outcomes is based on the expected relative changes in budgets and productivity over time. This is highly uncertain. Therefore, the discount rate for outcomes is uncertain. Awaiting further evidence on the most likely discount rate for outcomes in Belgium, the guidelines 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 applicant can choose to 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 pharmacoeconomic guidelines of other countries, a 3% discount rate for both costs and benefits can be considered. If comparison between evaluations is possible and useful, the 3% discount rate scenario for both costs and benefits could be presented.

**Discussion**

These methodological guidelines are developed as a tool to make pharmacoeconomic submissions and evaluations in Belgium more transparent and consistent but could actually serve a much broader goal, being to make all economic evaluations of health interventions more consistent and therefore more useful for health-care policy decisions, including evaluations not conducted to request drug reimbursement. These guidelines are also expected to enhance the power to differentiate between medicinal products which are “value for money” from those who are not.

The ultimate decision to reimburse or not to reimburse a drug is multifactorial. It will depend on the quality of the submitted document and the therapeutic value of the drug, and also on other aspects that may not be considered explicitly in the submission but may nevertheless be important from a health policy perspective, e.g., equity implications, severity of disease, patient characteristics, budget impact, and organizational issues. As such, the PE will be but one input in the decision-making process. The discussion about the appropriate threshold value against which ICERs of interventions should be compared, was considered an issue requiring additional research and discussion with policymakers. The project is ongoing at KCE. A report will be available by the end of 2008.

Based on the assessment of the file submitted for evaluation in the context of the pilot phase of the preliminary guidelines and extensive discussions with the representatives of the pharmaceutical industry, a number of issues were raised and some common pitfalls in economic evaluation files, such as selective presentation of evidence on effectiveness, underreporting of uncertainty ranges for input parameters of models, were highlighted.

Data requirements for good economic evaluations are high. However, pharmaceutical companies are often faced with no or very limited access to good quality Belgian data, although such data are available. This often hampers good quality and relevant PE. In Belgium, a lot of useful data for PE are routinely collected with public resources. For example, data on patients’ copayments for nondrug interventions are available but not accessible for companies, while these are needed in the calculation of the costs from the perspective of the health-care payer, including the health insurance and the patients. As long as access to routinely collected resource use data is limited for PE that are to inform healthcare policymakers, the quality of the evaluations, and ultimately the decisions, will remain suboptimal. With the expected increasing importance of cost-effectiveness considerations in reimbursement decisions, facilitating access to essential public resource use data to the people performing economic evaluations is indispensable, including the companies, their subcontractors for the economic evaluation and other experts performing health economic evaluations that serve resource allocation decisions. With increasing access to essential data for PE, guidelines can be revised to become more specific and precise, thereby increasing even more the relevance of the evaluations for Belgian policymakers. Lack of access to relevant Belgian data revealed the question from the pharmaceutical companies “to what extent the use of data from other countries would be acceptable.” While the preliminary guidelines contained a separate guideline on the assessment of the transferability of data used in the PE, the final guidelines included the transferability issue in each separate guideline where relevant. The idea was that it is not required to write a separate chapter in the drug reimbursement request on the transferability of each element “borrowed” from another country, but that the data sources and relevance of the data for Belgium should be discussed when they are presented. The ISPOR Good Research Practices on Economic Data Transferability Task Force recently reviewed what national pharmacoeconomic guidelines say about transferability and recommended good research practices for dealing with aspects of transferability [27]. The Belgian guidelines are in line with these recommendations, although they are not as specific as the Task Force’s on specific items and are slightly different on some items. The major emphasis in the Belgian guidelines is on transparency in methodology and sources used and justification of choices. This includes the choice of using data or models from other countries. The basic principle is that the PE should be relevant for Belgium. The guidelines are not specific about the methodology that should be used to assess transferability of data from other countries, but state that presumed transferability should always be justified with clear arguments. This might include a detailed presentation of the methods that were used to obtain the data in the other countries and, if data or models have been modified to better reflect the Belgian situation, the methodology that was followed to do this. The guidelines are more tolerant toward the use of clinical effectiveness data from other countries (e.g., relative risk reduction) than for the use of cost data, which is in line with the ISPOR Task Force recommendation. For the assessment of baseline risk, existing sources should be used as far as they are available and accessible.

In contrast to the Task Force, the Belgian pharmacoeconomic guidelines are silent about the use of individual patient data from multinational studies that included Belgium. While the guidelines do state that empirical data are the preferred source of inputs for the PE, implicitly including multinational studies, they do not give specific guidance about how to obtain the best Belgian data from these studies in cases where Belgium participated in the study. That this question did not come up during the discussions with the industry might be related to the fact that Belgium is, as
suggested by the Task Force, a relatively small market, and therefore, the number of Belgian patients included in these studies would be relatively limited.

For drug reimbursement decisions, it is preferred that the outcome data used in PE reflect the interventions’ effectiveness in daily practice (i.e., effectiveness in contrast to efficacy). Effectiveness is evaluated by means of a noninterventional study. However, it is clear that at the time of reimbursement request such evidence is rarely available, as the product is not (yet) widely used. Therefore, if companies would already plan the organization of an effectiveness evaluation study and the collection of economic data alongside this study at the time of submission of the registration request, this kind of evidence may be available at the time of the initial reimbursement request. This would strengthen the PE. 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 products 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.

Conclusions

The guidelines encompass today’s “state of the art” methodologies for PE. As this field of expertise is continuously evolving, these guidelines will have to be updated regularly to ensure that most appropriate designs and methods are used in Belgian PEs.

The authors wish to thank the external experts who have participated in the development of the guidelines for their valuable contributions: Philippe Beutels, Lieven Annemans, Dominique Dubois, Claude Le Pen, Sarah Dewilde, Hugo Robaey, Peter Verplanken, Steven Smeens, Leida Lamers and the representatives of Pharma.be, Françoise Stryckman, Yvette Vandriessche and Herman Van Eeckhout. We also thank Dirk Ramaekers who participated in the meetings and reviewed the draft guideline report. The external experts gave feedback on draft versions of the pharmacoeconomic guidelines. The final guidelines do not necessarily reflect the personal opinions of the external experts.

Source of financial support: No external funding was received for this project.

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