Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
KCE

Guidelines for pharmacoeconomic evaluations in Belgium

KCE reports 78C

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[1] External Expert for preliminary guidelines only (report 28C)

Executive summary

This report develops guidelines for pharmacoeconomic evaluations submitted in the context of a reimbursement request for pharmaceutical products for which pharmacoeconomic assessment is either compulsory or useful or a revision file 1.5 to 3 years after the initial reimbursement decision.

The guidelines are built around a reference case that defines the recommended methodology for each component of the economic evaluation. Each pharmacoeconomic submission should at least contain a reference case analysis. Additional analyses are allowed but cannot replace the reference case.

GUIDELINE 1: LITERATURE REVIEW

Each pharmacoeconomic evaluation should be accompanied by a description of the disease and the interventions studied and a systematic review of the existing clinical and economic studies on the intervention. The search strategy should be reproducible and selection criteria and procedures clearly presented. The review should reveal the up-to-date evidence for clinical effectiveness of the product and its cost-effectiveness relative to its comparator(s). The evidence should be critically appraised, its quality assessed and data presented in data extraction sheets. A clear and concise synthesis, substantiated with references, should be provided. Ongoing studies should be mentioned.

GUIDELINE 2: PERSPECTIVE OF THE EVALUATION

In pharmacoeconomic evaluations submitted in the context of a reimbursement request of pharmaceutical products, the reference case analysis should only include 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' co-payments. Health outcomes should be measured in patients but valued from a societal perspective.

GUIDELINE 3: TARGET POPULATION

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

If the implications of the drug on the effectiveness and/or costs differ between subgroups, separate subgroup analyses should be performed, provided that appropriate (statistical) justification for subgroup analysis is provided. Post-hoc subgroup analyses are only allowed if the costs between the subgroups are proven to be different based on appropriate statistical analyses. Relative effectiveness should be assumed equal across subgroups in this case. Epidemiological data for Belgium should be presented if available for both the entire target population and the relevant subgroups.

GUIDELINE 4: COMPARATORS

The drug should be compared with the most relevant alternative treatment for the proposed indication of the drug. The most relevant alternative treatment is 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. If this treatment cannot be identified, the recommended treatment according to the Belgian clinical guidelines should be used as a comparator. In some cases, multiple treatments will have to be included as comparator.

The comparators can be medical and/or non-medical treatments. Off-label use of products should not be used as a comparator in the reference case analysis but can be included in complementary analyses.

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

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

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 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.

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.

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

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

GUIDELINE 6: STUDY DESIGN

Pharmacoeconomic evaluations should always be based to some extent on data from RCTs or non-interventional studies comparing the study product 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.

GUIDELINE 7: CALCULATION OF COSTS

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

GUIDELINE 8: ESTIMATION AND VALUATION OF OUTCOMES

Outcomes in pharmacoeconomic 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 chronic conditions and acute conditions with long term sequelae or a relevant short term outcome for acute conditions with no long term consequences. Life expectancy estimates should be based on age-specific life tables for Belgium.

For cost-utility analyses, QALYs should be calculated. Life expectancy should be estimated based on Belgian age-specific life tables. Health-related quality of life weights should be based on empirical data, obtained with a descriptive system for health status for which corresponding preference values exist from the general public. The use of Belgian preference values is preferred. In the reference case, quality of life weights should be derived with a generic instrument. Scenarios with disease-specific measures for health-related quality of life can be presented as complementary analyses.

GUIDELINE 9: TIME HORIZON

The appropriate time horizon depends on the natural history of the disease. Chronic diseases call for a longer time horizon than acute diseases without long-term consequences. For chronic diseases and acute diseases with long-term sequelae, a lifetime horizon should be applied.

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 a product. Models should be 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. A justification for modelling should always be provided and the structural hypotheses, assumptions and sources of information should be presented in a clear and transparent way. Model inputs and outputs should be consistent with existing data and have 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 Drug Reimbursement Committee.

GUIDELINE 11: HANDLING UNCERTAINTY AND TESTING ROBUSTNESS OF 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 aspects of uncertainty in the evaluation should be addressed, including methodological uncertainty and data uncertainty. For models, probabilistic sensitivity analyses should be presented. A cost-effectiveness plane and cost-effectiveness acceptability curve or –for dominant interventions - the net monetary benefit function, should be presented. A Tornado diagram should show the most important contributors to the variability of the estimated incremental cost-effectiveness/cost-utility ratio.

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 can be presented.

POLICY RECOMMENDATIONS

Access to and provision of Belgian resource use data should be facilitated for pharmacoeconomic analyses that are supposed to serve Belgian pharmaceutical policy.

The Royal Decree of December 21st, 2001 may benefit from integration of guideline 2 of these Guideline for Pharmacoeconomic Evaluation. The costs included in a pharmacoeconomic should be the costs to the health care payer, including the governmental payers and the patients.

To increase the credibility and usefulness of pharmacoeconomic evaluations for drug reimbursement decisions, both the applicants and the RIZIV/INAMI should systematically apply these guidelines.

Scientific summary

TABLE OF CONTENTS

1 BACKGROUND

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. 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 (CRM-CTG). 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 Dec 2001 Ministerial Decree):[1]

- The therapeutic value, taking into account the efficacy, effectiveness, side effects, applicability and user-friendliness of the product,
- The market price of the drug and the requested reimbursement price,
- 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.

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], which is of particular importance to the subsequent pharmacoeconomic study.

The definition of therapeutic value used in the Royal Decree is larger 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 pharmacoeconomic 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 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 clear guidelines for conducting and reporting pharmacoeconomic evaluations. 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 appraisal process would benefit from consistency in the approaches used in the reimbursement requests files. In November 1995, the Belgian Society for Pharmacoepidemiology (BESPE) issued a standard reporting format for economic evaluations of pharmaceuticals. However, this format has not been reinforced. In 2002, the Drug Reimbursement Committee issued a circular including the formal requirements for a reimbursement request. The circular specified the criteria for submissions stipulated in the Royal Decree concerning the procedures, terms and conditions for the reimbursement by the health insurance of pharmaceutical specialties (Royal Decree of 21/12/2001,*B.S.* 29-12-2001). In this respect, the circular covered all elements needed in a reimbursement submission. The document paid special attention to the most important caveats in a submission.

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1 Koninklijk besluit van 21 december 2001 tot vaststelling van de procedures, termijnen en voorwaarden inzake de tegemoetkoming van de verplichte verzekering voor geneeskundige verzorging en uitkeringen in de kosten van farmaceutische specialiteiten, B.S. 29 december 2001. Arrêté royal de 21 décembre 2001 fixant les procédures, délais et conditions concernant l'intervention de l'assurance obligatoire soins de santé et indemnités dans le coût des spécialités pharmaceutiques, M.B. le 29 décembre 2001.

2 Van Wilder Ph, Dupont A. Introducing evidence based medicine (EBM) in reimbursement procedures: does it affect the outcome? Value in Health, Dec 2007. doi: 10.1111/j.1524-4733.2007.00299.x

2 OBJECTIVES

The objective of this study was to develop methodological and reporting guidelines for pharmacoeconomic evaluations submitted to the Drug Reimbursement Committee related to the reimbursement of a pharmaceutical product in Belgium. The study does *not* relate to budget impact analyses. Budget impact analyses have a number of particularities that need to be addressed separately. In a first endeavour, the focus is on guidelines for pharmacoeconomic evaluations, defined as a comparative analysis of at least two health interventions in terms of their costs and health consequences. The current pharmacoeconomic guidelines apply to all pharmaceutical products for which a pharmacoeconomic evaluation is required.

The guidelines are designed to assist companies to identify and format the information needed by the Drug Reimbursement Committee for the appraisal of a reimbursement request. The guidelines must be followed. Any deviations need a clear and detailed justification.

The guidelines aim to increase the methodological quality, transparency and uniformity of the pharmacoeconomic submissions. 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 pharmacoeconomic evaluations as specified in this report does not imply a positive reimbursement advice by the Drug Evaluation Committee. The better transparency and quality of the files will help the Drug Evaluation Committee in formulating a better informed advice, but the advice itself remains entirely the Committee's and is always motivated.

While the scope of these guidelines is currently limited to the economic evaluation of pharmaceutical products, many of the guidelines may actually be applicable to a much wider range of health interventions, including medical devices, health programmes and health care organisation. Development of similar guidelines for other interventions and the systematic consideration of health economic information in decision making should be seriously considered.

3 METHODS

Existing guidelines from other countries were reviewed. Only guidelines issued or updated after July 2003 were considered, because the field of pharmacoeconomics is continually evolving and regular updates are necessary. We based our guidelines mainly on the Dutch (CVZ[3]), French (CES[4]), Australian (PBAC[5]) and British (NICE[6]) guidelines.[7] Other guidelines were identified, but did not add knowledge or recommendations to the ones reviewed.

For most methodological aspects, different approaches exist. To improve consistency in the files, we present a "reference case", including the essential elements for each pharmacoeconomic evaluation together with the most appropriate methodology given the objectives of the reimbursement committee, i.e. maximising health gain within resource constraints. The committee could request a PE evaluation 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 9. 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 applicant. Therefore, the executive summary accompanying this report simply lists all guidelines to provide a quick overview. The appendices provide supportive documents for the pharmacoeconomic evaluation and elaborate on some technical aspects of the guidelines.

The development of these guidelines was done in two phases.

Phase one consisted of the development of a set of draft guidelines. 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.

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 pharmacoeconomic 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 organisation of the pharmaceutical industry in Belgium *Pharma.be*, the guidelines were adapted and finalised. The final guidelines are applicable to all new reimbursement request dossiers that (have to) include a pharmacoeconomic evaluation. Companies are strongly recommended to follow these guidelines for every pharmacoeconomic evaluation submitted in the context of a reimbursement dossier.

The guidelines for the actual evaluations are treated in Chapter 4, a general discussion related to the guidelines and use of pharmacoeconomic evaluations is provided in Chapter 5, recommendations for Belgian policy makers are formulated in Chapter 6 and Chapter 7 presents the reporting guidelines.

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3 College voor Zorgverzekeringen
4 Collège des Economistes de la Santé
5 Pharmaceutical Benefits Advisory Committee
6 National Institute for Clinical Excellence
7 Full references to these guidelines can be found in chapter 9

4 PHARMACOECONOMIC 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 a pharmacoeconomic evaluation and the recommended methodology for each component. We are aware that discussion about the appropriateness of the recommended methodology is possible. Such discussions may relate to value judgements (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 case is presented in Table 1.

Table 1: Reference case methods

Component of PE 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 payer (government + patients). Outcomes: society (for health-related quality of life: health state descriptions by patients, valuations from general public).	2
Target population	Consistent with the clinical file (Circular RIZIV/INAMI 2002). Relevant subgroups need to be defined. Post-hoc subgroup analyses only in case of statistical proof of difference in costs between the post-hoc subgroups.	3
Comparator	The treatment that is most likely to be replaced by the new treatment	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 RIZIV/INAMI, FOD/SPF Public Health and patients	7
Valuation of outcomes	Final endpoints. Cost-effectiveness analyses: life years gained for chronic conditions or acute conditions with long-term sequelae or a relevant short-term outcome in case of acute conditions without long-term sequelae. Cost-utility analyses: QALYs, with quality of life weights based on empirical data obtained with a generic quality of life instrument for which public preference values exist.	8
Time horizon	Lifetime (chronic conditions or acute conditions with long term sequelae) or duration of the treatment or disease and its consequences (acute conditions without long term sequelae)	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	Presentation of uncertainty around the ICER by means of confidence or credibility intervals and shown on the cost-effectiveness plane (add cost-effectiveness acceptability curve or incremental net benefit diagram) + probabilistic sensitivity analyses (for models) + scenario analyses for analyses of methodological uncertainty	11
Discount rate	3% on costs and 1.5% on outcomes	12

Before starting with the actual guidelines, some general remarks are made about pharmacoeconomic evaluations (section 4.1.).

Guidelines 1 to 12 relate to the methodological aspects of a pharmacoeconomic evaluation. Different methodological approaches will be discussed, with special attention to potential caveats.

4.1 GENERAL REMARKS

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 should be raised and some common pitfalls in economic evaluation files highlighted.

Data requirements for good economic evaluations are high. However, pharmaceutical companies are often faced with no or very limited access to good quality data for Belgium, although such data are available. This often hampers good quality and relevant pharmacoeconomic evaluations for Belgium. In Belgium a lot of useful data for pharmacoeconomic evaluations are routinely collected with public resources. For example, the calculation of the costs in a pharmacoeconomic evaluation should be performed from the perspective of the health care payer, including the health insurance and the patients. Data on patients' co-payments for non-drug interventions are available but not accessible for companies. As long as access to routinely collected resource use data is limited for pharmacoeconomic evaluations that are to inform health care policy makers, the quality of the evaluations, and ultimately the decisions, will remain sub-optimal.

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 sub-contractors for the economic evaluation and other experts performing health economic evaluations that serve resource allocation decisions. With increasing access to essential data for pharmacoeconomic evaluations, guidelines can be revised to become more specific and precise, thereby increasing even more the relevance of the evaluations for policy makers.

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 drug reimbursement decisions, it is preferred that the outcome data used in pharmacoeconomic evaluations reflect the interventions' effectiveness in daily practice (i.e. effectiveness in contrast to efficacy).

Effectiveness is evaluated by means of a non-interventional study, as defined in art 2, §8 of the Law of 7 May 2004 regarding experiments on human beings.

However, it is clear that at the initial submission, such evidence is rarely available, as the product is not (yet) widely used. Therefore, if companies would already think about the organisation 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 pharmacoeconomic 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 three 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 organising an active control study at the time of registration of a product.

Each pharmacoeconomic evaluation 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 for Belgium as possible. Whenever extrapolations are performed from Flemish or Walloon data to Belgium, methods for extrapolation should be clearly described.

Data should wherever possible be presented with their 95% confidence or credibility interval, whether it concerns data presented from literature in the literature review, input data for the economic model or results of the analysis. This is an absolute requirement, as only such reports allow assessors of a pharmacoeconomic dossier to evaluate the significance of a reported difference. For input data for which assumptions have to be made due to lack of data, the central estimate as well as the distribution should be explicated with their appropriate measures of variability.

Belgium does not use an explicit discrete threshold for incremental cost-effectiveness ratios below which an intervention is considered worthwhile and above which it is not. 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 threshold from another country in a Belgian pharmacoeconomic evaluation.

Key points

- **Access to good quality Belgian data on resource use should be facilitated to allow for pharmacoeconomic evaluations with higher relevance for health care policy makers.**
- **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.**
- **Point estimates subject to variability should always be presented with relevant measures of this variability (e.g. 95% confidence or credibility intervals, Q1-Q3).**
- **Referring to thresholds applied in other countries should be avoided.**

4.2 GUIDELINE 1: LITERATURE REVIEW

Each pharmacoeconomic evaluation should be accompanied by a description of the disease and the interventions studied and a systematic review of the existing clinical and economic studies on the intervention. The search strategy should be reproducible and selection criteria and procedures clearly presented. The review should reveal the best available up-to-date evidence for clinical effectiveness of the product and its cost-effectiveness relative to its comparator(s). The evidence should be critically appraised, its quality assessed and data presented in data extraction sheets. A clear and concise synthesis, substantiated with references, should be provided. Ongoing studies should be mentioned.

For a full overview of the clinical effectiveness and cost-effectiveness of a product, it is crucial to start with a thorough and systematic literature review. The value of a pharmacoeconomic evaluation crucially depends on the value of the evidence it is based upon. The pharmacoeconomic evaluation should be based on the best available up-to-date evidence on the intervention and the comparator. 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.

While 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 Commission 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 pharmacoeconomic 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 pharmacoeconomic evaluation should be explained. The literature review forms the basis of the pharmacoeconomic evaluation. As for pharmacoeconomic 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/report4.htm for clinical reviews, http://www.york.ac.uk/inst/crd/report6.htm for economic reviews[8]). 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, the outcomes and the study designs selected (PICO: Patient, Intervention, Comparator, Outcome). 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.

Databases searched should include at least:

- Medline
- Embase
- the Cochrane Controlled Trials Register
- Cochrane Database of Systematic reviews and
- NHS CRD review databases.

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, design of the studies, 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 pharmacoeconomic 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. The hierarchy of study designs for effectiveness evaluations and economic evaluations should be clearly recognized (Appendix 1). Quality assessment should be done using established quality assessment instruments (Appendix 2).

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

Data extraction sheets should be provided for all the studies retained for the synthesis. Appendix 3 provides examples for data extraction sheets for clinical and economic studies.

If modelling is used for the primary economic evaluation presented in the pharmacoeconomic file, 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 (Lancet 2005; 365:82-93). They relate to the setting of the trial, selection of patients, characteristics of selected patients, 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 is found in Appendix 4. 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 Drug Reimbursement Commission.

4.3 GUIDELINE 2: PERSPECTIVE OF THE EVALUATION

In pharmacoeconomic evaluations submitted in the context of a reimbursement request of pharmaceutical products, the reference case analysis should only include 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' co-payments. Health outcomes should be measured in patients but valued from a societal perspective.

In literature, it is often recommended to use the societal viewpoint for the pharmacoeconomic 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 *strictu 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 and patients' out-of-pocket expenses for health care. The aim of the health care decision maker is to maximise 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. However, in Belgium, where economic evaluations are only introduced in the decision making context since a few years, supporting resource allocation decisions within disease areas would already be a major step in the right direction. This approach will have implications for the recommended economic study design and outcome measures in these guidelines.

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 *and* the government. 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 important reductions in the absence from work, may be important factors in determining the value of a therapy. In addition, the decision maker will take other consequences into account: equity considerations, organisational 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 payer (government+patients). Analyses from a broader perspective are allowed but should be clearly distinguished from the reference case.

4.4 GUIDELINE 3: TARGET POPULATION

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

If the implications of the drug on the effectiveness and/or costs differ between subgroups, separate subgroup analyses should be performed, provided that appropriate (statistical) justification for subgroup analysis is provided. Post-hoc subgroup analyses are only allowed if the costs between the subgroups are proven to be different based on appropriate statistical analyses. Relative effectiveness should be assumed equal across subgroups in this case. Epidemiological data for Belgium should be presented if available for both the entire target population and the relevant subgroups.

The pharmacoeconomic evaluation should follow the clinical evidence. The target population described in the pharmacoeconomic file should be consistent with the target population identified for routine use of the product 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 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). 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 a product on the costs or effects of treatment are different between subgroups. These subgroups may already be described and analysed in the clinical file. In this case, subgroup analyses are also indispensable in the pharmacoeconomic evaluation.

While for the clinical file subgroup analyses are only allowed under specific conditions, there is more room for subgroup analyses in economic evaluations. An economic evaluation is rarely related to a product as such. The evaluation must consider differential cost-effectiveness for different indications and the characteristics of the affected population. Even if subgroups were *not* analysed 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. This means that the relative effectiveness in the different 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.[9] 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. Patient characteristics for the different subgroups should be specified enough in order to allow the evaluator to assess the appropriateness and relevance of the subgroups. Subgroups are therefore always clearly defined groups.

This notion is clearly distinct from the notion of outliers. Outliers are not a clearly identifiable homogenous group of patients with specific characteristics. Separate analyses on outliers are not acceptable.

Justification of post-hoc subgroup analysis includes testing for heterogeneity of costs across the subgroups. Post-hoc subgroup analyses are only allowed when costs are found to be different between clearly defined subgroups based on appropriate statistical analyses. Heterogeneity in effectiveness is not a sufficient condition 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. Only if costs are heterogeneous, post-hoc subgroup analyses are allowed.

When costs do not differ between subgroups, irrespective of the difference in relative effectiveness, post-hoc subgroup analyses should not be performed. In short, heterogeneity of costs across subgroups has to be demonstrated before a post-hoc subgroup analysis is performed.

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, care should be taken of the relevance of these data for Belgium.

9 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.

4.5 GUIDELINE 4: COMPARATORS

The drug should be compared with the most relevant alternative treatment for the proposed indication of the drug. The most relevant alternative treatment is 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. If this treatment cannot be identified, the recommended treatment according to the Belgian clinical guidelines should be used as a comparator. In some cases, multiple treatments will have to be included as comparator.

The comparators can be medical and/or non-medical treatments. Off-label use of products should not be used as a comparator in the reference case analysis but can be included in complementary analyses.

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

Indirect comparisons are only allowed under specific conditions: the choice of an indirect instead of 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 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 by the new treatment if it became available and reimbursed. This can be a medical or non-medical 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.

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. International guidelines should be treated with caution, as they are not necessarily relevant to Belgium. It is useful to provide a comprehensive list of possible therapeutic strategies for the target group of patients that is considered.

The comparator can be another 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 choice of the comparator should always be justified and supported by clear arguments. Consistency between the clinical and the pharmacoeconomic submission should be pursued. Off-label used products cannot be used as valid comparators in the pharmacoeconomic evaluation. The value of these products can be described, however, in the literature review.

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 pharmacoeconomic 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; Bucher et al. J Clin Epidemiol 1997; Song et al. BMJ 2003). A useful report about indirect comparisons is available on http://www.ncchta.org/fullmono/mon926.pdf. An example of a study applying this methodology is found in Lim et al, BMJ 2003.

If no direct comparisons between the standard treatment and the study treatment are available and if no indirect comparisons are possible, a pharmacoeconomic evaluation cannot be performed. Evidence about the relative effectiveness of the two treatments is indispensable for an economic evaluation. Without such evidence, a pharmacoeconomic evaluation will not be informative for the health care decision maker.

4.6 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 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.

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.

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

Results should be expressed as incremental cost-effectiveness or cost-utility ratios with their associated distribution. If a cost-utility ratio is presented as a reference case analysis result, 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 descriptions, i.e. descriptions of costs and consequences without calculation of an incremental cost-effectiveness ratio, are insufficient for a pharmacoeconomic evaluation but may be considered as a logical first step towards a formal economic evaluation.

4.6.1 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 one major clinical outcome parameter and a number of minor outcome parameters moving in the same direction). The choice of the outcome measure should be consistent with the objectives of the medical 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', the ICER, which is negative in that case, is generally not presented. Instead, the cost savings and incremental effects are presented in disaggregated form. In case of a negative ICER, it is recommended to present the incremental net benefit of the treatment in function of a range of thresholds. Because the threshold is unknown, the incremental net benefits should be presented graphically, with the threshold on the X-axis and the incremental net benefit on the Y axis (see for instance Stinnett & Mullahy 1998).

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 or a similar measure that includes the impact of the drug on symptoms related to the treatment. This sets the case for cost-utility analysis. 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.

4.6.2 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.[10] A cost-utility analysis should always complement a cost-effectiveness analysis.

Cost-utility analysis should 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 drugs which 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.

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.

To increase the usefulness of a cost-utility analysis for health care decisions, the Drug Reimbursement Committee must be provided with sufficient details about the methods used for valuing utilities in order to allow the Committee to evaluate the pharmacoeconomic evaluation separately.

4.6.3 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, an added therapeutic value (as defined by the aggregate value of the 5 items mentioned above). 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 a pharmacoeconomic 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.

[10] 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.

4.6.4 Cost-benefit analysis

Unlike cost-effectiveness analyses 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.

4.7 GUIDELINE 6: STUDY DESIGN

Pharmacoeconomic evaluations should always be based to some extent on data from RCTs or non-interventional studies comparing the study product 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.

Cost-effectiveness or cost-utility analysis can be performed alongside a clinical trial (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 the product under study is compared to its relevant comparator, are preferred as they offer a direct comparison between the 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.

4.7.1 Trial-based pharmacoeconomic evaluations

There are basically two types of trial-based pharmacoeconomic 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 pharmacoeconomic evaluation but rather to evaluate the efficacy of a therapy. 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 pharmacoeconomic evaluation. Some of the weaknesses of RCT for the purpose of pharmacoeconomic evaluations are: (1) a potentially inappropriate comparator, (2) an inadequate sample size, (3) a limited time horizon, (4) the occurrence of protocol-driven costs or outcomes, (5) inappropriate outcome measures and (6) patient selection. Moreover, 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. A randomised controlled trial 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 can 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 pharmacoeconomic 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. For the non-interventional studies, the guidelines developed by the Drug Reimbursement Committee should be followed (Appendix 7). Non-interventional studies avoid some of the weaknesses of RCTs but may nevertheless be insufficient to demonstrate long-term cost-effectiveness of a product. In designing a non-interventional study, it is important to include the specific features for the economic evaluation in the protocol. As for interventional studies, the time horizon and the comparator should be appropriate for the economic evaluation.

For pharmacoeconomic evaluations alongside RCTs or non-interventional trials, original data should be provided to the Drug Reimbursement Committee upon request.

4.7.2 Modelling

Even if a trial-based pharmacoeconomic 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.

Pharmacoeconomic 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 regression models or meta-analysis models.

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).

4.8 GUIDELINE 7: CALCULATION OF COSTS

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

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.

For co-payments, the general rule is to use the co-payments paid by regularly insured patients falling outside any of the specific categories that benefit from increased reimbursement. Deviations from this rule should be justified.

The perspective for the cost calculation is that of the health care payer (government and patient). Health care costs borne by the government (RIZIV/INAMI+FOD/SPF) 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.

4.8.1 Cost categories

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

Table 2: 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, home care
Indirect costs	Not included e.g. health care costs in life years gained *(unrelated health care costs)*	Not included e.g. productivity losses

Direct health care costs should be included. 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. The methods for valuing productivity losses should be clear.

4.8.2 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). Expert panels are preferably only used as a complementary source of information rather than as the sole source of information on resource use.

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 (https://tct.fgov.be/etct/index.html), 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 pharmacoeconomic evaluation. Other databases, such as the IMS Health Databases, IFEB/IPhRB, Farmanet/Pharmanet, etc. 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 Van De Sande et al., 2006 (http://kce.fgov.be/index_en.aspx?ID=0&SGREF=5220&CREF=9305).

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 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.

4.8.3 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 micro-costing approaches, can be presented in alternative scenarios, supported with arguments of why the analyst thinks these alternative cost estimates are more appropriate.

A specific recommendation applies to the hospital drug lump sum. If the use of drugs included in the hospital drug lump sum changes dramatically following the application of a new product or procedure, it is recommended to detail the costs of medication for hospitalised patients rather than to use the hospital drug lump sum. The lump sum should only be used if the impact on medication use is expected to be limited.

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. The rationale of this approach is that the limited use of the generics is a policy issue that is outside the scope of the pharmacoeconomic evaluation. The aim of the pharmacoeconomic 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.

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.

All costs should be expressed in values for the current year. This implies that costs from past years should be inflated using the appropriate Health Index figures. Index figures can be obtained from the web-site of the ministry of Economic Affairs (http://mineco.fgov.be/informations/indexes/indint1xls_2006_2008_22_nl.htm)

Table 3 presents the sources for unit prices/costs to be used for different types of resource inputs. Data from the FOD Volksgezondheid/SPF Santé Publique are not publicly available. There is an urgent need for making up-to-date information available on the web-site of the service. In the meantime, we present data as obtained directly from the FOD/SPF through personal communication.

Table 3: Sources for unit costs of resources

<table>
<tr><th></th><th>Source</th></tr>
<tr><td>Ambulatory and hospital health care services (honorarium fees)</td><td>Belgian reimbursement scheme (Nomenclatuur/Nomenclature)
http://www.riziv.be/care/nl/nomenclature/index.htm
Standard fees should be used for regularly insured patients. No account should be taken of additional charges for specific patients (e.g. in a private hospital room)</td></tr>
<tr><td>Drugs</td><td>http://www.riziv.fgov.be/drug/nl/index.htm
If a generic product exists for (additional) drugs that are used during the study or comparator treatment, the price of the generic should be used.</td></tr>
<tr><td>Hospitalisation (per diem)</td><td>Per diem prices (in euros) for Belgian hospitals are available at the FOD Volksgezondheid/SPF Santé Publique, but are not published. The table below presents the average per diem prices in different years (situation on January 1 of that year) and per type of hospital
<table>
<tr><th></th><th>2003</th><th>2004</th><th>2005</th><th>2006</th><th>2007</th></tr>
<tr><td>Acute</td><td>266,77</td><td>284,56</td><td>283,86</td><td>305,98</td><td>317,24</td></tr>
<tr><td>Burns</td><td>1.013,43</td><td>1.059,23</td><td>1.065,51</td><td>1.125,85</td><td>1 137.35</td></tr>
<tr><td>Geriatrics</td><td>171,70</td><td>167,37</td><td>186,11</td><td>176,14</td><td>184.88</td></tr>
<tr><td>Palliative</td><td>390,91</td><td>401,70</td><td>399,95</td><td>416,88</td><td>421.49</td></tr>
<tr><td>Psychiatric</td><td>159,86</td><td>175,83</td><td>176,51</td><td>182,52</td><td>190.28</td></tr>
<tr><td>Specialized</td><td>174,88</td><td>188,73</td><td>188,79</td><td>198,70</td><td>208.78</td></tr>
</table>
Source: SPF Santé Publique, DG 1 Organisation des Etablissements de Soins

Standard 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, clinical biology should be added to the per diem price.
Other useful information may be found at :
1. financial indicators for hospitals
http://www.health.fgov.be/TBH/FR/Home.jsp
2. financial statistics
https://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/GEZONDHEIDZORG1_MENU/ZORGINSTELLINGEN1_MENU/REGISTRATIESYSTEMEN1_MENU/FINHOSTAFINANCIERINGHOSPITALEN1_MENU/PUBLICATIONS25_HIDE/PUBLICATIONS25_DOCS/STATISTIQUES%20FINANCI%C3%88RES%20ET%20COMPTABLES%2091%20%C3%80%2001.PDF

Other important data with respect to costs for hospitalised and ambulatory patients are found on http://www.riziv.fgov.be/insurer/nl/rate/index.htm#forfaits</td></tr>
</table>

Co-payments for the regularly insured should be used and not those for special categories of insured citizens, such as WIGW/VIPO 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 payer, 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.

4.9 GUIDELINE 8: ESTIMATION AND VALUATION OF OUTCOMES

Outcomes in pharmacoeconomic 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 chronic conditions and acute conditions with long term sequelae or a relevant short term outcome for acute conditions with no long term consequences. Life expectancy estimates should be based on age-specific life tables for Belgium.

For cost-utility analyses, QALYs should be calculated. Life expectancy should be estimated based on Belgian age-specific life tables. Health-related quality of life weights should be based on empirical data, obtained with a descriptive system for health status for which corresponding preference values exist from the general public. The use of Belgian preference values is preferred. In the reference case, quality of life weights should be derived with a generic instrument. Scenarios with disease-specific measures for health-related quality of life can be presented as complementary analyses.

The aim of the pharmacoeconomic evaluation is to assess the additional costs associated with the better outcome of the drug treatment. 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.

4.9.1 Effectiveness evaluation in cost-effectiveness analysis

For cost-effectiveness analyses, the outcomes should be consistent with the results from the clinical file. If this file contains only short term outcomes and long term outcomes are considered important for the pharmacoeconomic evaluation, modelling may be needed (cfr. Guideline 10). For chronic diseases or acute diseases with long term sequelae including significant mortality risks, outcomes should be expressed in terms of "number of life years gained", unless there are strong arguments in favour 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. These data are available at the National Institute of Statistics (NIS/INS: www.statbel.fgov.be).

If the relevant outcome parameter in a cost-effectiveness analysis is life years gained, 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. 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 (see ISPOR's Principles of Good Practice for Decision Analytic Modelling in Health Care Evaluation: http://www.ispor.org/workpaper/healthscience/tfmodeling.asp). 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.

4.9.2 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 (yet) QALYs should not be weighted in the pharmacoeconomic analysis. This means that in submitted pharmacoeconomic 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, requires two steps. The first step is the health state description. Health states should be described on a standardised descriptive system. The second step is the valuation of these health states. Health state values should be valued on a 0 (=value for dead) to 1 (=value for perfect health) scale. To avoid possibilities for manipulation of the quality of life values, it is strongly recommended to use the same descriptive instrument and the same set of values across all pharmacoeconomic evaluations. Moreover, it is strongly recommended to calculate QALYs based on original Belgian empirical data.

4.9.2.1 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 done by patients on a generic descriptive system, such as the EQ-5D or SF-36. Other instruments 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-36 in similar patient populations in other countries may be used, provided that the criteria for valuation as explained in 4.9.2.2 are fulfilled.

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 to create an ad hoc disease-specific questionnaire for a single pharmacoeconomic 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 results. Development of health-related quality of life instruments requires thorough methodology and verification of reliability, validity and consistency. If disease-specific instruments are used, references to publications that document the psychometric properties should be provided. The description of health states on a disease specific quality of life instrument should not be left to experts only if patients in the target population can be surveyed themselves. There is evidence that expert opinions are not always close to the descriptions given by patients. Therefore, 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 with clear arguments.

4.9.2.2 Health state valuation

Values assigned to the health state descriptions should come from (a representative sample of) the general public. For EQ-5D descriptions, values from the general population study in Flanders are available (see appendix 6). If the EQ-5D is used it is recommended to use the Flemish index values.

For other instruments a similar preference valuation set is not available yet for Belgium. Use of other instruments, e.g. the SF-36 or SF-6D, would hence first require an original study in the general Belgian population to value the health states from the societal perspective. Such newly set-up general population surveys should comply with the methodological standards for this kind of research. Sampling methods, survey techniques, check of representativeness, valuation methods etc. should be clearly described. Studies with inappropriate methodology or insufficiently detailed description of the followed methodology cannot make an appeal on representativeness for the

general public and can therefore not be accepted as a valid source for health state valuations.[11] As long as Belgian valuation sets for other instruments are not available, the use of the Flemish valuations for the EQ-5D health states is recommended.

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 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. 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 sub-set of valuations derived from the general public, either TTO or 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 in detail.

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

4.10 GUIDELINE 9: TIME HORIZON

The appropriate time horizon depends on the natural history of the disease. Chronic diseases call for a longer time horizon than acute diseases without long-term consequences. For chronic diseases and acute diseases with long-term sequelae, a lifetime horizon should be applied.

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.

A particular issue that may be important for some drug treatments is the rapid evolution in development of new drugs.

11 If a Visual Analogue Scale (VAS) is used for the derivation of health state preference values from the general public, the choice of the states valued by the general public, the methods used to interpolate values for states that were not directly valued and the technique used to re-scale the original VAS scores to a 0 (=dead) to 1 (=perfect health) scale should be described.

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.

4.11 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 a product. Models should be 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. A justification for modelling should always be provided and the structural hypotheses, assumptions and sources of information should be presented in a clear and transparent way. Model inputs and outputs should be consistent with existing data and have 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 Drug Reimbursement Committee.

4.11.1 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, extrapolation modelling may be necessary.

Another reason for modelling is the simulation of final outcomes based on observed data on 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).

Modelling can also be used to simulate the real life application of a drug 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.

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 pharmacoeconomic model.

Sometimes, modelling is needed to take externalities associated with the disease or treatment into account (e.g. communication 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 for comparisons between interventions that have never been directly compared in a clinical trial.

The decision to model should be justified in the pharmacoeconomic submission. Modelling is optional. If good quality Belgian data from clincal studies are available over a relevant time period, including all appropriate outcome measures and reflecting the methodological standards for trial-based pharmacoeconomic evaluations (guideline 6), modelling is not needed.

Guidelines for good modelling practices have been developed by the modelling task force of ISPOR (http://www.ispor.org/workpaper/healthscience/tfmodeling.asp). These guidelines ought to be followed whenever a model is built. In this report, we simply highlight a number of points of attention.

4.11.2 Choice of the model design

Different types of models can be used, the major categories being decision trees, Markov models and discrete event simulation models. The main principle is that a model should be kept as simple as possible and that its 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.

4.11.3 Precision of model structure and hypotheses

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

If primary data or expert opinions are used, the original data set 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:

Variable's name	Description	Mean value	Type of distribution + appropriate parameters (e.g. standard deviation, 95% confidence interval, alpha1 and alpha2 …)	Source

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). 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.

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 (Drummond et al. Med Care 2005):

- 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 judgement. 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 Drug Reimbursement Committee upon request. Confidentiality will be guaranteed by the Committee. The choice of the modelling software is free.

4.11.4 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. 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.

4.12 GUIDELINE 11: HANDLING UNCERTAINTY AND TESTING ROBUSTNESS OF 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 aspects of uncertainty in the evaluation should be addressed, including methodological uncertainty and data uncertainty. For models, probabilistic sensitivity analyses should be presented. A cost-effectiveness plane and cost-effectiveness acceptability curve or –for dominant interventions - the net monetary benefit function, should be presented. A Tornado diagram should show the most important contributors to the variability of the estimated incremental cost-effectiveness/cost-utility ratio.

Uncertainty in economic evaluations of healthcare interventions is omnipresent, and should be properly described and accounted for in the submitted pharmacoeconomic file.

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 a methodological reference case, as described in Table 1, and other scenarios) (2) the 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) (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 economic evaluation.

Methodological uncertainty arising from the applied discount rate or the extrapolation method used in models should be tested using scenario analysis. 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).

Data uncertainty applies to trial-based pharmacoeconomic evaluations as well as to models. In trial-based pharmacoeconomic evaluations, statistical analyses can be used to estimate the uncertainty around individual cost and effects data due to sampling variability. Detailed descriptive statistics, showing the distribution and variability of costs and effects data, should be presented.

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. The central estimate of the ICER results directly from the probabilistic sensitivity analysis as the mean of the simulated ICERs. This is not necessary 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 the product and 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. 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.

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 (see technical note in appendix 4).

ICERs of pharmaceutical products for which a pharmacoeconomic evaluation is requested are expected to belong to the North-East quadrant of the cost-effectiveness plane (more costly and more effective treatment). The cost-effectiveness plane, with the results of the Monte Carlo simulations or bootstrapping, should always be presented, both for the cost-per-QALY gained and for the cost-per-LYG.

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.

If the central estimate of the ICER belongs to the south-east quadrant (more effective and less costly), then the natural ordering of ICERs (the lower the ICER, the better) does not hold any more. Therefore, in case of a negative ICER, it is suggested to present the incremental net monetary benefit (NMB) function and report the incremental costs and effects separately.

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).

The relative impact of uncertain variables on the ICER should be presented by means of a Tornado diagram.

4.13 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 can 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 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 that the choice of the discount rate should be based on the changing value of costs and effects over time. 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 change in the value of health over time and the expected relative changes in budgets and productivity over time (Gravelle & Smith, Health economics 2001; Brouwer et al., BMJ; van Hout). 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, 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 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. Alternative scenarios include a 0% discount rate for both costs and benefits or a 5% discount rate for both costs and benefits. The inclusion of alternative scenarios is not a formal requirement. 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.

5 DISCUSSION

These methodological and reporting guidelines are developed as a tool to make pharmacoeconomic evaluations in Belgium more consistent.

The ultimate decision to reimburse or not reimburse a drug will depend on the quality of the submitted document and the therapeutic value of the drug but may also depend 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 and organisational issues. As such, the pharmacoeconomic evaluation will be but one input in the decision making process. 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. A drug treatment with a relatively high incremental cost-effectiveness ratio may still be worthwhile if other elements weighted heavily in the decision process. As such, references to ICER thresholds are inappropriate in a pharmacoeconomic submission. Nevertheless, the pharmacoeconomic evaluation is a very important element for the decision maker, as it gives clues about efficient allocation of scarce resources. Consistency in pharmacoeconomic submissions is a first step in the improvement of the reimbursement decision process.

6 POLICY RECOMMENDATIONS

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

First, access to data is a major problem in Belgium. Even data collected with public resources are not readily available for use in analyses that should serve an improved health care policy. Examples include the average per diem price of different categories of hospitals, annual frequency of different interventions, average cost per patient with a specific disease, etc. These data, although available at different actors in the Belgian health care system, cannot be obtained by those who are held to perform analyses with relevant Belgian data to inform the decision maker. This can be done in compliance with the privacy regulation by provision of aggregated rather than individual data. The additional resources needed to address this problem should be acknowledged by the public health authorities.

Second, the Royal Decree of December 21, 2001 would benefit from an integration of guideline 2 concerning the perspective of the cost calculation in a pharmacoeconomic 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 payer, including the government and the patient.

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

Key points

- **Access to and provision of Belgian resource use data should be facilitated for pharmacoeconomic analyses that are supposed to serve Belgian pharmaceutical policy.**
- **The Royal Decree of December 21st, 2001 may benefit from integration of guideline 2 of these Guideline for Pharmacoeconomic Evaluation. The costs included in a pharmacoeconomic should be the costs to the health care payer, including the governmental payers and the patients.**
- **To increase the credibility and usefulness of pharmacoeconomic evaluations for drug reimbursement decisions, both the applicants and the RIZIV/INAMI should systematically apply these guidelines.**

7 REPORTING GUIDELINES

The recommended structure of a pharmacoeconomic report is presented below. This structure is based on the reporting guidelines developed by the Pharmacoeconomic Committee of the Belgian Society for Pharmacoepidemiology (BESPE). Some specific reporting guidelines for models are presented in chapter 8.

7.1 EXECUTIVE SUMMARY

Includes:

- objectives: specifying study medication, 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

7.2 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

7.3 OBJECTIVES

- study medication: therapeutic group, product name (+ generic name), galenic type, 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

7.4 LITERATURE REVIEW

7.4.1 Clinical literature review

7.4.1.1 Methods

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

7.4.1.2 Results

- flow diagram
- evidence tables
- synthesis of the extracted evidence

Data need to be accompanied by relevant measures of variability.

7.4.1.3 Discussion and Conclusions of the clinical literature review

Data extraction sheets are provided in annex.

7.4.2 Economic literature review

7.4.2.1 Methods

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

7.4.2.2 Results

- flow diagram
- evidence tables
- synthesis of the extracted evidence

Data need to be accompanied by relevant measures of variability.

7.4.2.3 Discussion and Conclusions of the clinical literature review

Data extraction sheets are provided in annex.

7.5 BASIC ELEMENTS OF THE PHARMACOECONOMIC STUDY

7.5.1 Analytic technique

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

7.5.2 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.

7.5.3 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

7.5.4 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

7.5.5 Method of analysis of the data: statistical analysis techniques, handling missing data, statistical techniques for the sensitivity analysis

7.5.6 Time horizon

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

7.5.7 Sensitivity analysis

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

7.6 RESEARCH METHODS

7.6.1 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

7.6.2 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

7.7 RESULTS

7.7.1 Basic results

- Results should be presented in a tabular form. The table should contain the discounted costs, outcomes, incremental costs and incremental outcomes in a disaggregated form and separately for the study intervention and the comparator. Incremental cost-effectiveness ratios should be presented if the treatment is not dominant (lower costs and better effectiveness).
- For the presentation of cost data, the expected total costs of each alternative should be presented as well as the average incremental cost, together with its confidence interval. Unit costs (in Euros) and quantities of resources used should be reported separately.

7.7.2 Uncertainty analysis

- Present cost-effectiveness or cost-utility plane
- Cost-effectiveness acceptability curve and/or incremental net benefit diagram
- Present confidence interval around the incremental cost-effectiveness ratio

7.8 DISCUSSION

- weaknesses of the study

7.9 CONCLUSION

7.10 TRANSPARENCY OF FINANCIAL SUPPORT

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

7.11 REFERENCES

7.12 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

8 PRESENTATION OF A MODEL

8.1 DATA

The data used in a model should be presented in tabular form, with references, as in the table below:

Variable's name	Description	Mean value	Type of distribution + appropriate parameters (e.g. standard deviation, 95% confidence interval, alpha1 and alpha2 …)	Source

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 characterised by their mean and standard deviation. 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 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.

8.1.1 Results

The total costs as well as total outcomes should be presented for each option compared in tabular form. The table presents the discounted costs, outcomes, incremental costs and incremental outcomes in a disaggregated form and separately for the study intervention and the comparator.

Incremental cost-effectiveness ratios should be presented if appropriate.

For Markov models, it is recommended to present the proportion of patients in each state, the total costs and outcomes and the incremental cost-effectiveness after each cycle (in graphical or tabulated form). Comment on how the findings correspond with the expected trace.

8.1.2 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. This graphically shows the probability that a treatment is cost-effective compared to its alternative. The contribution of each uncertain parameter to the uncertainty in the ICER can be presented in case of probabilistic sensitivity analysis, using expected-value-of-information methods.

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.

8.1.3 Presentation of results

Extrapolation scenario	**Mean ICER with 2% discount rate for costs, 1.5% for effects**	**Lower limit of the 95% credibility interval***	**Upper limit of the 95% credibility interval***
1			
2			
3			

if relevant, i.e. if it is not negative and if there is no dominance

9 METHODOLOGICAL REFERENCES BY TOPIC

GUIDELINES

CVZ. Richtlijnen voor farmaco-economisch onderzoek (versie 2006). 2005 (www.cvz.nl).

CES. French Guidelines for the Economic Evaluation of Health Care Technologies. Sept. 2004. (http://www.ces-asso.org/Pages/defaut_fr.htm)

Australian Government – Department of Health and Ageing. Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee (PBAC). Sept. 2004 (www.health.gov.au/internet/wcms/publishing.nsf)

NICE. Guide to the Methods of Technology Appraisal. 2008 (http://www.nice.org.uk/page.aspx?o=114264 and for the review of the technology appraisal process guide in 2008)

(Updated Guide to the Methods of Technology Appraisal (status of "draft for consultation" in February 2008): http://www.nice.org.uk/media/8AE/5C/TAMethodsGuideUpdateFINALFORCONSULTATION281107.pdf at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technologyappraisalmethodsreview/technology_appraisal_methods_review.jsp)

GENERAL

Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. 3rd edition. Oxford: Oxford University Press, 2005.

LITERATURE REVIEW

Rothwell P, External validity of randomised controlled trials: "To whom do the results of this trial apply?", *Lancet.* 365: 82-93, 2005.

STUDY DESIGN

Trial-based economic evaluations

O'Sullivan AK et al, Collection of health economic data alongside clinical trials: is there a future for piggyback evaluations ?, Value in Health vol 8, N0 1, pp67-79, Jan 2005.

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Butler N A; Schapira, M M.; Warren, JL; Earle, CC. Methodological Issues in the Use of Administrative Claims Data to Study Surveillance After Cancer Treatment**.** *Medical Care. 40(8) Supplement:IV-69-IV-74, August 2002.*

Modelling

Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. Journal of Health Services Research & Policy. 2004;9(2):110-118

Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of good practice for decision analytic modelling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modelling Studies. Value Health. 2003;6(1):9-17.

Drummond M, Sculpher M. Common Methodological Flaws in Economic Evaluations. Med Care. 2005; 43(7): II-5-II-14.

CALCULATION OF COSTS

Measurement of resource use

Van de Sande S, De Wachter D, Swartenbroeckx N, Peers J, Debruyne H, Moldenaers I, Lejeune B, Van Damme V, Ramaekers D, Leys M. Inventaris van databanken gezondheidszorg. KCE Reports vol.30A Brussel: Federaal Kenniscentrum voor de gezondheidszorg (KCE) ; Mei 2006.. Ref. D/2006/10.273/14. (http://kce.fgov.be/index_en.aspx?SGREF=5220&CREF=9305)

HANDLING UNCERTAINTY

Overview

Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technology Assessment. 1999;3(2). (http://www.ncchta.org/execsumm/summ302.htm)

Stinnett AA, Mullahy J. Net Health Benefits. A new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 18(2):S68-S80, 1998.

Confidence Interval around the ICER

Chaudhary MA, Stearns SC. Estimating confidence intervals for cost-effectiveness ratios: an example from a randomized trial. Stat Med. 1996;15(13):1447-58.

Briggs AH, Mooney CZ, Wonderling DE. Constructing confidence intervals for cost-effectiveness ratios: an evaluation of parametric and non-parametric techniques using Monte Carlo simulation. Stat Med. 1999;18(23):3245-62.

O'Brien B, J., Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. Stat Methods Med Res. 2002;11:455-468.

INDIRECT COMPARISONS

Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. Bmj. 2003;326(7387):472.

Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. Health Technology Assessment. 2005;9(26). (http://www.ncchta.org/execsumm/summ926.shtml)

Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683-91.

Lim E, Ali Z, Ali A, Routledge T, Edmonds L, Altman DG, et al. Indirect comparison meta-analysis of aspirin therapy after coronary surgery. Bmj. 2003;327(7427):1309.

Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.

Baker SG, Kramer BS. The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? BMC Med Res Methodol. 2002;2:13.

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Claxton K, Sculpher M, Culyer A, McCabe C, Briggs A, Akehurst R, Buxton M and Brazier J. Discounting and cost-e¡ectiveness in NICE: stepping back to sort out a confusion. Health Econ. 2006; 15: 1–4.

Bos JM, Postma MJ, Annemans L. Discounting health effects in pharmacoeconomic evaluations : current controversies. Pharmacoeconomics 2005;23(7):639-49.

Gravelle H., Smith D.. Discounting for Health Effects in Cost-benefit and Cost-effectiveness Analysis. Health Econ. 2001: 587-599.

10 APPENDICES

APPENDIX 1: HIERARCHY OF EVIDENCE

HIERARCHY OF STUDY DESIGNS FOR STUDIES OF EFFECTIVENESS (CRD REPORT 4)

Level	Description
1	Experimental studies (e.g. RCT with concealed allocation)
2	Quasi-experimental studies (e.g. experimental study without randomisation)
3	Controlled observational studies
3a	Cohort studies
3b	Case control studies
4	Observational studies without control groups
5	Expert opinion based on pathophysiology, bench research or consensus.

Experimental

A study in which some conditions, particularly decisions concerning the allocation of participants to different intervention groups, are under the control of the investigator

Randomised controlled trial

Follow-up of participants randomly allocated to intervention or control groups, with a comparison of outcome rates during the time covered. Randomisation (with concealment of allocation sequence) avoids bias because both known and unknown determinants of outcome are on average evenly distributed between intervention and control groups.

Quasi-experimental

A study in which the allocation of participants to different intervention groups is controlled by the investigator but the method falls short of genuine randomisation and allocation concealment.

Observational

A study in which natural variation in interventions or exposure among study participants is investigated to explore the effect of the interventions or exposure on health outcomes.

Cohort study

Comparison of outcomes between participants who have received an intervention and a group that has not (i.e. not allocated by investigator) in a follow-up study.

Case-control study

Comparison of exposure to interventions between participants with the outcome (cases) and those without the outcome (controls).

Cross-sectional study

Examination of the relationship between disease and other variables of interest as they exist in a defined population at one particular time.

Before-and-after study

Comparison of findings in study participants before and after an intervention.

Case series

Description of a number of cases of an intervention and outcome (without comparison with a control group).

HIERARCHY OF ECONOMIC STUDIES

Level	Description
I	Evaluation of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement, and including a clinically sensible sensitivity analysis
2	Evaluation of important alternative interventions comparing a limited number of outcomes against appropriate cost measurement, but including a clinically sensible sensitivity analysis
3	Evaluation of important alternative interventions comparing all clinically relevant outcomes against inappropriate cost measurement, but including a clinically sensible sensitivity analysis
4	Evaluation without a clinically sensible sensitivity analysis
5	Expert opinion with no explicit critical appraisal, based on economic theory

(Sackett D, Straus S, Richardson W, Rosenberg W, Haynes R. Guidelines. In: Sackett D, Straus S, Richardson W, Rosenberg W, Haynes R, editors. *Evidence-based medicine: how to practice and teach EBM*. 2nd ed. Edinburgh: Churchill Livingstone; 2000.)

APPENDIX 2: QUALITY ASSESSMENT CRITERIA

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES

(Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The delphi list a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by delphi consensus. *J Clin Epidemiol* 1998;51:1235-1241.)

1. Was the assignment to the treatment groups really random?

   Adequate approaches to sequence generation
   - Computer-generated random numbers
   - Random numbers tables

   Inadequate approaches to sequence generation
   - Use of alternation, case record numbers, birth dates or week days

2. Was the treatment allocation concealed?

   Adequate approaches to concealment of randomisation
   - Centralised or pharmacy-controlled randomisation
   - Serially-numbered identical containers
   - On-site computer based system with a randomisation sequence that is not readable until allocation
   - Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients

   Inadequate approaches to concealment of randomisation
   - Use of alternation, case record numbers, birth dates or week days
   - Open random numbers lists
   - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include an intention to treat analysis

QUALITY CRITERIA FOR ASSESSMENT OF OBSERVATIONAL STUDIES

Cohort studies

- Is there sufficient description of the groups and the distribution of prognostic factors?
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all important confounding factors?

- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose-response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was follow-up long enough for the outcomes to occur?
- What proportion of the cohort was followed-up?
- Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Case-control studies

- Is the case definition explicit?
- Has the disease state of the cases been reliably assessed and validated?
- Were the controls randomly selected from the source of population of the cases?
- How comparable are the cases and controls with respect to potential confounding factors?
- Were interventions and other exposures assessed in the same way for cases and controls?
- How was the response rate defined?
- Were the non-response rates and reasons for non-response the same in both groups?
- Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
- Was an appropriate statistical analysis used (matched or unmatched)?

Case series

- Is the study based on a representative sample selected from a relevant population?
- Are the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of sub-series are being made, was there sufficient description of the series and
- the distribution of prognostic factors?

QUALITY CRITERIA FOR ASSESSMENT OF QUALITATIVE RESEARCH

Popay et al (Popay J, Rogers A, Williams G. Rationale and standards in the systematic review of qualitative literature in health services research. Qualitative Health Research 1998;8:341-351.)

- A primary marker : is the research aiming to explore the subjective meanings that people give to particular experiences of interventions?
- Context sensitive: has the research been designed in such a way as to enable it to be sensitive/flexible to changes occurring during the study?
- Sampling strategy: has the study sample been selected in a purposeful way shaped by theory and/or attention to the diverse contexts and meanings that the study is aiming to explore?

- Data quality: are different sources of knowledge/understanding about the issues being explored compared?
- Theoretical adequacy: do the researchers make explicit the process by which they move from data to interpretation?
- Generalisability: if claims are made to generalisability do these follow logically and/or theoretically from the data?

Mays and Pope (Mays N, Pope C. Qualitative research in health care. London: BMJ Publishing Group; 1996.)

- Adequate description: Is sufficient detail given of the theoretical framework informing the study and the methods used? Is the description of the context for the study clear? Is there an adequate justification and description of the sampling strategy? Is the description of the fieldwork clear?
- Data analysis: Are procedures for analysis clearly described? Is the analysis repeated by more than one researcher? Are findings from quantitative research used to 'test' qualitative findings? Is there evidence that the researchers have looked for contradictory observations?
- Link to theory: Is the study design and sampling strategy theoretically grounded? Does the link to theory inform the analysis and any claims for generalisability? Is sufficient original evidence provided to support relationship between interpretation and evidence?

BSA Medical Sociology Group (BSA Medical Sociology Group. Criteria for the evaluation of qualitative research papers. Medical Sociology News 1996;22.)

- Are research methods appropriate to the question being asked?
- Is there a clear connection to an existing body of knowledge/wider theoretical framework?
- Are the criteria for/approach to sample selection, data collection and analysis clear and systematically applied?
- Is the relationship between the researcher and the researched considered and have the latter been fully informed?
- Is sufficient consideration given to how findings are derived from the data and how the validity of the findings were tested?
- Has evidence for and against the researcher's interpretation been considered?
- Is the context for the research adequately described and accounted for?
- Are findings systematically reported and is sufficient original evidence reported to justify a relationship between evidence and conclusions?
- Are the researchers clear about their own position in relation to the research topic?

CHECKLIST FOR ASSESSING ECONOMIC EVALUATIONS

(Adapted from Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj. 1996;313(7052):275-83.)

- 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

DATA EXTRACTION SHEET FOR CLINICAL STUDIES

Reference	
Sponsor(s) of the study	
Country	
Research question	
Study Design	
Interventions compared	
Population + inclusion and exclusion criteria	
Patient characteristics (intervention and control group)	
Time horizon	
Health care setting (primary, secondary, tertiary)	
Outcome parameter	
Measurement method outcomes	
Baseline measures	
Statistical analysis techniques, adjustments	
Results:	
Primary outcomes	
Secondary outcomes	
Side effects	
Sensitivity analysis	
Conclusions	
Remarks	Specify weaknesses of the study

DATA EXTRACTION SHEET FOR PHARMACOECONOMIC EVALUATION

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 (Y/N + 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.

ASSESSMENT OF EXTERNAL VALIDITY

This list of issues for external validity has been derived from a paper published by Rothwell in the Lancet 2005; 365:82-93.

Setting of the trial

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

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

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

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

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

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

OUTCOME VALUATION

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 pharmacoeconomic 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 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 drug reimbursement involve 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 outcome measure, broad comparisons across diseases are possible.

Profile measures are less useful for pharmacoeconomic evaluations unless they allow translation into one single index that can then serve as a weight for life years gained. However, apart from the EQ-5D, HUI 2/3 and the SF-36, there are very few profile measures for health-related quality of life that can be translated into an 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, 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 for health states in the assessment of utilities.

There are three major 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-36). The utilities corresponding to these descriptions should be derived from preferences for health states expressed by the general public.

MODELLING

Definition of model structure

The model structure should be presented and described in clear terms. All assumptions and uncertainties (model uncertainties as well as parameter uncertainty) should be disclosed. Specifications should be provided on the sensitivity analyses performed: which variables were included in the sensitivity analysis, what were the distributions assumed for the uncertain parameters, how many Monte Carlo replications were performed …

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:

(a) the criteria for selecting the experts;

(b) the number of experts approached;

(c) the number and identity of experts who participated;

(d) whether a declaration of potential conflict(s) of interest was sought from all experts or medical specialty groups whose opinions were sought;

(e) whether the participants were blinded to the purpose of the study

(f) whether the experts were remunerated for their participation and how

(g) the background information provided and its consistency with the totality of the evidence provided in the submission;

(h) the detailed method that was followed to collect the opinions;

(i) the medium used to collect the opinions (direct interview, telephone interview or self-administered questionnaire, etc…);

(j) the questions asked (with a copy of the questionnaire or an outline of the interview);

(k) whether iteration was used in the collation of opinions and, if so, how it was used;

(l) the number of responses received for each question;

(m) whether all experts agreed with each response, and, if not:

(n) the approach used to finalise the estimates. For example, a Delphi technique could be applied; or the majority opinion, the median, or the mean could be presented.

(o) 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 pharmacoeconomic evaluation and how is dealt with the uncertainty around the expert opinions.

UNCERTAINTY AROUND THE ICER

The ICER is a measure of the additional cost of one intervention over another per unit difference in effectiveness. It usually appears as a point estimate, as no exact method exists to compute the confidence interval (as the ratio of 2 random variables, either of which can take the value zero, may cause statistical problems, due to the instable distribution with discontinuities around zero). However, several methods, based on different assumptions, have already been published and compared in the literature. These methods can be divided in three groups; the parametric approach (such as the confidence box approach, the Taylor series approximation, the Fieller's method) and the non-parametric approach (also called bootstrap) and the Monte Carlo simulations. The non-parametric methods and Monte Carlo simulation are the most commonly used. These methods are described briefly below.

Non Parametric (Bootstrap) Methods

The bootstrap methods do not depend on parametric assumption concerning the sampling distribution of the ICER. It is important that the bootstrap mechanism for the observed data mirror the mechanism by which the original data were obtained. So the bootstrap replicates should be based on the joint sampling costs and effects from patients in the two groups, and then calculating the ICER for each of the bootstrap samples. Once the sampling distribution of the ICER is known, based on the bootstrap replicates, several approaches exist to estimate confidence limits around the ICER:

- *The Normal approximation method*. This method computes the standard error of the ICER based on the bootstrap distribution and assumes that the sampling distribution of the statistic is normal. This method might be seriously misleading if this assumption does not hold.
- *The Percentile method:* This method computes the confidence limits based directly on the sampling distribution of the ICER (percentile values). The advantage is that it is easy to compute, and that it does not depend on any assumption of normality. Some authors have also criticised this approach, on the ground that it assumes that the bootstrap replicates of the ICER are unbiased, while this is not the case.
- *The Bias-Corrected and Accelerated (BCa) percentile method.* This is a modification of the previous method, which seeks to adjust for the bias and skew of the sampling distribution. The percentile computed via the previous method are adjusted algebraically

Monte Carlo Simulations

In that approach, straightforward Monte Carlo simulations of the numerator and denominator of the ratio are performed, on the basis of parametric assumptions and on the observed means and variances of the data.

In addition to the ICER, the uncertainty can also be represented on the CE plane, which can bring additional information. Two methods are recommended: the display of the bootstrap replicates or the ellipses based on the joint normal distribution of the data.

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. 2005) have done an excellent overview of the literature, with some additional research to compare the different methods. A summary of their findings follows, focussing 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 2 of the treatments arms.

Method 2: Adjusted Indirect Comparison. This method has been discussed by Bucher et al, for the case of binary data, but it can be generalized to any kind of data (continuous, time to event, etc..). First, from the 2 RCTs, estimated from treatments effect and their SE 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, etc… . 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 (Glenny et al. 2005).

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 to follow up. This situation has been illustrated graphically by Baker (2002).

APPENDIX 6: FLEMISH EQ-5D INDEX VALUES

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

APPENDIX 7: DRUG REIMBURSEMENT COMMITTEE'S RECOMMENDATION ON NON-INTERVENTIONAL STUDIES

DUTCH VERSION : CTG-AABEVELING OMTRENT NIET-INTERVENTIONELE STUDIES

1. Inhoudstafel

2. Executive summary

Waarom een aanbeveling rond niet-interventioneel onderzoek

De tegemoetkoming voor geneesmiddelen wordt geregeld door het K.B. van 21 december 2001; naast werkzaamheid (efficacy) is hierin doeltreffendheid (effectiveness)-gedefinieerd als het aantonen van een therapeutisch effect in de dagelijkse praktijk-uitdrukkelijk vermeld als parameter ter bepaling van de therapeutische waarde; niet-interventionele studies (proeven zonder interventie in de Belgische Wet van 7mei 2004 omtrent experimenten op de menselijke persoon) kunnen hierbij worden aangewend om zo goed als mogelijk de dagelijkse praktijk te benaderen. Deze aanbeveling richt zich hoofdzakelijk naar niet-interventionele studies, wegens

- de uitermate beperkte regelgeving omtrent dit type studies in vergelijking met de interventionele klinische studies die sinds de opkomst van de Good Clinical Practice (GCP) in Europa in 1991 aanleiding hebben gegeven tot tal van wetgevende en regelgevende initiatieven
- het essentiële methodologisch verschil met interventionele studies door afwezigheid van randomisatie en de daaraan gekoppelde beperkingen qua inferentie
- de geringe ervaring en expertise met dit type studies binnen het kader van de tegemoetkoming

Doel van de aanbeveling rond niet-intervenioneel onderzoek

De aanbeveling poogt in essentie duidelijk te maken waar niet-interventionele studies wel aanleunen bij interventionele studies en waar ze wezenlijk verschillen met interventionele studies; het aangenomen perspectief is dat van iedere belangstellende (aanvrager, Commissie, …) betrokken bij dit soort studie in het kader van de procedure tot tegemoetkoming; de focus ligt op een voorstel tot methodologische aanpak met vereisten voor kwaliteitscontrole bij opzet, uitvoering, analyse en rapportering van dit type studies; de focus ligt niet op het uitdiepen van klinische, statistische of epidemiologische expertise.

Toepassingsgebied

Deze aanbeveling is van toepassing op alle niet-interventioneel onderzoek, voorgelegd ter ondersteuning van aanvragen tot tegemoetkoming, ongeacht de gekozen studiedesign.

Meer in het bijzonder is ze van toepassing op :

- de individuele klasse I – herzieningen zoals beschreven in het K.B. VAN 21/12/2001
- initiële aanvragen voor klasse 1 en 2, bij studies omtrent "ervaring met het product", zoals beschreven in de aanbeveling voor indienen van een klasse 1 of 2-aanvraag, punt 5.3

Opbouw

De aanbeveling omvat volgende secties:

- introductie en rationale: situering van niet-interventionele studies en hun actuele regelgeving in het kader van de tegemoetkoming en van de Belgische Wet omtrent experimenten op de menselijke persoon
- Kernbegrippen bij niet-interventioneel onderzoek vanuit methodologische perspectief
- Kwaliteitscriteria voor opzet, uitvoering, analyse en rapportering

Sleutelelementen van de aanbeveling

- **Niet-interventioneel onderzoek is niet-experimenteel onderzoek** en onderscheidt zich bij gevolg van experimenteel onderzoek (bv. de RCT of randomized controlled trial) doordat de blootstelling aan één of ander agens niet experimenteel kan worden toegewezen; het gevolg is dat een **oorzakelijk verband** tussen een welbepaalde gebeurtenis en een voorafgaande blootstelling aan een bepaald agens **niet met zekerheid** kan worden gesteld.
- Niet-interventionele studies zijn **geen alternatief** voor interventionele klinische studies. De keuze van een specifiek niet-interventioneel onderzoeksontwerp (design) wordt bepaald door de specifieke onderzoeksvraag en de onderzoekscontext.
- Fysieke integriteit van de patiënt en gegevensintegriteit verdienen in se dezelfde aandacht bij niet-interventioneel als bij interventioneel onderzoek, zij het via een aangepaste aanbeveling, in lijn met
- de wet inzake experimenten op de menselijke persoon
- de wet op de bescherming van de privé levenssfeer

Aan deze aanbeveling werkten mee

Eerste fase / groep van deskundigen:

Marc Bogaert, Michel Boutsen, Ralph Crott, Alain Dupont, Geert Molenberghs, Hugo Robays, Joost Weyler (Voorzitter)

Tweede fase / Commissieleden:

Marc-Henry Cornely, Jean Creplet, Alain Dupont, Heidi Goethals, Herwig Proesmans, Hugo Robays, François Sumkay, Herman Van Eeckhoudt

Interne evaluatoren: Pierre Chevalier, Gert Verpooten & Philippe Van Wilder (Secretaris)

3. Introductie

De Commissie Tegemoetkoming Geneesmiddelen maakt voorstellen tot tegemoetkoming van geneesmiddelen conform het K.B. van 21 december 2001; dit K.B. vermeldt expliciet dat het geheel van studies ingediend ter ondersteuning van een aanvraag tot tegemoetkoming moet gericht zijn naar :

- **werkzaamheid** (efficacy): waarbij een farmacologische werking, bij toepassing in klinisch onderzoek, tot therapeutisch effect leidt
- **bijwerkingen**
- **doeltreffendheid** (effectiveness): indien specialiteit werkzaam en, bij toepassing in de dagelijkse praktijk, leidt dit tot therapeutisch effect
- **toepasbaarheid**: de mate waarin de eigenschappen van een specialiteit (contra-indicaties, overgevoeligheid, …) het gebruik bij verschillende rechthebbenden of door verschillende zorgverleners beperkt
- **gebruiksgemak**: de wijze waarop een specialiteit door de zorgverlener en/of de rechthebbende kan worden gebruikt zodanig dat het comfort van toediening kan worden verbeterd en/of fouten en vergissingen bij gebruik kunnen worden vermeden

Het geheel van deze 5 elementen wordt in overweging genomen (K.B. 21 dec 2001) ten einde de **therapeutische waarde** van een geneesmiddel te bepalen; de bepaling van de therapeutische waarde omvat derhalve

- één of meerdere "**Randomized Controlled Trials**" (RCT), studies met minstens één controlegroep, gericht naar werkzaamheid evenals veiligheid wat betreft niet zeldzame nevenwerkingen;
- één of meerdere studies gericht naar doeltreffendheid, zeldzame nevenwerkingen, toepasbaarheid en gebruiksgemak, zoals ze zich voordoen in de "**dagelijkse praktijk**".

De informatie die in een initiële aanvraag vervat zit, is vaak beperkt tot werkzaamheid en veiligheid uit klinische studies (= vereiste voor registratie); bovendien kunnen de eindpunten uit klinisch onderzoek intermediair zijn en is het op dat ogenblik onduidelijk welk effect de behandeling heeft op mortaliteit, morbiditeit of levenskwaliteit, parameters die vooropgesteld worden door het K.B.

Studies met betrekking tot de effecten van behandeling in de dagelijkse praktijk, beogen de therapeutische waarde te onderzoeken in omstandigheden die de interacties tussen arts en patiënt zo natuurgetrouw mogelijk weergeven.Deze laatste soort studies zijn vaak (maar hoeven niet per se) "niet-interventioneel" zoals gedefinieerd in de Belgische Wet van 7 mei 2004 omtrent experimenten op de menselijke persoon.

Uit wat voorafgaat is dus duidelijk dat **beide soort studies zich niet aan mekaar kunnen substitueren maar eerder complementair zijn**.

N.Black, 'Why we need observational studies to evaluate the effectiveness of health care', BMJ 1996;312:1215-1218

N.Black, 'What observational studies can offer decision makers', Horm Res 1999;51(suppl 1):44-49

S.MacMahon, R.Collins, 'Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies', Lancet 2001;357:455-462

Ten slotte, **doelmatigheid** (efficiency) of de verhouding tussen de therapeutische waarde en de netto economische weerslag van een specialiteit, is bovendien vereist voor klasse-1 aanvragen;ook hier is kennis omtrent effekten en kosten in reële omstandigheden van primordiaal belang.

D.A.Revicki, L.Frank, 'Pharmacoeconomic evaluation in the real world', Pharmacoeconomics 1999;15(5):423-434

Niet-interventionele studies verschillen onder meer van interventionele klinische studies in de zin dat:

- Ervaring met klinische studies is aanzienlijk en dergelijke studies zijn uitvoerig beschreven en gereglementeerd op basis van **Good Clinical Practice (**GCP) Richtlijnen; er bestaat tot nog toe geen GCP-equivalente reglementering omtrent niet-interventioneel onderzoek;de Europese Directive omtrent klinisch onderzoek (2001/20/EG) heeft wel aanleiding gegeven tot de Belgische Wet (7 mei 2004) inzake experimenten op de menselijke persoon; deze wet in het bijzonder legt het juridisch onderscheid vast tussen "**klinische proeven**" enerzijds en "**proeven zonder interventie**" anderzijds.
- Methodologisch is er een wezenlijk verschil ***doordat de blootstelling aan één of ander agens niet experimenteel kan worden toegewezen*** (= geen randomisatieprincipe!); één der belangrijke gevolgen is dat de evidentiegraad van dergelijke niet-interventionele studies als lager wordt beschouwd dan deze van gecontroleerde interventionele studies (zie bijvoorbeeld de Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)).
- Het oorzakelijk verband tussen het waargenomene en de ingestelde behandeling kan niet worden aangetoond en er zijn meerdere voorbeelden waarbij effekten afgeleid uit niet-interventioneel onderzoek later werden tegengesproken door interventioneel onderzoek (denken we maar aan de effekten van hormonale substitutietherapie bij menopausale vrouwen: BCFI, 'Themanummer: Hormonale Substitutie: stand van zaken in 2003', Folia Pharmacotherapeutica 2003;30(10):82-90).
    - Langs de zijde van de aanvrager, maakt het pre-registratie klinisch onderzoek vaak deel uit van een internationaal onderzoeksprogramma van de internationale R&D centra die instaan voor:
    - opzet, uitvoering, analyse en rapportering van de studies conform eigen *standard operating procedures* (SOPs)
    - financiering van de studie (onderzoekers, geneesmiddelen, personeel, archivering, expertise (klinisch, statistisch, bibliografisch, regulatory, kwaliteitscontrole, …)

De niet-interventionele studie daar tegenover is vaak op initiatief van het lokale filiaal dat zowel voor de nodige budgettering zal moeten instaan als voor de noodzakelijke expertise en kwaliteitscontrole.

Niet-interventionele studies zijn dus <u>geen alternatief</u> voor interventionele klinische studies.

De keuze van een specifiek niet-interventioneel onderzoeksontwerp (design) wordt bepaald door de onderzoeksvraag en de onderzoekscontext (m.a.w. het studieobject), net zoals bij interventioneel onderzoek.

N.Black, 'Why we need observational studies to evaluate the effectiveness of health care', BMJ 1996;312:1215-1218

Deze aanbeveling richt zich, wegens de hierboven aangehaalde punten, voornamelijk naar niet-interventionele studies: het aangenomen perspectief is dat van iedere belangstellende (aanvrager, Commissie, …) betrokken bij dit soort studie in het kader van de tegemoetkomingsprocedure; de focus ligt op een voorstel tot methodologische aanpak en niet op het uitdiepen van klinische, statistische of epidemiologische expertise.

Ze omvat:

- een zeer beknopt overzicht van methodologische beschouwingen en gangbare studiedesigns in dit domein: dit is enkel ter illustratie om de mogelijkheden binnen het niet-interventioneel studiegebied te schetsen.

- een uitgebreid overzicht van de noodzakelijke elementen voor kwaliteitscontrole die bij iedere niet-interventionele studie in overweging dienen te worden genomen, en dit bij
    - o het opstellen van de onderzoeksvraag
    - o het vastleggen van de studiedesign
    - o de uitvoering van de studie
    - o de gegevensverwerking en de statistische analyse als bij
    - o de rapportering van de studieresultaten

4. Toepassingsgebied :

Deze aanbeveling is van toepassing op alle niet-interventioneel onderzoek, voorgelegd ter ondersteuning van aanvragen tot tegemoetkoming, ongeacht de gekozen studiedesign.

Meer in het bijzonder is ze van toepassing op :

- de klasse I – herzieningen
- initiële aanvragen voor klasse 1 en 2, bij studies ter ondersteuning van punt 5.3 omtrent "ervaring met het produkt".

5. Methodologische beschouwingen en gangbare studiedesigns

Niet-interventioneel onderzoek is niet-experimenteel onderzoek en onderscheidt zich bij gevolg van experimenteel onderzoek (bv. De RCT of randomized controlled trial) ***doordat de blootstelling aan één of ander agens niet experimenteel kan worden toegewezen*** ; het gevolg is dat een **oorzakelijk verband** tussen een welbepaalde gebeurtenis en een voorafgaande blootstelling aan een bepaald agens niet met zekerheid kan worden gesteld. Meerdere verklarende factoren kunnen simultaan aanwezig zijn en het effekt van de ene factor kan door het effekt van een andere factor worden gemaskerd.

Bv. Het statistisch verband tusseen luciferconsumptie en longkanker wordt verklaard door een vermenging met het effekt van roken!

Heel wat observationeel onderzoek wordt beschreven en gedefinieerd in de context van etiognostisch (etiologisch) onderzoek. Hierdoor wordt vaak verwezen naar het voorkomen van ziekte als afhankelijke variabele. Dit is nauw gerelateerd aan de traditionele definitie van de epidemiologie (studie naar voorkomen van ziekte…).

Doelstellingen van niet- interventioneel onderzoek:

Bestuderen van het voorkomen van gebeurtenissen (ziekte, sterfte, hospitalisatie, werkhervatting, …) in functie van determinanten (naast behandeling ook: leeftijd, geslacht, comorbiditeit, …).

Keuze van design type

Zoals eerder vermeld, wordt de keuze van een specifiek niet-interventioneel onderzoeksontwerp bepaald door de onderzoeksvraag en de onderzoekscontext.

Studiedesigns die in het kader van deze aanbeveling van bijzonder belang zijn

- Cohort & longitudinale studies
- Case control studies
- Cross sectionele studies
- Case series & historical control studies

Een meer uitgebreide bespreking van de verschillende studiedesigns vindt men in de basistekst van de werkgroep der externe experten (zie bijvoegsel); het verdient sterk de aanbeveling om het formuleren van studiehypothesen en de daaraan verwante keuze van studiedesigns, in nauw overleg met experten in het domein uit te voeren.Bijzondere aandacht is telkens vereist bij:

- De externe validiteit (= veralgemeenbaarheid) is de mate waarin de resultaten van de studie kunnen worden veralgemeend naar de algemene populatie: deze is sterk afhankelijk van de gebruikte steekproef-methoden;
- Interne validiteit: Bias is een systematische afwijking tussen de bekomen resultaten en de reële populatiewaarde: het beïnvloedt derhalve op een negatieve manier de validiteit; er zijn verschillende vormen van bias mogelijk en de voornaamste zijn selectiebias (bij case-control studies is de keuze van de controlegroep bijzonder kritisch), informatiebias en verstoring (zie ook de Cochrane Reviewers ' handbook (versie 4.2.0 pp.47-50).

Gevorderde statistische analysetechnieken zijn bij niet-interventioneel onderzoek nodig om de resultaten te corrigeren voor optredende verstoring; op hun best kunnen deze analysetechnieken corrigeren voor de effekten van gekende interfererende factoren; ze kunnen, in tegenstelling tot de randomisatie, niet corrigeren voor ongekende interfererende faktoren.

D.A.Grimes, K.F.Schulz, 'Bias and causal associations in observational research', Lancet 2002;359:248-252

- In principe gaat het bij deze 'niet-interventionele' studies over niet experimenteel onderzoek dat desondanks een hoge validiteit moet opleveren met een optimale efficiëntie.

6. Kwaliteitscriteria

De inspiratiebron voor deze kwaliteitscriteria voor niet-interventioneel onderzoek is de "Good Clinical Practice" richtlijn zoals deze in Europa sinds 1991 stapsgewijs werd ingevoerd

- CPMP GCP-aanbeveling in Europa in 1991
- ICH-Guideline for Good Clinical Practice in jan 1997
- Europese Directive omtrent klinisch onderzoek (2001/20/EG)
- Belg. Wet van 7 mei 2004

ICH Guideline on Good Clinical Practice (GCP) (http://www.emea.europa.eu/Inspections/GCPgeneral.html)

Bovendien werd de aanbeveling voor pharmaco-epidemiologisch onderzoek van de International Society for Pharmaco-epidemiology (ISPE, revised aug.2004) eveneens geraadpleegd (zie bijlage).

Good Clinical Practice legt de nadruk op de bescherming van de fysieke integriteit van de patiënt en op de integriteit van de studiegegevens :

" Compliance with this standard (= GCP) provides public assurance that the **rights, safety and well-being of trial subjects** are protected, consistent with the principles that have their origin in the Declaration of Helsinki**, and that the clinical trial data are credible**."

(from: ICH Topic E6 CPMP/ICH/135/95, Introduction)

Fysieke integriteit van de patiënt en gegevensintegriteit verdienen in se dezelfde aandacht bij niet-interventioneel onderzoek, zij het via een aangepaste aanbeveling, in lijn met

- de wet inzake experimenten op de menselijke persoon
- de wet op de bescherming van de privé levenssfeer

Bij uitvoeren van klinisch interventioneel onderzoek is de ICH-Guideline for Good Clinical Practice en zijn afgeleiden van toepassing; ICH harmonised tripartite guideline, E6, Guideline for good clinical practice .

De Belgische Wet van 7 mei 2004 omtrent experimenten op de menselijke persoon en haar uitvoeringsbesluiten, zijn van toepassing op zowel interventioneel als niet-interventioneel onderzoek uitgevoerd op de menselijke persoon.

6.1. Aanvraag tot individuele herziening

In het kader van de klasse-1 herzieningen, kan de Commissie zich tot de aanvrager richten om bijkomende studies op te zetten en uit te voeren, die een antwoord moeten bieden aan de op het moment van het initiële voorstel tot tegemoetkoming nog aanwezige vragen omtrent de therapeutische en/of economische waarde van het betrokken geneesmiddel. De Commissie identificeert de criteria en resterende factoren van onzekerheid die het opgelost wil zien bij de herziening. De indiener kan autonoom beslissen hoe zij de resterende vragen van de CTG willen oplossen; hierbij rekening houdend met de aanbevolen methodologie in de richtlijnen voor farmaco-economische evaluaties in België.

Deze studies kunnen zowel interventioneel als niet-interventioneel zijn; het verdient derhalve aanbeveling

- om in dit stadium de eventuele onderzoeksvragen en –context, op basis van de voorgestelde herzieningscriteria, zo precies en zo expliciet mogelijk te formuleren
- de argumentatie op te bouwen en te beschrijven die geleid hebben tot de formulering van onderzoeksvraag, studiedesign, studiepopulatie en studie-eindpunten; afwijkingen ten opzichte van het randomisatieprincipe dienen in het bijzonder te worden toegelicht.

6.2 Uitvoering van niet-interventionele studies

6.2.1 Protocol

Elke studie moet een schriftelijk protocol bevatten.
Het protocol moet minstens volgende elementen bevatten:

1. Een beschrijvende titel en identificatie van de versie (bv. datum);
2. De namen, titels, graden, adressen van alle verantwoordelijke partijen en hun organisaties;
3. De naam en het adres van elke opdrachtgever en zijn afgevaardigde(n);
4. Een opsomming van de onderzoeksdoelstellingen, specifieke studiehypothesen (a priori en a posteriori) en –eindpunten (met hun prioriteit) evenals de rationale voor het onderzoek;
5. Een beschrijving van de onderzoeksmethodes, met inbegrip van;
   - onderzoeksdesign met argumentatie om het voorgestelde studiedesign te kiezen
   - De populatie die moet worden bestudeerd
   - De populatie wordt gedefinieerd in termen van personen, plaats, tijdsperiode en selectiecriteria. De rationale voor de inclusie- en exclusiecriteria en de impact ervan op het aantal personen die beschikbaar zijn voor analyse moet worden beschreven.
   - De gebruikte methode voor de steekproeftrekking
   - Bepaling en definiëring van de eindpunten van de studie waarbij zoveel mogelijk gevalideerde meetinstrumenten worden gebruikt
   - Methodes voor gegevensbeheer met o.a.;

- Beschrijving van de gegevensbronnen
- Procedures voor gegevensbeheer, van inzameling tot goedgekeurde database
- Procedures om inconsistenties of fouten te corrigeren, het inbrengen van waarden of het wijzigen van ruwe gegevens
- Methodes voor gegevensanalyse met o.a.;
- Geplande omvang van de studie, statistische precisie en de basis voor de bepaling hiervan
- Voorstelling van de te gebruiken statistische methoden en hun rationale
- Bespreking van statistische technieken om te corrigeren voor bias
- Bespreking van de studie beperkingen inzake design, verloop en analyse.
- Er moet minstens rekening worden gehouden met eventuele tekortkomingen op statistisch, epidemiologisch, therapeutisch en/of economisch vlak en een bespreking van hun impact op de interpretatie van de verwachtte resultaten.

6. Een beschrijving van de procedures voor kwaliteitsverzekering en kwaliteitscontrole voor alle fasen van de studie;
7. Het voorgestelde studieverloop met de studietaken opgesplitst per fase met tijdsschema;
8. Een kritische literatuurreview om pertinente informatie en kennislacunes die verband houden met de studiehypothese en kritische elementen betreffende de veiligheid te beoordelen;
9. Maatregelen ter bescherming van de fysieke integriteit van de menselijke persoon;

Dit hoofdstuk moet informatie bevatten over

- het indienen van het protocol ter goedkeuring door onafhankelijke Ethische Comités
- Het toestemmingsformulier van de studiedeelnemer dient in overeenstemming zijn met de plaatselijke wetgeving onder andere omtrent de voorzorgen om de vertrouwelijkheid van informatie over deelnemers te behouden, met inbegrip van de potentiële omstandigheden waaronder identifieerbare persoonlijke informatie aan entiteiten buiten de studie kan worden bezorgd.
- de vraag of studiepersonen ten gevolge van de studie in gevaar zullen worden gebracht; indien de studie een bijkomend risico inhoudt, dan dient het vereiste toestemmingsformulier dit uitdrukkelijk te vermelden.
- De omstandigheden waaronder de studie kan worden stopgezet ("stopping rules") moeten worden vastgelegd en de aan te wenden procedures moeten worden beschreven.

10. Een beschrijving van plannen om studieresultaten mee te delen en te verspreiden;

Er bestaat een ethische plicht om bevindingen die een potentieel wetenschappelijk belang of een belang voor de volksgezondheid hebben, mee te delen.

Manuscripten dienen te worden opgesteld volgens de richtlijnen die zijn opgesteld door het International Committee of Medical Journal Editors (http://www.icmje.org/).; studierapportering dient in lijn te zijn met de principes van de "Consolidated Standards of Reporting Trials (CONSORT) " statement of afgeleiden (http://www.consort-statement.org/statement/revisedstatement.htm).

Potentiële belangenconflicten moeten aan het licht worden gebracht. Het akkoord om deze richtlijnen na te leven moet in het protocol worden beschreven.

6.2.2 Verantwoordelijkheden

De organisaties en personen die het onderzoek leiden en sponsoren zijn volledig verantwoordelijk voor het onderzoek. De onderlinge relaties, de rol, de studietaken en de verantwoordelijkheden van de organisaties en/of personen die de studie leiden en sponsoren moeten worden beschreven evenals van personen en/of organisaties die deze studietaken uitvoeren in opdracht van de opdrachtgever (hierna contractanten genoemd bv. academische instellingen, project gebonden externe organisaties, …).

De taken en verantwoordelijkheden moeten duidelijk zijn afgebakend tussen de opdrachtgever van de studie en de contractant(en) inzake opzet en uitvoering van de verschillende aspecten van de studie waaronder het eigendom en de archivering van de gegevens.

Personeel

Het personeel dat epidemiologische research en hiermee samenhangende activiteiten uitvoert, zowel dat van de opdrachtgever als dat van de contractant, moet de nodige opleiding, training en/of ervaring hebben om de toegewezen opdrachten op bekwame wijze uit te voeren. De organisatie moet een bijgewerkte samenvatting bijhouden van de opleiding en ervaring van die personeelsleden. Een lijst van personen die activiteiten uitvoeren of superviseren moet worden bijgehouden en regelmatig bijgewerkt, met vermelding van hun huidige functie(s).

Bescherming van personen

Voor alle research waarbij mensen betrokken zijn moet vooraf een onafhankelijke Ethische Commissie zijn goedkeuring verlenen en een 'informed consent' moet worden bekomen voor iedere studiedeelnemer, conform de Belgische wet op de bescherming van de persoonlijke levenssfeer; indien de studie een bijkomend risico inhoudt, dan dient het vereiste toestemmingsformulier dit uitdrukkelijk te vermelden.

6.2.3 Studieverloop

De opdrachtgever van de studie zal in het finaal studierapport informatie geven over het tijdsverloop van de studie, vanaf de eerste indiening van het protocol bij een Ethische Commissie, via de eerste en laatste studiedeelnemer die tot de studie toetreedt en ze verlaat, tot het schrijven en kenbaar maken van het finaal studierapport en publicaties.

De ongewone beslissing om een studie voortijdig stop te zetten moet gebaseerd zijn op deugdelijke wetenschappelijke en ethische redenen en schriftelijk worden gedocumenteerd en deze beslissing met argumentatie moet worden overgenomen in het final studierapport.

Gegevensinzameling, gegevensbeheer en gegevenscontrole

De personen die verantwoordelijk zijn voor de integriteit van de gegevens, zowel geïnformatiseerde gegevens als gegevens op papier, moeten worden geïdentificeerd en moeten de nodige opleiding, training en ervaring hebben om de hen toegewezen taken te vervullen.

Alle toegepaste procedures om de kwaliteit en de integriteit van de gegevens te verzekeren, van bij de gegevensbron tot de gevalideerde gegevensbank met bijhorend studierapport, moeten voldoende gedetailleerd worden uitgewerkt, zodat anderen ze kunnen herhalen. Er moet een historisch dossier van deze procedures worden bijgehouden, inclusief alle herzieningen en de data ervan.

De gevalideerde gegevensbank dient te worden gearchiveerd en de toegang ertoe dient zodanig te worden gereglementeerd dat iedere toegang kan worden getraceerd met vermelding van o.a. datum, naam van de betrokkenen, aangebrachte wijzigingen en reden voor toegang.

Analyse

Alle programma's voor gegevensbeheer en statistische analyse die in de analyse worden gebruikt, moeten gedocumenteerd en gearchiveerd worden. Een getekend exemplaar van het statistisch analyse plan en analyse rapport dient eveneens te worden gearchiveerd.

Studieverslag

De studie moet worden samengevat in een eindverslag dat de doelstellingen, methoden en resultaten van de studie en de interpretatie van de bevindingen op accurate en volledige wijze weergeeft.

De rapportering dient te gebeuren **naar de geest** van de aanbeveling ICH HARMONISED TRIPARTITE GUIDELINE document E3 on "STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS".

Het eindverslag moet hierbij minstens het volgende omvatten:

- Een beschrijvende titel;
- Een samenvatting van de voornaamste studieresultaten conform het protocol;
- Doel (doelstellingen) van het onderzoek, zoals in het protocol is vermeld;
- De namen, titels, graden, adressen en organisaties van de hoofdonderzoeker en alle co-onderzoekers;
- Naam en adres van elke opdrachtgever en contractant;
- Data waarop de studie is begonnen en beëindigd;
- Inleiding met achtergrond, doel en specifieke doelstellingen van de studie;
- Een beschrijving van de onderzoeksmethoden, inclusief doelpopulatie en selectie van de steekproef;
- Methodes voor gegevensinzameling ;
- Belangrijke transformaties, berekeningen of bewerkingen op de gegevens toegepast; beschrijving van de beperkingen van de ingezamelde gegevens (bv. ontbrekende of onvolledige gegevens);
- Statistische methoden gebruikt in de gegevensanalyse;
- Gegevensanalyse met voldoende beschrijvende statistieken (parameters van spreiding en positie, verdelingstabellen, -grafieken en illustraties) om de pertinente gegevens voor te stellen, gekoppeld aan aangepaste vergelijkende statistische analyses ;
- Een overzicht van de conclusies uit de gegevensanalyse;
- Geaggregeerde studieresultaten omtrent de veiligheid van de gebruikte behandelingen;
- Een bespreking van de implicaties van de studieresultaten met vermelding van vroeger onderzoek dat de huidige bevindingen ondersteunt of tegenspreekt; *b*espreking van mogelijke bias of beperkingen van het huidig onderzoek;
- Een beschrijving van de toegepaste procedures voor controle van de kwaliteit en de integriteit van de gegevens ;
- Referenties;

Communicatie

Er bestaat een ethische plicht om bevindingen die een potentieel wetenschappelijk belang of een belang voor de volksgezondheid hebben, te verspreiden; studieresultaten zullen worden kenbaar gemaakt door publicatie in de wetenschappelijke literatuur, bij

voorkeur in een 'peer-reviewed' tijdschrift. De auteurs van studieverslagen moeten de richtlijnen volgen die zijn opgesteld door het International Committee of Medical Journal Editors (http://www.icmje.org/). Alle auteurs moeten beantwoorden aan de criteria voor auteurschap en alle mensen die hieraan voldoen moeten auteur zijn. Potentiële belangenconflicten moeten aan het licht worden gebracht. Het akkoord om deze richtlijnen na te leven moet in het protocol worden beschreven.

Meedelen van ongewenste gebeurtenissen (adverse events)

De bevindingen van epidemiologische studies over gezondheidsrisico's die gepaard gaan met geneesmiddelen moeten door de farmaceutische opdrachtgevers worden meegedeeld aan officiële instanties, overeenkomstig de Belgische Wet van 7 mei 2004 omtrent experimenten op de menselijke persoon en haar uitvoeringsbesluiten .

De geaggregeerde studieresultaten omtrent de veiligheid van de gebruikte behandelingen dienen in het eindverslag van het studierapport voor te komen.

Archivering

Er moeten beveiligde archieven worden bijgehouden voor het ordelijk opslaan en het snel terugvinden van alle materiaal dat op de studie betrekking heeft.

Het archief moet minstens gedurende **tien jaar** worden bijgehouden na het eindverslag of de eerste publicatie van het geheel van de studieresultaten, afhankelijk van wat eerst komt. Het archief van de studie moet minstens volgende elementen bevatten of ernaar verwijzen:

- Het studieprotocol en alle goedgekeurde wijzigingen;
- De vervolledigde studie inzamelingsformulieren voor iedere studiedeelnemer;
- Het eindverslag van de studie;
- Een uitgeprint staal van de relevante studiegegevens (zijnde deze die in het protocol, het statistisch analyseplan of het eindverslag van de studie worden vermeld);
- De gevalideerde gegevensbank met de ruwe gegevens die de basis vormden voor de eindanalyse van de studie. Kopieën van de elektronische versies van analytische gegevensbestanden en programma's, computer print-outs, indien mogelijk met de relevante uitvoeringscode, die de basis vormen van alle tabellen, grafieken, discussies en interpretaties in het eindrapport;
- Alle briefwisseling over de studie, de standaard werkprocedures, de formulieren voor informed consent, de kopieën van de ondertekende dokumenten van de Ethische Commissies en kopieën van alle rapporten in verband met kwaliteitscontrole en externe audit;
- De communicatie van studieresultaten aan de opdrachtgever, de beslissingnemers en de wetenschappers moet worden gedocumenteerd;

6.2.4 Materiaal te overhandigen aan de Commissie

Alle persoonsgerelateerde gegevens moeten worden geanonimiseerd overeenkomstig de wet op de bescherming van de persoonlijke levenssfeer.

De volgende elementen moeten op het einde van de studie aan de Commissie worden bezorgd:

- lijst van de deelnemende centra, met inbegrip van de hoofdonderzoekers en co-onderzoekers;
- de aantallen gescreende en geregistreerde patiënten per centrum;
- lijst van alle contractanten, meewerkende instellingen en andere relevante studiesites;
- het studieprotocol en de eventueel bijgewerkte versies;

- een kopij van de blanco formulieren voor gegevensinzameling;
- het eindverslag van de studie;
- een kopie van de gevalideerde gegevensbank in een voor analyse toepasselijk formaat;

7. Bijlagen

Bijlage 1 : Referenties omtrent (pharmaco)epidemiologie (uit de basistekst van externe experten)

1 J. M. Last, A dictionary of Epidemiology, Oxford University Press1995
2 M.H. Gail, J. Benichou, Encyclopedia of Epidemiologic Methods, Wiley 1999
3 K. Rothman, S. Greenland, Modern Epidemiology, Lippincott – Raven 1998
4 O.S. Miettinen, Theoretical Epidemiology. Principles of occurrence research in medicine. Wiley 1985
5 ICH Topic E6 CPMP/ICH/135/95. Harmonised Tripartite guideline for Good Clinical Practice, januari 1997
6 European Directive on Implementing Good Clinical Practice; Directive 2001/20/EC
7 Belgische Wet inzake experimenten op de menselijke persoon van 7 mei2004

Longitudinale data:

8 Verbeke, G. and Molenberghs, G. (2000). Linear Models for Longitudinal Data. New York: Springer Verlag. 568 pages. ISBN 0-387-95027-3
9 Fahrmeir L. and Tutz G. (2001) Multivariate Statistical Modelling Based on Generalized Linear Models. New York: Springer Verlag. 517 pp. ISBN 0-387-94233-5 (?)
10 Diggle P, Heagerty P, Liang KY and Zeger S (2002). Analysis of Longitudinal Data. Oxford Press. 350 pp. ISBN 0-198-52484-6

Algemeen naslagwerk:

11 Ström "Pharmacoepidemiology" Wiley, third edition 2000

Bijlage 2: Extract uit Wet van 7 mei 2004:

«**klinische proeven**»: elke onderzoek bij proefpersonen dat bedoeld is om de klinische, farmacologische en/of andere farmacodynamische effecten van één of meer experimentele geneesmiddelen vast te stellen of te bevestigen, en/of eventuele ongewenste effecten van een of meer experimentele geneesmiddelen aan te tonen en/of de absorptie, de distributie, het metabolisme en de eliminatie van een of meerdere experimentele geneesmiddelen te bestuderen, teneinde de veiligheid en/of de werkzaamheid ervan vast te stellen;
«**proef zonder interventie**»: studie binnen het kader waarvan het of de geneesmiddel(en) op een gebruikelijke manier zijn voorgeschreven, conform de in de toestemming om op de markt te worden gebracht bepaalde voorwaarden. De aanwijzing van de patiënt voor een gegeven therapeutische strategie is niet bij voorbaat vastgelegd door een proefprotocol, doch maakt deel uit van een courante praktijk, terwijl de beslissing om het geneesmiddel voor te schrijven volledig losstaat van deze die het opnemen van de patiënt in de studie betreft. Geen enkele bijkomende procedure inzake diagnose of bewaking moet op de patiënt worden toegepast, terwijl epidemiologische methodes worden gebruikt om de ingezamelde gegevens te analyseren.

Bijlage 3 : Volledige basistekst van externe experten
enkel na specifieke aanvraag

Bijlage 4 : Wet van 7 mei 2004
via internetadres:
ttps://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/GENEESMIDDELEN1_MENU/LISTEDESLOISETARRETES1_HIDE/LISTEDESLOISETARRETES1_DOCS/LOI-WET-2004-05-07_0.PDF

Bijlage 5 : ISPE aanbeveling van aug 2004
via internetadres: http://www.pharmacoepi.org/resources/guidelines_08027.cfm

Bijlage 6 : ICH GCP document E6
via internetadres: http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254

Bijlage 7 : Cochran e Reviewer's handbook:
bias definitions / via internetadres http://www.cochrane.org/admin/manual.htm

FRENCH VERSION : RECOMMANDATIONS DE LA CRM AU SUJET D'ETUDES NON-INTERVENTIONNELLES

1. Sommaire

2. Résumé Exécutif

Pourquoi une recommandation au sujet d'études non-interventionnelles

Le remboursement de médicaments est réglementé par l'A.R. du 21 décembre 2001;

À côté de l'efficacité (efficacy), l'utilité (effectiveness) est clairement mentionnée pour la détermination de la valeur thérapeutique ; elle est définie comme l'atteinte du but escompté du traitement, non pas dans la pratique strictement réglementée des essais cliniques, mais en pratique quotidienne.

Les études non-interventionnelles (essais sans intervention dans la Loi Belge du 7 mai 2004 concernant les expérimentations sur la personne humaine) peuvent être utilisées afin de refléter au mieux la pratique quotidienne.

Cette recommandation s'adresse principalement aux études non-interventionnelles, en raison de :

- la réglementation extrêmement restreinte concernant ce type d'études par rapport aux études cliniques interventionnelles qui ont été sujet, depuis l'introduction des Bonnes Pratiques Cliniques (GCP) en Europe en 1991, d'innombrables initiatives législatives et de réglementation
- la différence méthodologique essentielle avec les études interventionnelles par l'absence de randomisation et des restrictions qui y sont liées au niveau de l'inférence
- la faible expérience et expertise avec ce type d'études dans le cadre du remboursement

But de la recommandation au sujet d'études non-interventionnelles

La recommandation tente à éclaircir là où les études non-interventionnelles diffèrent singulièrement des études interventionnelles et là où elles sont essentiellement similaires aux études interventionnelles ;

La perspective adoptée est celle de toute partie intéressée (demandeur, Commission,…) impliquée dans ce type d'étude dans le cadre de la procédure de remboursement ; l'accent est mis sur une proposition d'approche méthodologique avec des exigences pour le contrôle de qualité dans l'organisation, l'exécution, l'analyse et l'écriture de rapport de ce type d'étude, et non sur l'approfondissement de l'expertise clinique, statistique ou épidémiologique.

Champ d'application

Cette recommandation est d'application pour toute étude non-interventionnelle, présentée comme support aux demandes de remboursement, malgré le design d'étude choisi.

Plus particulièrement elle s'applique à :

- la classe I - les révisions individuelles comme décrites dans l'A.R. du 21/12/2001
- des demandes initiales pour les classes I et 2, lors d'études concernant « expérience avec le produit », comme décrit dans les recommandations pour l'introduction d'un dossier classe I ou 2, point 5.3

Structure

La recommandation contient les sections suivantes :

- introduction et rationnel : situation des études non-interventionnelles et de leur réglementation actuelle dans le cadre du remboursement et de la loi belge concernant les expérimentations sur la personne humaine
- Les notions clés de la recherche non-interventionnelle dans une perspective méthodologique
- Les critères de qualité pour l'organisation, l'exécution, l'analyse et l'écriture de rapport de ce type d'étude

Eléments clés de la recommandation

- Etude non-interventionnelle signifie étude non expérimentale et se discerne par conséquent de la recherche expérimentale (p.e. les études RCT ou randomized controlled trial) du fait même que l'exposition à l'un ou l'autre agent ne peut pas être désignée expérimentalement; la conséquence est qu'un *lien causal* entre un événement particulier et une exposition précédente à un certain agent ne peut pas être prouvée *avec certitude*.
- Les études non-interventionnelles ne sont pas une *alternative* aux études cliniques interventionnelles. Le choix d'un projet (design) d'étude non-interventionnelle est déterminé par l'hypothèse et le contexte spécifiques d'étude.
- L'intégrité physique du patient et l'intégrité des données méritent la même attention dans les études non-interventionnelles qu'interventionnelles, et ceci via une recommandation adaptée, en lignée avec
    - la loi en matière des expérimentations sur la personne humaine
    - la loi sur la protection de la vie privée

Ont travaillé à cette recommandation :

Première phase / groupe des experts :

Marc Bogaert, Michel Boutsen, Ralph Crott, Alain Dupont, Geert Molenberghs, Hugo Robays, Joost Weyler (Président)

Seconde phase / Membres de la Commission :

Marc-Henry Cornely, Jean Creplet, Alain Dupont, Heidi Goethals, Herwig Proesmans, Hugo Robays, François Sumkay, Herman Van Eeckhoudt

Evaluateurs Internes: Pierre Chevalier, Gert Verpooten & Philippe Van Wilder, Secrétaire

3. Introduction

La Commission de remboursement des médicaments fait des propositions en vue du remboursement de médicaments conformément à l'AR du 21 décembre 2001 ; cet AR mentionne explicitement que l'ensemble des études introduites pour étayer une demande de remboursement doit inclure les éléments suivants:

- efficacité (efficacy) : une spécialité est efficace si l'activité pharmacologique lors de la mise en œuvre dans le cadre d'un essai clinique engendre un effet thérapeutique
- effets indésirables
- utilité (effectiveness) : une spécialité est utile si elle est efficace et si l'examen atteste que son utilisation dans la pratique quotidienne permet d'atteindre l'effet thérapeutique
- applicabilité : la mesure dans laquelle les propriétés d'une spécialité (les contre-indications, l'hypersensibilité, ...) limitent l'utilisation auprès de différents bénéficiaires ou par différents dispensateurs de soins
- confort : la manière dont une spécialité peut être utilisée par le dispensateur de soins et/ou le bénéficiaire, de telle façon que le confort de l'administration puisse être amélioré et/ou que des fautes et des erreurs lors de l'utilisation puissent être évitées.

L'ensemble de ces 5 éléments est pris en considération (AR 21 décembre 2001) afin de déterminer la **valeur thérapeutique** d'un médicament ; la détermination de la valeur thérapeutique comprend donc :

- une ou plusieurs "**Etudes cliniques randomisées**" (Randomized Controlled Trials) (RCT) visant l'efficacité de même que la sécurité concernant les effets indésirables non rares ;
- une ou plusieurs études de la "**pratique quotidienne**" visant l'utilité, les effets secondaires rares, l'applicabilité et le confort.

L'information comprise dans une demande initiale se limite souvent à l'efficacité et à la sécurité telles qu'elles apparaissent dans les études cliniques (= exigence pour l'enregistrement) ; en outre, les critères de jugement mesurés lors d'un examen clinique sont souvent **intermédiaires** et il n'est dès lors pas évident de connaître l'effet du traitement sur la **mortalité, la morbidité ou la qualité de vie,** critères de jugement qui sont demandés par l'AR.

Les études concernant les effets d'un traitement dans la pratique quotidienne visent l'examen de la valeur thérapeutique dans des circonstances qui reflètent le plus fidèlement possible les interactions entre le médecin et le patient .Ces études sont souvent (mais pas nécessairement) **non-interventionnelles** comme définies par la Loi belge du 7 mai 2004.

De ce qui précède, il devient clair que **les deux types d'étude ne se substituent pas mais sont plutôt complémentaires.**

N.Black, 'Why we need observational studies to evaluate the effectiveness of health care', BMJ 1996;312:1215-1218

N.Black, 'What observational studies can offer decision makers', Horm Res 1999;51(suppl 1):44-49

S.MacMahon, R.Collins, 'Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies', Lancet 2001;357:455-462

Enfin, l'efficience ou le rapport entre la valeur thérapeutique d'une spécialité et son incidence économique nette, est en outre exigée pour des demandes d'admission en classe I ; ici également la connaissance des effets et des coûts en pratique réelle, est d'une importance primordiale.

D.A.Revicki, L.Frank, 'Pharmacoeconomic evaluation in the real world', Pharmacoeconomics 1999;15(5):423-434

Les études non-interventionnelles diffèrent entre autres des études cliniques interventionnelles en ce sens que :

- L'expérience avec les études cliniques est considérable et de telles études sont amplement décrites et réglementées sur base des recommandations de **bonnes pratiques cliniques (GCP ou Good Clinical Practice)** ; il n'existe jusqu'à présent pas de réglementation GCP équivalente relative à l'étude non-interventionnelle ; la directive européenne relative à la recherche clinique (2001/20/CE) a bien donné lieu à la loi belge (7 mai 2004) relative aux expérimentations sur la personne humaine ; cette loi fixe juridiquement la distinction entre "**essais cliniques**" d'une part et les "essais **sans intervention**" d'autre part.
- Au niveau de la méthode, il y a une différence essentielle **du fait que l'exposition à l'un ou l'autre agent ne peut pas être attribuée d'une manière expérimentale** (= pas de principe de randomisation !) ; une des conséquences importantes concerne le degré d'évidence des études non interventionnelles qui est considéré plus faible que celui des essais contrôlés randomisés. (voir par exemple 'Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)).La relation causale entre ce qui est observé et le traitement instauré ne peut être établie et il y a plusieurs exemples où des effets constatés lors d'essai sans intervention sont rejetés par la suite lors d'essai interventionnel (par exemple les effets d'un traitement de substitution hormonale en cas de ménopause :
- *CBIF, 'Numéro à thème: Substitution hormonale: état de la question en 2003', Folia Pharmacotherapeutica 2003;30(10):82-90).*
- Du côté du demandeur, la recherche clinique de pré enregistrement fait souvent partie d'un programme international de recherche des centres internationaux R&D qui assurent :
    - o le concept, l'exécution, l'analyse et la rédaction de rapports des études conformément à leurs procédures opérationnelles standards (POS).
    - o Le financement de l'étude (chercheurs, médicaments, personnel, archivage, expertise (clinique, statistique, bibliographique, régulatrice, contrôle de la qualité, ...).

L'étude non-interventionnelle est par contre souvent laissée à l'initiative de la filiale locale qui devra assurer la budgétisation nécessaire tout comme l'expertise indispensable et le contrôle de la qualité.

Les études non-interventionnelles ne constituent donc pas une alternative pour les études cliniques (interventionnelles).

Le choix d'un projet de recherche non-interventionnelle spécifique est déterminé par l'hypothèse de recherche ainsi que par son contexte, tout comme pour l'essai interventionnel.

N.Black, 'Why we need observational studies to evaluate the effectiveness of health care', BMJ 1996;312:1215-1218

Cette recommandation, en vue des éléments précédents, s'oriente principalement vers les études non-interventionnelles. La perspective adoptée est celle de chaque partie intéressée (demandeur, Commission, ...) associée à ce genre d'étude ; une proposition d'approche méthodologique et non pas d'approfondissement d'expertise clinique, statistique ou épidémiologique est mise en lumière.

La recommandation comprend

- **un aperçu très succinct des concepts d'études usuels dans ce domaine** : ceci uniquement à titre d'illustration, pour esquisser les possibilités au sein du domaine d'étude non-interventionnelle
- **une liste étendue des éléments indispensables pour le contrôle de la qualité** qui doivent être pris en considération lors de chaque étude non-interventionnelle, et ce lors
  - de la rédaction de l'hypothèse de recherche
  - de la détermination du concept d'étude
  - de l'exécution de l'étude
  - du traitement de données et de l'analyse statistique
  - de la rédaction des rapports d'études

4. Champ d'application

Cette recommandation est d'application pour toute étude non-interventionnelle, présentée comme support aux demandes de remboursement, malgré le design d'étude choisi.

Plus particulièrement elle s'applique à :

- la classe I - les révisions individuelles comme décrites dans l'A.R. du 21/12/2001
- des demandes initiales pour les classes I et 2, lors d'études concernant « expérience avec le produit », comme décrit dans les recommandations pour l'introduction d'un dossier classe I ou 2, point 5.3

5. Considérations méthodologiques et concepts d'études usuels

Une étude non expérimentale se distingue d'une étude expérimentale (par exemple l'étude clinique randomisée) **par le fait que l'exposition à un quelconque agent ne peut être attribuée de manière expérimentale** avec comme conséquence qu'un **lien de cause à effet** ne peut être établi avec certitude entre un événement bien précis et une exposition préalable à un agent quelconque. Plusieurs facteurs explicatifs peuvent être présents simultanément et l'effet d'un facteur peut être masqué par celui d'un autre.

Par exemple : le lien statistique entre l'utilisation d'allumettes et le cancer des poumons s'explique par l'effet du tabagisme !

Bon nombre d'études observationnelles sont décrites et définies dans le contexte de l'étude étiologique. Par conséquent, on s'en réfère souvent à **l'apparition de la maladie comme variable dépendante**. Ceci est en relation étroite avec la définition traditionnelle de l'épidémiologie (étude de la fréquence de la maladie, etc.).

Objectifs de l'étude (non) expérimentale :

Etude de l'apparition d'événements (maladie, décès, hospitalisation, reprise du travail, etc.) en fonction de déterminants (outre le traitement : l'âge, le sexe, la co-morbidité, etc.)

Choix du concept d'étude

Comme mentionné ci-dessus, le choix d'un concept d'étude non-interventionnelle spécifique est déterminé par l'hypothèse de recherche et le contexte de l'étude.

Concepts d'étude relativement importants dans le cadre de cette recommandation

- Etudes de cohorte & longitudinales
- Etudes cas-témoin
- Etudes cross-sectionnelles

- Séries de cas & études cas-témoin historique

L'examen approfondi des différents concepts d'étude figure dans le texte de base du groupe de travail des experts externes (voir annexe). Il est fortement recommandé lors de la formulation des différentes hypothèses d'étude et des choix de concepts d'étude y afférents, de procéder en étroite concertation avec des experts en la matière.

Les points suivants méritent une attention particulière :

- La validité externe (= généralisation) représente la mesure dans laquelle les résultats de l'étude peuvent être généralisés à l'ensemble de la population : elle dépend fortement des méthodes d'échantillonnage utilisées ;
- La validité interne : Le biais représente l'écart systématique entre les résultats obtenus et la valeur réelle de la population : elle affecte donc la validité d'une manière négative. Il existe différentes formes de biais et les principales sont le biais de sélection (dans le cadre des études cas-témoin, le choix du groupe témoin s'avère particulièrement critique), le biais d'information et la perturbation (cf. également *le Cochrane Reviewers' handbook* (version 4.2.0 pp. 47-50).

Dans le cas d'une étude non-interventionnelle, les techniques d'analyse statistique avancées sont nécessaires pour corriger les résultats en cas de perturbation ; ces techniques d'analyse peuvent tout au plus corriger les effets de facteurs interférents connus. A l'inverse de la randomisation, elles ne peuvent corriger les facteurs interférents inconnus.

D.A.Grimes, K.F.Schulz, 'Bias and causal associations in observational research', Lancet 2002;359:248-252

Dans le cadre d'étude «non-interventionnelle», il s'agit en principe d'une étude non expérimentale qui doit avoir malgré tout une validité élevée et une efficience optimale.

6. Critères de qualité

La recommandation sur les « Bonnes Pratiques Cliniques », depuis son introduction en Europe en 1991, fait office de source d'inspiration pour ces critères de qualité dans le cadre de l'étude non-interventionnelle :

- CPMP recommandation GCP : en Europe en 1991
- ICH-Guideline for Good Clinical Practice en janvier 1997
- Directive européenne relative aux essais cliniques (2001/20/CE)
- Loi belge du 7 mai 2004

ICH Guideline on Good Clinical Practice (GCP) (http://www.emea.europa.eu/Inspections/GCPgeneral.html)

En outre, la recommandation pour la recherche pharmaco-épidémiologique réalisée par la *International Society for Pharmaco-epidemiology* (ISPE, revue en août 2004) a également été consultée (cf. annexe).

Les Bonnes Pratiques Cliniques mettent l'accent sur la protection de l'intégrité physique du patient et sur l'intégrité des données d'étude :

*« Compliance with this standard (= GCP) provides public assurance that the **rights, safety and well-being of trial subjects** are protected, consistent with the princinciples that have their origin in the Declaration of Helsinki**, and that the clinical trial data are credible**. »*

(Source : introduction, ICH Topic E6 CPMP/ICH/135/95)

L'intégrité physique du patient et l'intégrité des données méritent le même intérêt dans le cadre de l'étude non-interventionnelle, et ce via une recommandation adaptée, conformément à :

- la loi relative aux expérimentations sur la personne humaine ;

- la loi sur la protection de la vie privée.

Dans le cadre d'études cliniques interventionnelles, la recommendation " ICH harmonised tripartite guideline, E6, Guideline for good clinical practice " et ses dérivés sont d'application.

La Loi belge du 7 mai 2004 relative aux expérimentations sur la personne humaine et ses arrêtés d'exécution sont d'application tant sur les études interventionnelles que non-interventionnelles, effectuées sur la personne humaine.

6.1. Demande de révision individuelle

Dans le cadre des **révisions** de la **classe 1**, au moment de la proposition initiale de remboursement, la Commission peut s'adresser au demandeur afin de concevoir et d'exécuter des études supplémentaires qui devront répondre aux questions non solutionnées à ce stade, au sujet de la valeur thérapeutique et/ou économique du médicament concerné. La commission identifie les questions et les points encore à éclaircir qu'elle desire voir résolus dans le dossier de revision. La société garde la liberté de décider comment ces questions seront résolues, en accord avec les recommendations méthodologiques dans les guidelines pour les évaluations pharmacoéconomiques en Belgique.

Ces études pouvant être des études tant interventionnelles que non-interventionnelles, il est recommandé

- de formuler d'une façon aussi précise et explicite que possible l'hypothèse de recherche ainsi que le concept d'étude approprié, le choix de la population d'étude ainsi que les paramètres principaux d'étude.
- De développer et de décrire l'argumentation utilisée pour cette formulation d'hypothèse de recherche, de concept d'étude, de population et de critères de jugement d'étude envisagés ; les écarts par rapport au principe de randomisation devront en particulier être étayés.

6.2. Exécution d'études non-interventionnelles

6.2.1. Protocole

Chaque étude doit disposer d'un protocole écrit.

Le protocole comprendra au minimum les éléments suivants:

1. Un titre descriptif et une identification de la version (ex.: date);
2. Les noms, titres, degrés, adresses de toutes les parties responsables et de leurs organisations ;
3. Les noms et adresses de chaque promoteur et de ses représentant(s);
4. L'énumération des objectifs de l'étude, des hypothèses de recherche spécifiques (a priori et a posteriori) et des critères de jugement d'étude (par priorité) ainsi que le rationnel de la recherche;
5. Une description de la méthodologie de recherche, y compris:
    - Le concept de recherche, ainsi que l'argumentation menant au choix du concept
    - La population à étudier

    La population est définie en termes de personnes, de lieu, de période et de critères de sélection. La motivation pour les critères d'inclusion et d'exclusion et leur impact sur le nombre de sujets disponibles pour l'analyse doivent être décrits.
    - La méthode d'échantillonnage utilisée
    - La détermination et la définition des critères de jugement de l'étude en utilisant des outils de mesures validés lorsque c'est possible

- Les méthodes utilisées pour le traitement des données, incluant
  - Description des sources de données
  - Les procédures de traitement de données, de la collecte à la base de données autorisée
  - Les méthodes de correction des incohérences ou des erreurs, l'imputation de valeurs ou la modification des données brutes
- Les méthodes pour l'analyse des données, incluant
  - La taille prévue de l'étude, la précision statistique et la base pour les déterminer
  - Présentation des méthodes statistiques à utiliser et leur rationnel
  - Discussion ayant trait aux techniques statistiques de correction du biais
- Les limites de l'étude au niveau du concept, de la conduite et de l'analyse.

Au minimum, les questions relatives aux limites éventuelles sur le plan statistique, épidémiologique, thérapeutique et/ou économique devraient être examinées et le protocole inclut une discussion de leur impact sur l'interprétation des résultats attendus.

6. Une description des procédures de garantie de qualité et de contrôle de qualité lors de toutes les phases de l'étude;
7. La conduite proposée pour l'étude avec les tâches et leur timing en fonction de la phase de l'étude ;
8. Une étude de littérature critique pour évaluer les informations pertinentes et les manques au niveau de la connaissance, liés aux hypothèses de recherche ainsi que pour l'évaluation des éléments critiques concernant la sécurité;
9. Mesures pour la protection de l'intégrité physique de la personne humaine

Cette section devrait présenter des informations concernant:

- le besoin de soumettre le protocole à un Comité d'éthique pour approbation
- les exigences relatives au consentement éclairé du participant d'étude en fonction des lois locales entre autres en ce qui concerne les précautions à prendre au niveau du maintien de la confidentialité des informations relatives aux participants, et les circonstances potentielles selon lesquelles les informations personnelles identifiables peuvent être transmises à des entités externes à l'étude
- le fait que les sujets participant à l'étude soient ou non exposés à certains risques résultant de l'étude; si l'étude comporte un risque supplémentaire, cela doit clairement être mentionné par le consentement requis
- les conditions dans lesquelles l'étude pourrait se terminer (« stopping rules ») ainsi que les procédures à appliquer le cas échéant devraient être décrites

10. Une description du plan de dissémination et de communication des résultats de l'étude

Il existe une obligation éthique de disséminer les résultats ayant une importance scientifique ou de santé publique potentielle. La rédaction du manuscrit de l'étude devrait suivre les directives établies par l'International Committee of Medical Journal Editors (http://www.icmje.org); le rapport d'étude devrait s'aligner sur les principes de la recommandation de « The Consolidated Standards of Reporting Trials (CONSORT) (http://www.consort-statement.org/statement/revisedstatement.htm) ou ses dérivés.

6.2.2. Responsabilités

Les organisations et personnes qui guident et sponsorisent la recherche seront totalement responsables de la recherche. La relation, les rôles, les tâches d'étude et les responsabilités d'étude des organisations et/ou des individus menant et sponsorisant l'étude ainsi que des personnes et/ou organisations qui exécutent ces tâches d'étude sur demande du promoteur (appelées organisations contractantes par la suite p.e. institutions académiques, organisations externes liées au projet, …), devraient être définis.

Il y a lieu de clairement délimiter les rôles et les responsabilités entre le promoteur de l'étude d'une part et le(s) contractant(s) d'autre part au niveau du concept et du déroulement des différents aspects de l'étude incluant la propriété et de l'archivage des données.

Personnel

Le personnel engagé dans le cadre d'une recherche épidémiologique et des activités s'y rapportant, qu'il vienne du promoteur ou du contractant, devrait posséder le niveau de formation et/ou l'expérience nécessaires pour accomplir les fonctions prévues de manière compétente. L'organisation devrait posséder un résumé à jour de la formation et de l'expérience de ce personnel. Une liste des personnes engagées pour les activités ou pour leur supervision, ainsi que leurs titres, devrait être tenue à jour.

Protection de personnes

L'approbation d'un Comité d'éthique indépendant devrait être obtenue pour toute recherche impliquant des personnes et le consentement éclairé sera nécessaire pour toute personne conformément à la loi belge sur la protection de la vie privée. Lorsque la recherche impose un risque supplémentaire pour les participants, ce consentement éclairé en fera clairement mention.

6.2.3. Conduite de l'étude

Le promoteur de l'étude fournira dans le rapport de fin d'étude de l'information concernant le déroulement de l'étude en fonction du temps (incluant : soumission au Comité d'éthique, inclusion du premier et dernier participant d'étude, dernier participant terminant l'étude, rédaction du rapport de fin d'étude, publication(s) des résultats d'étude).

La décision inopinée de clôturer prématurément une étude devrait se baser sur de bonnes raisons scientifiques et éthiques et être étayées de documents écrits, et cette décision devrait être reprise dans le rapport de fin d'étude tout comme son argumentation.

Collecte, traitement et vérification des données

Le(s) personne(s) responsable(s) de l'intégrité des données, informatisées et sur copie papier, sera/seront identifiée(s) et pourront revendiquer la formation et l'expérience afin de s'acquitter des tâches confiées.

Toutes les procédures pour assurer la qualité et l'intégrité des données devraient être suffisamment détaillées pour que d'autres puissent les reproduire et ce de la source des données jusqu'à la base de données validée et le rapport d'étude y associé. Un dossier relatif à l'historique de ces procédures sera tenu à jour, avec toutes les révisions et leurs dates. Toute modification concernant les entrées de données feront l'objet d'une note.

La base de données validée devrait être archivée et l'accès doit y être réglementé de façon à pouvoir tracer tout accès avec mention, entre autres, de la date, le nom des personnes y accédant, les modifications apportées et la raison d'accès.

Analyse

Tous les programmes de traitement des données et d'analyse statistique utilisés pour l'analyse devraient être documentés et archivés. Un exemplaire signé du plan d'analyse statistique et du rapport d'analyse devraient également être archivés.

Rapport de l'étude

L'étude fera l'objet d'un résumé sous la forme d'un rapport final qui présente de manière précise et complète les objectifs, la méthodologie, les résultats ainsi que leur interprétation.

La rédaction du rapport se fera à l'esprit de la recommandation « ICH HARMONISED TRIPARTITE GUIDELINE document E3 on "STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS".

Le rapport final inclura au minimum:

- Un titre descriptif;
- Un résumé des résultats principaux conformément au protocole;
- Le but (les objectifs) de la recherche, tels que mentionnés dans le protocole;
- Les noms, titres, diplômes, adresses et origines de l'investigateur principal ainsi que des investigateurs adjoints;
- Le nom et l'adresse de chaque promoteur et organisation contractante;
- Les dates de début et de fin de l'étude;
- Une introduction, avec un contexte, le but et les objectifs spécifiques de l'étude;
- Une description de la méthodologie de recherche, y compris la population cible et la sélection de l'échantillonnage;
- La méthode de collecte de données ;
- Les principales transformations, calculs ou autres opérations effectués sur les données; description des limites des données recueillies (p.e. données manquantes ou incomplètes) ;
- La méthodologie statistique utilisée lors de l'analyse des données;
- Analyse des données, incluant suffisamment de statistiques descriptives (paramètres d'écart et de position, les tables, graphiques et illustrations présentant la distribution de données), afin de présenter les données pertinentes, ainsi que les analyses comparatives y associées;
- Les conclusions tirées de l'analyse des données;
- Des résultats d'étude compilés concernant la sécurité des traitements utilisés
- Une discussion de l'implication des résultats de l'étude : citer des recherches précédentes qui étayent ou contrastent avec les conclusions. Discussion du biais éventuel et des limites de la recherche actuelle;
- Une description des procédures appliquées pour le contrôle de qualité et l'intégrité des données;
- Les références.

Communication

Il existe une obligation éthique de disséminer les conclusions d'importance scientifique ou de santé publique potentielle ; les résultats d'étude seront publiés dans la littérature scientifique, de préférence dans une revue adoptant le principe de peer-review.

La paternité du rapport de l'étude devrait suivre les directives établies par l'International Committtee of Medical Journal Editors (http://www.icmje.org).

Tous les auteurs devraient répondre aux critères de paternité, et toutes les personnes qui satisfont à ces critères devraient être auteurs. Les conflits d'intérêt potentiels doivent être mis à jour. L'accord d'adhésion à ces directives devrait être décrit dans le protocole.

Rapport d'événements indésirables (adverse events)

Les conclusions d'études épidémiologiques de risques de santé associés aux médicaments doivent faire l'objet d'un rapport de la part des promoteurs pharmaceutiques aux agences officielles, conformément à la Loi belge du 7 mai 2004 et ses arrêtés d'exécution, concernant les expérimentations sur la personne humaine.

Les résultats d'étude compilés concernant la sécurité des traitements utilisés devraient figurer dans le rapport de fin d'étude.

Archivage

Des archives sécurisées doivent être tenues à jour pour un stockage ordonné en vue d'une récupération appropriée de tout le matériel lié à l'étude.

Les archives devraient être gardées **10 ans** au moins après la rédaction du premier des 2 documents suivants : rapport final ou première publication des résultats de l'entièreté de l'étude.

Au minimum, les archives de l'étude devraient contenir ou faire référence aux éléments suivants:

- Le protocole de l'étude et toutes les modifications approuvées;
- Les formulaires de saisie de l'étude complétés de chaque participant d'étude ;
- Le rapport final de l'étude;
- Un exemplaire imprimé des données d'étude relevantes (celles spécifiées par le protocole, le plan d'analyse statistique ou le rapport final d'étude) ;
- La base de données validée avec les données brutes qui constituent la base de l'analyse finale de l'étude. Les copies des versions électroniques des séries de données et de programmes analytiques, les copies papier et, si possible, le code d'exécution correspondant, qui forment la base de tous les tableaux, graphiques, discussions ou interprétations dans le rapport final;
- La correspondance relative à l'étude, les procédures opérationnelles standards, les formulaires de consentement éclairé, les copies des documents signés par les Comités d'éthique et les copies de tous les rapports de contrôle de qualité et d'audit externe ;
- La communication des résultats de l'étude au promoteur, aux décideurs et à la communauté scientifique devrait être bien documentée ;

6.2.4. Matériel à transmettre à la Commission

Tout le matériel ayant trait aux données relatives à une personne devrait être anonymisé conformément à la loi sur la protection de la vie privée.

Les éléments suivants doivent être transmis à la Commission en fin d'étude :

- la liste des centres qui participent, y compris les spécifications des 'investigateurs principaux et des investigateurs adjoints ;
- les nombres de patients pris en compte et enregistrés par centre;
- liste des organisations contractantes, institutions participantes et autres sites d'étude relevants ;
- le protocole d'étude et ses amendements;
- une copie du formulaire vierge de saisie de données;
- le rapport final de l'étude;
- une copie de la base de données validée dans un format prêt à l'analyse ;

7. Annexes

Annexe 1 : Références concernant la (pharmaco)épidémiologie (extrait du texte de base des experts externes)

1. J. M. Last, A dictionary of Epidemiology, Oxford University Press 1995
2. M.H. Gail, J. Benichou, Encyclopedia of Epidemiologic Methods, Wiley 1999
3. K. Rothman, S. Greenland, Modern Epidemiology, Lippincott – Raven 1998

4. O.S. Miettinen, Theoretical Epidemiology. Principles of occurrence research in medicine. Wiley 1985
5. ICH Topic E6 CPMP/ICH/135/95. Harmonised Tripartite guideline for Good Clinical Practice, januari 1997
6. European Directive on Implementing Good Clinical Practice; Directive 2001/20/EC
7. Loi belge concernant les expérimentations sur la personne humaine du 7 mai2004

Données longitudinales:
8. Verbeke, G. and Molenberghs, G. (2000). Linear Models for Longitudinal Data. New York: Springer Verlag. 568 pages. ISBN 0-387-95027-3
9. Fahrmeir L. and Tutz G. (2001) Multivariate Statistical Modelling Based on Generalized Linear Models. New York: Springer Verlag. 517 pp. ISBN 0-387-94233-5
10. Diggle P, Heagerty P, Liang KY and Zeger S (2002). Analysis of Longitudinal Data. Oxford Press. 350 pp. ISBN 0-198-52484-6

Travail de référence générale:
11. Ström "Pharmacoepidemiology" Wiley, third edition 2000

Annexe 2 : Extrait de la loi du 7 mai 2004

"**essai clinique**": toute investigation menée chez la personne humaine, afin de déterminer ou de confirmer les effets cliniques, pharmacologiques et/ou les autres effets pharmacodynamiques d'un ou de plusieurs médicaments expérimentaux et/ou de mettre en évidence tout effet indésirable d'un ou de plusieurs médicaments expérimentaux et/ou d'étudier l'absorption, la distribution, le métabolisme et l'élimination d'un ou de plusieurs médicaments expérimentaux dans le but de s'assurer de leur innocuité et/ou efficacité;

"**essai non-interventionnel**" : étude dans le cadre de laquelle le ou les médicaments sont prescrits de manière habituelle conformément aux conditions fixées dans l'autorisation de mise sur le marché. L'affectation du patient à une stratégie thérapeutique donnée n'est pas fixée à l'avance par un protocole d'essai, elle relève de la pratique courante et la décision de prescrire le médicament est clairement dissociée de celle d'inclure le patient dans l'étude. Aucune procédure supplémentaire de diagnostic ou de surveillance ne doit être appliquée aux patients et des méthodes épidémiologiques sont utilisées pour analyser les données recueillies;

Annexe 3 : Texte complet des experts externes

uniquement sur requête spécifique

Annexe 4 : Loi du 7 mai 2004

via adresse internet:
ttps://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/GENEESMIDDELEN1_MENU/LISTEDESLOISETARRETES1_HIDE/LISTEDESLOISETARRETES1_DOCS/LOI-WET-2004-05-07_0.PDF

Annexe 5 : ISPE recommandation d'août 2004

via adresse internet : http://www.pharmacoepi.org/resources/guidelines_08027.cfm

Annexe 6 : ICH GCP document E6

via adresse internet: http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254

Annexe 7 : Cochrane Reviewer's handbook:

bias définitions / via adresse internet : http://www.cochrane.org/admin/manual.htm

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