Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique

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Contact

Centre fédéral d'expertise des soins de santé (KCE).
Résidence Palace (10ème étage)
155 Rue de la Loi
B-1040 Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@centredexpertise.fgov.be
Web : http://www.centredexpertise.fgov.be

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IRINA CLEEMPUT, RALPH CROTT, FRANCE VRIJENS,
MICHEL HUYBRECHTS, PHILIPPE VAN WILDER, DIRK RAMAEKERS

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Auteurs :	Cleemput Irina*, Crott Ralph*, Vrijens France*, Huybrechts Michel*, Van Wilder Philippe**, Ramaekers Dirk* (* KCE, ** RIZIV/INAMI)
Experts externes :	Beutels Philippe (University Antwerp), Dewilde Sarah MSc (Health Care Analytics Group, United BioSource Corporation), Lamers Leida (iMTA and Erasmus University Medical Center, NL), Robays Hugo (UGent), Rumeau-Pichon Catherine (Health economics and public health (HAS), FR), Simoens Steven (KULeuven), Van Eeckhout Herman (Pharma.be).
Validateurs :	Annemans Lieven (UGent, IMS), Dubois Dominique (Janssen Pharmaceutica), Le Pen Claude (Université Dauphine, Paris, FR).
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Préface

Le progrès en soins de santé est en grande partie animé par la recherche de l'industrie du médicament. De son point de vue, il est bien évident qu'elle encourage l'usage le plus large possible de ses produits et veille à leur remboursement rapide.

Tous les développements dans ce secteur d'activité n'ont cependant pas une plus-value sociétale de la même importance. Les pouvoirs publics doivent pouvoir évaluer la 'valeur ajoutée' d'un produit par rapport à ses coûts afin de répartir ses moyens de façon efficiente.

Depuis la création de la Commission de Remboursement des Médicaments en 2002, l'évaluation du rapport coût-efficacité des médicaments joue un rôle important dans la décision de remboursement.

C'est le fabricant qui, en Belgique, doit apporter la preuve du rapport coût-efficacité. Les règles de démonstration du rapport coût-efficacité sont cependant vagues et laissent le champ libre à des choix méthodologiques contestables. Il s'en suit un manque de transparence et de cohérence dans les dossiers.

En conséquence, l'INAMI et le KCE ont réfléchi ensemble. Ce qui est présenté ici est, à l'instar d'autres pays, un faisceau de recommandations pour les évaluations pharmaco-économiques introduites dans le cadre d'une demande de remboursement d'un médicament. Ces recommandations pharmaco-économiques sont un moyen d'améliorer la transparence et la qualité des dossiers et de contribuer ainsi à une meilleure appréciation de ceux-ci.

Le développement de recommandations constitue la première étape d'un projet en 2 phases.

La seconde étape consistera en un projet pilote d'évaluation au cours d'une phase test où les soumissionnaires testeront l'applicabilité des recommandations. L'évaluation des recommandations doit conduire 'in fine' à des directives définitives pour tous les nouveaux dossiers.

Ce rapport traite des évaluations économiques des médicaments. Dans ce domaine, les évaluations économiques, malgré des problèmes méthodologiques encore importants, sont entre-temps devenues usuelles. A l'avenir, des évaluations similaires en économie de santé dans d'autres secteurs comme par exemple ceux du matériel implantable, des prothèses et des tests diagnostiques, auront un impact renforcé. Les premiers rapports d'évaluation des technologies de la santé produits par le KCE indiquent dès à présent les besoins pressants dans ces domaines restés en grande partie inexplorés à ce jour. L'économie de la santé paraît dès lors aussi un excellent choix de carrière pour de jeunes économistes, du moins dans les systèmes de santé mis sous contrainte budgétaire.

Jean-Pierre Closon
Directeur général adjoint

Dirk Ramaekers
Directeur général

Synthèse des recommandations

Ce rapport développe des recommandations pour la soumission d'évaluations pharmaco-économiques dans le cadre d'une demande de remboursement de médicaments pour laquelle cette évaluation est impérative ou utile. Ces recommandations sont préliminaires. Elles seront mises à l'épreuve avant d'être finalisées. Cette phase test durera plusieurs mois. Les recommandations finales sont prévues en 2007.

Les recommandations s'articulent autour d'une analyse de référence qui précise la méthode recommandée à chaque étape de l'évaluation économique. Toute soumission pharmaco-économique contiendra au moins une analyse de référence présentée selon la méthodologie recommandée. Des analyses supplémentaires sont autorisées mais ne remplacent pas l'analyse de référence.

Recommandation 1 : revue de la littérature

Toute évaluation pharmaco-économique doit s'accompagner d'une revue systématique des études cliniques et économiques qui couvrent l'intervention, y compris celles non publiées ou dont les résultats sont négatifs. La stratégie de recherche doit être reproductible, et présenter les critères ainsi que les procédures de sélection. La revue doit décliner toutes les *évidences* d'efficacité clinique et d'efficience du produit. Il faut évaluer les *évidences* de manière critique, apprécier leur qualité et les présenter sous la forme de tables d'extraction de données. L'auteur doit en fournir une synthèse claire et concise. Les études en cours doivent être mentionnées.

Recommandation 2 : perspective de l'évaluation

L'analyse de référence ne peut prendre en compte que les seuls coûts de santé directs pour le payeur des soins de santé. Ceci comprend aussi bien les paiements issus du budget fédéral des soins de santé, que la participation des patients. Les résultats en matière de santé doivent être évalués dans une perspective sociétale.

Recommandation 3 : population cible

La population des patients pour laquelle s'applique l'évaluation pharmaco-économique doit correspondre à la population de patients définis dans le volet clinique du dossier de remboursement. Si les effets du médicament sur l'efficacité et/ou les coûts diffèrent entre les sous-groupes, des analyses distinctes par sous-groupes doivent être effectuées, pour autant que cette analyse par sous-groupes soit étayée par une justification (statistique) appropriée. Les données épidémiologiques applicables à la Belgique doivent être présentées, le cas échéant, à la fois pour l'ensemble de la population cible et les sous-groupes pertinents.

Recommandation 4 : comparateurs

Le médicament doit être comparé au traitement alternatif le plus pertinent dans l'indication proposée du médicament. Le traitement alternatif le plus pertinent est soit le traitement qui se verra le plus vraisemblablement remplacé par le nouveau traitement soit le traitement actuel si le nouveau traitement s'ajoute au traitement existant. S'il n'est pas possible d'identifier un traitement pertinent, le comparateur doit être le(s) traitement(s) de base selon les recommandations belges de bonne pratique. Les comparateurs peuvent être des traitements médicaux ou non médicaux.

Le choix du comparateur doit toujours se justifier.

Des comparaisons indirectes sont uniquement autorisées s'il est satisfait aux deux conditions suivantes: La légitimité du choix d'une comparaison indirecte plutôt que directe. L'exposé clair des limites de la comparaison indirecte puisque une telle comparaison ne peut conduire qu'à des conclusions restreintes.

Recommandation 5: technique analytique

L'analyse coût-utilité doit être utilisée si le traitement a un impact relevant sur la qualité de vie liée à la santé du patient, ou s'il existe différents résultats cliniques qui, pertinents pour les patients considérés, utilisent des unités de mesure différentes (c'est-à-dire, des unités de mesures différentes pour les complications évitées et pour les effets secondaires créés).

L'analyse coût-efficacité doit être utilisée si le gain d'espérance de vie représente le principal objectif du traitement et aussi le résultat le plus important pour le patient, ou s'il existe un résultat clinique dominant, clairement précisé et pertinent pour le patient (éviter des complications), sans qu'un autre résultat pertinent pour le patient (provoquer des effets secondaires) ne soit exprimé en unités différentes.

Les divergences d'opinion récurrentes sur la méthodologie à utiliser pour les analyses coût-bénéfice ne permettent pas d'accepter ces dernières comme analyses de référence pour les soumissions pharmaco-économiques.

Les résultats doivent être exprimés sous forme de rapports incrémentiels coût-efficacité ou coût-utilité.

Recommandation 6 : schéma de l'étude

Les évaluations pharmaco-économiques doivent toujours être basées sur des données observationnelles issues de comparaisons directes 'face à face' (études longitudinales contrôlées avec tirage aléatoire ou études non interventionnelles) entre le produit étudié et un comparateur pertinent dans une certaine mesure. Si la modélisation est nécessaire parce que les études cliniques fournissent des informations insuffisantes pour une évaluation économique, le nombre d'hypothèses non basées sur des évidences cliniques doit être réduit à un minimum.

Recommandation 7 : calcul des coûts

L'identification, la mesure et la valorisation des coûts doivent correspondre à la perspective du payeur des soins de santé belge. Des sources pertinentes doivent être utilisées pour les coûts unitaires. Les frais non liés aux soins de santé ou les frais de soins de santé sans rapport avec l'affection ne peuvent pas être inclus dans l'analyse de référence.

Il convient de fournir des informations sur la proportion de données manquantes relatives aux coûts dans l'étude (étude longitudinale contrôlée avec tirage aléatoire ou étude observationnelle), sur les raisons de l'absence de ces données et sur les méthodes utilisées pour y remédier.

Recommandation 8 : estimation et valorisation des résultats

Les résultats des évaluations pharmaco-économiques doivent être exprimés en termes de résultats finaux au lieu de résultats intermédiaires. Il est recommandé que la mesure de résultats limpides fasse appel, à des échelles de mesure qui prêtent peu à discussion.

Pour les analyses coût-utilité, il convient de calculer les années de vie ajustées pour la qualité (QALYs pour quality-adjusted life years). Les pondérations attribuées à la qualité de vie doivent être basées sur des données observationnelles, obtenues par un système descriptif de l'état de santé, pour lequel des valeurs de préférence correspondantes existent déjà ou ont été recueillies récemment auprès de la population générale. L'utilisation des valeurs de préférence belges est privilégiée.

Pour les analyses coût-efficacité, les résultats doivent être exprimés en termes d'années de vie gagnées au cours de maladies chroniques ou en termes du résultat pertinent à court terme au cours de maladies aiguës sans conséquences à long terme. L'espérance de vie doit être calculée à partir des tables belges de mortalité selon l'âge.

Recommandation 9 : horizon temporel

L'horizon temporel approprié dépend de l'histoire naturelle de la maladie. Les maladies chroniques requièrent un horizon temporel plus long que les maladies aiguës sans conséquences à long terme. Pour les maladies chroniques ou aiguës qui entraînent des séquelles à long terme, il convient d'appliquer un horizon portant sur la vie entière.

Recommandation 10 : modélisation

Il convient d'envisager la modélisation si les données observationnelles disponibles sont insuffisantes pour permettre une évaluation complète du coût-efficacité ou du coût-utilité d'un produit. La modélisation doit toujours faire l'objet d'une justification et les hypothèses sous-jacentes, suppositions et sources d'informations doivent être présentées de manière claire et transparente. Les données primaires et les sources d'information originelles qui ont été utilisées pour définir les valeurs numériques des paramètres d'entrée, ainsi que le modèle informatique originel doivent être tenus à la disposition de la Commission de Remboursement des Médicaments.

Recommandation 11 : traitement de l'incertitude et vérification de la robustesse des résultats

Quelque soit le canevas de l'étude, l'incertitude entourant les estimations de coût-efficacité/coût-utilité doit être analysée à l'aide des techniques statistiques appropriées. L'évaluation économique doit présenter l'intervalle de confiance estimé pour chaque paramètre. L'évaluation doit traiter chacun des différents aspects de l'incertitude. En cas de modélisation, il convient d'adjoindre des analyses de sensibilité probabilistiques.

Recommandation 12 : taux d'escompte

Il convient d'appliquer un taux d'escompte de 3 % aux coûts futurs et de 1,5 % aux bénéfices futurs. Pour évaluer la sensibilité des résultats au taux d'escompte appliqué, différents scénarios doivent être présentés :

- 0 % pour les bénéfices et 3 % pour les coûts ;
- 0 % ou 3 % ou 5 % à la fois pour les bénéfices et les coûts et
- 0 % pour les bénéfices, combiné à 5 % ou 3 % pour les coûts.

Recommandation 13 : utilisation de données provenant d'autres pays

En cas d'utilisation de données provenant d'autres pays, il convient de réaliser une analyse de transférabilité. Cette analyse doit énumérer et commenter tous les obstacles susceptibles d'entraver la transférabilité vers la Belgique. Il convient de veiller à ce que l'étude corresponde aux exigences imposées par l'analyse de référence ou du moins se prête à des adaptations de manière à faire correspondre l'étude à l'analyse de référence.

Scientific summary

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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 pharmaco-economic evaluation. Class 1 drugs are drugs with a therapeutic added value compared to existing therapeutic alternatives, class 2 drugs are those with comparable therapeutic value and class 3 drugs are mainly generics. Reimbursement requests are evaluated by the Drug Reimbursement Committee (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 2002-2003, it appeared that the claim of 'added therapeutic value' was approved after evaluation in only 50% of class-1 submissions, which is of particular importance to the subsequent pharmaco-economic study.

The definition of therapeutic value used in the Ministerial 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 pharmaco-economic evaluations are morbidity, mortality and/or health-related quality of life, additional reflections and analysis may be necessary to describe the therapeutic (added) value of a product. Based on an evaluation 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 pharmaco-economic analyses has been hampered by the absence of clear guidelines for conducting and reporting pharmaco-economic 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[2] (Royal Decree of 21/12/2001,*B.S.* 29-12-2001). In this respect, the circular covered all

[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.

elements needed in a reimbursement submission. The document paid special attention to the most important caveats in a submission.

2 OBJECTIVES

The objective of this study was to develop methodological and reporting guidelines for pharmaco-economic evaluations submitted to the Drug Reimbursement Committee with the objective to obtain reimbursement of a pharmaceutical product in Belgium. These guidelines apply to all pharmaceutical products for which a pharmaco-economic evaluation is required.

The guidelines are designed to assist companies to identify and format the information needed by the Drug Evaluation 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 pharmaco-economic submissions. They do not relate to the procedures for the evaluation of reimbursement request dossiers, nor to the methods used to arrive at a recommendation for reimbursement. Hence, compliance with the methodological and reporting guidelines for pharmaco-economic 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 hers.

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 pharmaco-economics 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. 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 pharmaco-economic 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 appendix 8. The core text of the guidelines is deliberately kept brief, to serve as an easy working document for both evaluators and applicant. The appendices provide supportive documents for the pharmaco-economic evaluation and elaborate on some technical aspects of the guidelines.

Part one of this project consists 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. Part two of the project consists of a practical implementation of these guidelines during a 12-month test period. This pilot phase will lead to conclusions about the practicality and usefulness of the guidelines and to potential improvements in the guidelines. Part one of this project consists 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.

Part two of the project consists of a practical implementation of these guidelines during a 6m to 12-month test period. This pilot phase will lead to conclusions about the practicality and usefulness of the guidelines and to potential improvements in the guidelines. Participation in the pilot test will be voluntary. The evaluation of the feasibility and usefulness of the guidelines will be strictly separated from the procedural evaluation of the content of the reimbursement request file. For the evaluation of the pharmaco-economic guidelines, the dossiers will be anonymised and the methodological feasibility be assessed by experts who were not involved in the procedural evaluation of the content of the file. Hence, compliance with the pharmaco-economic guidelines will neither have a positive nor a negative effect on the admissibility of the dossier or the concrete reimbursement evaluation, proposition and decision. After the pilot test, the guidelines will be adapted according to the results of the formal evaluation and finalised. The final guidelines will be binding for all new reimbursement request dossiers that (have to) include a pharmaco-economic evaluation after approval by the competent authorities.

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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

4 PHARMACO-ECONOMIC 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 pharmaco-economic 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	Reproducible search strategy according to methodological standards	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 sub-groups need to be defined.	3
Comparator	Standard treatment in Belgium	4
Analytic technique	Cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), choice should be justified	5
Study design	Economic evaluation based on observational data from head-to-head comparisons between the study product and the comparator and/or modeling	6
Calculation of costs	Health care costs paid out of the health care budget, by the RIZIV/INAMI and patients	7
Valuation of outcomes	Final outcome parameters: life years gained (CEA) or QALYs gained (CUA) for chronic conditions or other relevant outcome variable, as in the clinical file, for acute conditions	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
Modeling	Based on observational data from trials comparing the study medication and the comparator, observational databases and literature	10
Handling uncertainty	Presentation of uncertainty around the ICER by means of confidence interval and/or shown on the cost-effectiveness plane (add cost-effectiveness acceptability curve or incremental net benefit diagram) + probabilistic sensitivity analyses (for models)	11
Discount rate	3% on costs and 1.5% on outcomes	12
Use of data from other countries	Qualitative transferability analysis	13

Each pharmaco-economic 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 pharmaco-economic guidelines are related to the methodological aspects of a pharmaco-economic evaluation. Different methodological approaches will be discussed, with special attention to potential caveats.

4.1 GUIDELINE 1: LITERATURE REVIEW

Each pharmaco-economic evaluation should be accompanied by a systematic review of the existing clinical and economic studies on the intervention, including unpublished studies and studies with negative results. The search strategy should be reproducible and selection criteria and procedures presented. The review should reveal all existing evidence for clinical effectiveness and cost-effectiveness of the product. The evidence should be critically appraised, its quality assessed and data presented in data extraction sheets. A clear but concise synthesis 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. Selective presentation of evidence must be avoided. Therefore, it is important to follow the methodology of a systematic literature review. Studies with negative and/or unpublished results should be disclosed. An overview of ongoing studies should be provided as well.

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[7]).

A good review starts with identification of the review questions. This includes specification of the population, the interventions compared, outcomes and study designs selected. The review should moreover contain the search strategy, study selection criteria and procedures followed for selecting studies, study quality assessment, data extraction sheets, and a synthesis of the evidence found.

The methodology used for the literature search should be clear and reproducible. Databases searched should include at least:

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

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). Data extraction sheets should be provided for all the studies retained for

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

the synthesis. Appendix 3 provides examples for data extraction sheets for clinical and economic studies.

If modeling is used for the primary economic evaluation presented in the pharmaco-economic file, all (clinical) studies that served as a basis for the modeling input parameters' valuation should be described in detail (including methodology used, assumptions, results). Relevance and appropriateness should be discussed in detail.

4.2 GUIDELINE 2: PERSPECTIVE OF THE EVALUATION

In pharmaco-economic 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 valued from a societal perspective.

In general, it is recommended to use the societal viewpoint for the pharmaco-economic analysis, i.e. costs and outcomes for society as a whole should be valued. This would include costs born 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. 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.

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 reduction in 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. If these consequences are expected to be important for a specific treatment, additional analyses or information can be presented. This should be clearly distinguished from the reference care pharmaco-economic analysis. The analyst should not change the values of specific parameters in the pharmaco-economic analysis based on the argument that one aspect or another should get more weight in the decision making process. Presenting the information separately improves the transparency of the pharmaco-economic assessment.

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

perspectives, such as the provider's or patients' perspective, are not acceptable for a pharmaco-economic evaluation submitted in the context of a reimbursement request.

4.3 GUIDELINE 3: TARGET POPULATION

The patient population to which the pharmaco-economic 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 sub-groups, separate sub-group analyses should be performed, provided that appropriate (statistical) justification for sub-group analysis is provided. Epidemiological data for Belgium should be presented if available for both the entire target population and the relevant sub-groups.

The pharmaco-economic evaluation should follow the clinical evidence. The target population described in the pharmaco-economic 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 sub-group of the patients studied in the trial. Sometimes the implications of a product on the costs or effects of treatment are different between sub-groups. These sub-groups may already be described and analysed in the clinical file. In this case, sub-group analyses are also indispensable in the pharmaco-economic evaluation. If the analysis of sub-groups was not already explicitly included in the trial protocol, sub-group analyses should be clearly justified based on statistical considerations: the sub-group effect and homogeneity of treatment effect across sub-groups should be demonstrated before separate analyses are performed. In addition, care should be taken of sufficient statistical power to perform sub-group analyses.

While for the clinical file sub-group analyses are only allowed under specific conditions, there is more room for sub-group 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 sub-groups were *not* analysed in the clinical study, sub-group 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 sub-groups with significant results is not acceptable. There should be a clear rationale behind the choice of sub-groups 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 sub-groups. It is essential to use an assumption of constant relative treatment effect. This means that the relative effectiveness in the different sub-groups 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 sub-groups

are different.[8] Other assumptions cannot be justified in the absence of clinical effectiveness data for the different sub-groups. Again, appropriate justification should be provided for the sub-group analyses and uncertainty associated with assumptions related to the analyses assessed. Patient characteristics for the different sub-groups should be specified enough in order to allow the evaluator to assess the appropriateness and relevance of the sub-groups.

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 transferability of these data (see Guideline 13).

4.4 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 standard 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.

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, relating to the more restricted inferences one may draw from this type of comparison.

The drug should be compared with a treatment with proven efficacy (in RCTs) and considered the treatment of reference 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.

The treatment most likely to be replaced by the new treatment can be identified through market research, surveys, database analsyses 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.

[8] 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 sub-groups, but the absolute effect will differ, due to the higher baseline survival in younger patients.

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 0 costs and effects.

The choice of the comparator should always be justified. Consistency between the clinical and the pharmaco-economic submission should be pursued.

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 standard treatment defined at the time of the clinical trials may no longer be the standard treatment at the time of the pharmaco-economic evaluation. In this case, indirect comparisons and/or modeling 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 (see Appendix 4).

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

4.5 GUIDELINE 5: ANALYTIC TECHNIQUE

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.

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.

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

Results should be expressed as incremental cost-effectiveness or cost-utility ratios.

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 pharmaco-economic evaluation but may be considered as a logical first step towards a formal economic evaluation.

4.5.1 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.

Cost-utility analysis should be used 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.

4.5.2 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 comparator's, 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.

If different patient-relevant clinical outcomes are expressed in different units (e.g. life years gained and complications avoided), cost-effectiveness analysis is not 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.

4.5.3 Cost-minimisation analysis

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

Pharmaceutical products for which a pharmaco-economic 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 pharmaco-economic evaluation, while other elements of the therapeutic value (e.g. applicability or user-friendliness), which are not captured in the QALY or LYG-estimate, are still different. In that case, cost-minimisation analysis is recommended and additional reflections on the impact of the treatment on the other non-health outcome parameters should be provided.

In practice, it is often impossible to know a priori that cost-minimisation analysis is appropriate. The analysis will therefore usually be preceded by a cost-effectiveness or cost-utility approach, during which it becomes clear that health outcomes are identical. One exception is when a thorough effectiveness evaluation, including all outcome measures that are relevant for the economic evaluation, has shown equal outcomes for all treatment alternatives. In this sense, a cost-minimisation analysis can be interpreted as a special case of cost-effectiveness or cost-utility analysis with equal outcomes.

4.5.4 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.

4.6 GUIDELINE 6: STUDY DESIGN

Pharmaco-economic evaluations should always be based on observational data from head-to-head comparisons (RCTs or non-interventional studies) between the study product and a relevant comparator to some extent. If modeling is needed because clinical trials provide insufficient information for the economic evaluation, the number of assumptions not based on strong 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. 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.

4.6.1 Trial-based pharmaco-economic evaluations

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

The weaknesses of **piggy-back trials** are directly related to the purposes of the RCT. RCTs are not set up for pharmaco-economic 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 pharmaco-economic evaluation. Some of the weaknesses of RCT for the purpose of pharmaco-economic evaluations are: (1) a potentially inappropriate comparator, (2) an inadequate sample size, (3) a limited time horizon, (4) the occurrence of protocol-driven costs, (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 modeling.

Besides weaknesses, piggy-back trials 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. Before reimbursement of a product it is often the only information available on efficacy.

Piggy-back trials are useful if the economic evaluation is included in the protocol before the start of the study. This implies that the weaknesses of piggy-back trials are tackled in advance: sample size calculations are not only based on expected clinical effects but also on expected differences in costs and outcomes relevant for the economic evaluation, methods to deal with protocol driven costs are developed, an appropriate comparator and a relevant outcome measure for the pharmaco-economic evaluation is included in the design of the study.

In conclusion, piggy-back trials are acceptable for a pharmaco-economic submission under the following conditions:

- Appropriate comparator
- Appropriate time horizon (i.e. the treatment effect and the effect of the treatment on costs and effects has fully worked out at the end of the trial period. No additional cost or effects can be expected after the last observational time point of the trial)
- Appropriate resource use measurement
- Efficacy is an appropriate surrogate for effectiveness
- Economic evaluation included in the protocol

The Drug Reimbursement Committee developed guidelines for **non-interventional studies**, defined as clinical trials without randomisation. 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 revision file, 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 pharmaco-economic evaluations alongside RCTs or non-interventional trials, original data should be provided to the Drug Reimbursement Committee upon request.

4.6.2 Modeling

Even if a trial-based pharmaco-economic evaluation exists, some modeling is likely to be needed (e.g. to extend the time horizon to longer time spans or to model comparators which have become more relevant in practice since completion of the trial). Very often, already in the analysis of a piggy-back trial 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.

Pharmaco-economic models allow the analyst to combine information from a variety of sources and to link these data to outcomes of interest to decision makers. 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 … 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, …). The arguments to use a modeling approach should be set out clearly and sources for hypotheses should be presented.

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

4.7 GUIDELINE 7: CALCULATION OF COSTS

The identification, measurement and valuation of costs should be consistent with the perspective of the Belgian health care payer. Relevant sources should be used for unit costs. Non-health care costs or unrelated health care costs should not be included in the reference case analysis.

Information should be provided on the proportion of missing cost data in the study (longitudinal RCT or observational), on the reasons for these missing data, and on the methods used to deal with this.

The perspective for the cost calculation is that of the health care payer (government and patient). Valuation of resource use in monetary units must be consistent with the perspective of the analysis.

4.7.1 Cost categories

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

Table 2: Included and excluded costs

	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
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. Productivity losses should in this case be calculated using the human capital approach.

4.7.2 Measurement of resource use

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

Use of expert panels for resource use measurement is subject to specific conditions (Appendix 4). Expert panels are preferably only used as a complementary source of information rather than as the sole source of information on resource use.

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 Cellulle 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". Other databases can be used, provided that the data in the database are validated against the data of the Cellulle Technique/Technische cel.

4.7.3 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. 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. Table 3 presents the sources for unit prices/costs to be used for different types of resource inputs.

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>https://www.inami.fgov.be/inami_prd/SSP/CNS/Pages/p1_1.asp
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 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></tr>
<tr><td>Acute</td><td>266,77</td><td>284,56</td><td>283,86</td><td>305,98</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></tr>
<tr><td>Geriatrics</td><td>171,70</td><td>167,37</td><td>186,11</td><td>176,14</td></tr>
<tr><td>Palliative</td><td>390,91</td><td>401,70</td><td>399,95</td><td>416,88</td></tr>
<tr><td>Psychiatric</td><td>159,86</td><td>175,83</td><td>176,51</td><td>182,52</td></tr>
<tr><td>Specialized</td><td>174,88</td><td>188,73</td><td>188,79</td><td>198,70</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</td></tr>
</table>

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

4.8 GUIDELINE 8: ESTIMATION AND VALUATION OF OUTCOMES

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

For cost-utility analyses, QALYs should be calculated. Life expectancy should be estimated based on Belgian age-dependent life tables. Health-related quality of life weights should be based on observational data, obtained with a descriptive system for health status for which corresponding preference values already exist or are newly collected from the general public. The use of Belgian preference values is preferred.

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-dependent life tables for Belgium.

The aim of the pharmaco-economic 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, in cost-utility analyses outcomes are expressed in QALYs gained.

4.8.1 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 pharmaco-economic evaluation, modeling may be needed (cfr. Guideline 10). For chronic diseases or acute diseases with long term sequelae, 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).

4.8.2 Utility assessment in cost-utility analysis

In cost-utility analyses, the valuation methods for health-related quality of life should be equal for all comparators. Data on survival and health-related quality of life should be presented separately. As no weights that represent distributional preferences of the general public according to the populations affected are available (yet) QALYs should not be weighted in the pharmaco-economic analysis. This means that 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 pharmaco-economic evaluations. Moreover, it is strongly recommended to calculate QALYs based on original Belgian observational data.

4.8.2.1 Health state description

The use of a generic health-related quality of life measure is recommended 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 the Belgian population.

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 ad hoc disease-specific instruments for a single pharmaco-economic evaluation and use these in the reference case analysis to estimate the number of QALYs gained. 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 well argumented.

4.8.2.2 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. If other instruments are used, e.g. the SF-36, first an original study in the general Belgian population should be performed 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.[9]

If no original Belgian data are collected but generic health state descriptions and valuations are available from other countries in the same patient population, these values can be used, provided that the source of the valuations is transparent and that potential problems of transferability are discussed. Also in this case, health states should be valued from a societal perspective, i.e. derived from a representative sample of the general public. Details about the population to which the valuations refer and references to publications describing the general population survey should be provided.

Disease-specific health state descriptions, obtained with a validated instrument, 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

[9] 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.

the general public. Selection of people from the general public, representativeness and methods for surveying the subjects should be described in detail. Mapping of disease specific instruments to generic instruments is only allowed if mapping functions are based on or validated with empirical data. This implies that data are available for both the generic and the disease-specific instrument for the same patient group.

4.9 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. 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.

4.10 GUIDELINE 10: MODELING

Modeling should be considered if the available observational data are insufficient to allow a full assessment of the cost-effectiveness or cost-utility of a product. A justification for modeling should always be provided and the structural hypotheses, assumptions and sources of information should be presented in a clear and transparent way. 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.

4.10.1 Need for modeling

Modeling may be needed for the extension of the analysis beyond observed time periods. In order to know the effects of a treatment on long term mortality, extrapolation modeling may be necessary.

Another reason for modeling 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).

Modeling 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 modeling may be useful to assess effectiveness instead of efficacy as presented by the RCTs.

Modeling 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 pharmaco-economic model.

Sometimes, modeling 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, modeling 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 pharmaco-economic submission. Modeling is optional. If good quality Belgian data from observational studies are available over a relevant time period, including all appropriate outcome measures and reflecting the methdological standards for trial-based pharmaco-economic evaluations (guideline 6), modeling is not needed.

4.10.2 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 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 modeling input parameters.

All variables in the model must be listed and documented, preferably in a table:

Variable's name	Description	Value (range or confidence interval)	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 argumented.

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, 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, there is no best or worst option. Therefore, it is not possible to recommend one single approach for the reference case. 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 and scenarios for discounting of costs and effects as specified in guideline 12.

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.

4.11 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 parameter in the economic evaluation. All different aspects of uncertainty in the evaluation should be addressed. For models, probabilistic sensitivity analyses should be presented.

Uncertainty in economic evaluations of healthcare interventions is omnipresent, and should be properly described and accounted for in the submitted pharmaco-economic 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 generalisability of the study results to other population and/or other contexts (handled via descriptive transferability analysis). 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 pharmaco-economic evaluations as well as to models. In trial-based pharmaco-economic 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 modeling, 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. 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. In addition to probabilistic sensitivity analyses, univariate sensitivity analysis should be performed on uncertain modelling parameters that are decisive for the cost-effectiveness ratio (e.g. if there is uncertainty about the life expectancy after treatment with a new medication, the impact of different assumptions should be tested in univariate sensitivity analyses).

In the case of observed cost and effects data in a trial based pharmaco-economic study the parametric approach based on the Fieller's theorem or non-parametric bootstrapping 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 pharmaco-economic evaluation is requested are expected to belong to the North-East quadrant of the cost-effectiveness plane (more costly and more effective treatment). A cost-effectiveness acceptability curve should be presented in order to show the probability that the treatment is cost-effective, given varying threshold values for the cost-effectiveness ratio. If 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.

4.12 GUIDELINE 12: DISCOUNT RATE

Future costs should be discounted at a rate of 3%; future benefits at a rate of 1.5%. To assess the sensitivity of the results to the discount rate applied, different scenarios should be presented: 0% for benefits and 3% for costs, 0% or 3% or 5% for both benefits and costs and finally 0% for benefits combined with 5% or 3% for costs.

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 literature (e.g. Gravelle & Smith, Health economics 2001). We recommend a rate of 1.5% for discounting outcomes.

International guidelines recommend to present different scenarios, in order to allow the decision maker to judge the relative importance of using different discount rates for the final result. The following scenarios are suggested:

- 3% for costs, 1.5% for benefits (reference case)

- 3% for both costs and benefits
- 5% for both costs and benefits
- 5% for costs, 0% for benefits
- 3% for costs, 0% for benefits
- 0% for both costs and benefits

4.13 GUIDELINE 13: USE OF DATA FROM OTHER COUNTRIES

When data from other countries are used, a transferability analysis must be made. The analysis should list and comment on all variables that potentially hamper the transferability to Belgium. Care should be taken that the study is in line with the requirements imposed by the reference case (Table 1) or at least allows adjustments to make the analysis in line with the reference case.

Transferability of results from economic evaluations performed in other countries is a major issue for the Drug Reimbursement Committee. Performing an original Belgian study for each product is often not feasible due to monetary, time or sample size constraints but the use of results from studies performed in other countries is only acceptable if transferability to a Belgian context is possible. If this is not the case, efforts should be made to perform an original Belgian pharmaco-economic analysis.

To assess whether studies are tranferable to Belgium, a transferability analysis should be performed. A transferability analysis reviews the factors for which transferability may be an issue. The transferability analysis is mainly descriptive in nature. A number of transferability factors have been identified in literature. Important aspects (adapted from Welte et al. 2004) are presented in

Table 4.

The table should be seen as a checklist for items to be taken into consideration in the transferability analysis. For each of the factors, the correspondence with the methods defined in the reference case (table 1), the correspondence with the Belgian situation, and the expected impact on ICER for Belgium should be described. Not for all studies all factors will be important.

Table 4: Transferability analysis

Transferability factor	Correspondence with reference case	Correspondence with Belgian situation	Estimated impact on ICER for Belgium
Methodological characteristics			
perspective of the evaluation	Yes/No	Yes/No/partly	Estimated to result in an ICER that is unbiased/higher/lower than the ICER for Belgium
comparator			
discount rate			
cost calculation: unit prices practice patterns resource use			
Patient characteristics			
disease incidence/prevalence			
ethnicity			
case-mix			
life expectancy			
health status preferences			
disease spread			
Health care system characteristics			
role of GP			
organisation of hospitals			
reimbursement/health insurance system			

Some of the factors preclude transferability to the Belgian situation, e.g. the drug studied (this has to be the same as the drug for which reimbursement is requested, including administration of the drug, dosage, packaging, etc.) and the comparator (should be the same than the standard treatment in Belgium). These are called knock-out criteria.

Models almost always require adjustments to the national situation due to differences in treatment protocols, relative prices and incidence/prevalence of the target disease. Especially resource use and cost estimation is a critical issue. Only if the study model provides sufficient detail, adjustment is possible.

A decision algorithm is proposed in Appendix 5. This appendix elaborates on the knock-out criteria.

5 REPORTING GUIDELINES

The recommended structure of a pharmaco-economic report is presented below. This structure is based on the reporting guidelines developed by the Pharmaco-economic Committee of the Belgian Society for Pharmacoepidemiology (BESPE). Some specific reporting guidelines for models are presented in chapter 7.

5.1 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

5.2 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

5.3 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 sub-groups + justification for choice of patients and sub-groups in a Belgian context
- Based on this information: formulate a clear question in answerable form

5.4 LITERATURE REVIEW

5.4.1 Clinical literature review

5.4.1.1 Methods

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

5.4.1.2 Results

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

5.4.1.3 Discussion and Conclusions of the clinical literature review

Data extraction sheets are provided in annex.

5.4.2 Economic literature review

5.4.2.1 Methods

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

5.4.2.2 Results

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

5.4.2.3 Discussion and Conclusions of the clinical literature review

Data extraction sheets are provided in annex.

5.5 BASIC ELEMENTS OF THE PHARMACO-ECONOMIC STUDY

5.5.1 Analytic technique

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

5.5.2 Study design

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

5.5.3 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

5.5.4 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

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

5.5.6 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)

5.5.7 Sensitivity analysis

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

5.6 RESEARCH METHODS

5.6.1 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

5.6.2 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 sub-groups
- 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

5.7 RESULTS

5.7.1 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.

5.7.2 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

5.8 DISCUSSION

- weaknesses of the study

5.9 CONCLUSION

5.10 TRANSPARENCY OF FINANCIAL SUPPORT

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

5.11 REFERENCES

5.12 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

6 PRESENTATION OF A MODEL

6.1 DATA

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

Variable's name	Description	Value (range or confidence interval)	Source

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.

6.1.1 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.

6.1.2 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.

6.1.3 Presentation of results

Extrapolation scenario	**Discount rate costs 0%, effects 0%**	**Discount rate costs 3%, effects 1.5%**	**Discount rate costs 3%, effects 3%**	**Discount rate costs 5%, effects 5%**
1	ICER (CI)			
2				
3				

7 DISCUSSION

These methodological and reporting guidelines are developed as a tool to make drug reimbursement requests submitted to the Drug Reimbursement Committee 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 pharmaco-economic 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 reimbursing if other elements weighted heavily in the decision process. The pharmaco-economic evaluation is, however, a very important element for the decision maker, as it may help him to allocate resources in the most efficient way. Consistency in pharmaco-economic submissions is a first step in the improvement of the reimbursement decision process.

8 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

(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.)

Level	Description
1	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

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 PHARMACO-ECONOMIC 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. A selected bibliography by methodological topics is also available in Appendix 8.

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 pharmaco-economic evaluations. There are disease specific and generic health-related quality of life measures, profile measures or single index measures, health-related quality of life can be assessed by patients themselves or by health care providers or family and valuation of a health state can be done by means of a Time-Trade-Off, Standard Gamble or Rating Scale.

Disease-specific quality of life measures are useful to get an insight into the domains of life that are affected by a disease or treatment. They are 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 pharmaco-economic 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.

MODELING

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 observational 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 pharmaco-economic 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, the non-parametric approach (also called bootstrap) and the Monte Carlo simulations. A brief summary of the methods follows.

Parametric methods

- *The confidence box approach.* This method combines the limits of the CI for the costs and for the effects separately, and gives an estimate of the best/worst cases scenario. The advantage of this method is that it is very easy to compute and to draw on the CE plane. The disadvantage is that it tends to overestimate the true interval, and that it does not use the joint density between the costs and the effects.
- *The Taylor series approximation:* This method uses the Taylor series approximation of the variance of a function of 2 random variables to estimate the variance of the ICER ratio. The advantage of this method is that it accounts for the correlation between the costs and the effects; the disadvantage is that it assumes that the ICER has a normal sampling distribution, which is not always the case.
- *The Fieller's method.* This method makes the assumption that the costs and effects follow a joint normal distribution. The advantage of this method over the previous one is that it takes into account the skew of the ratio estimator. This is the preferred parametric method.

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, 2005 #6} 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 are usually noted as $_{BA}$ and $_{CA}$, and 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, 2005 #6}.

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 {Baker, 2002 #7}

HANDLING MISSING COST DATA

In studies where patients are followed during a certain period of time (longitudinal design, RCT or non-interventional study), it is inevitable that some information (health status, costs) will be missing for some patients. Data can be missing for several reasons (lost to follow up, missed visit, etc…). Different methods that take the characteristics of the pattern of missing data into account exist to deal with the problem of missing data. In the special case where cost data are no longer observed after a certain time point (for example after a lost to follow up), data are said to be censored (this terminology comes from the analysis of survival data, where the date of death is not observed, but is know to occur after a certain time point).

When individual cost data are available, different methods are available to deal with missing observations.

- *Complete case analysis (CCA).* With this method, no imputation is performed, and all cases with missing data are excluded from the analysis. The advantage of the method is that it is very easy to implement, and therefore it may sound appealing to those researchers that do not wish to "create" data. However, drawbacks of this approach are that they may reduce substantially the power (by reducing the sample size) and also lead to biased results in some cases (if the mechanism that generates the data is not completely random).
- *Single Imputation (SI).* With that approach, missing data are replaced by a value based on the observed data (the mean of the sample of the observed data, the last/next value observed, etc.). Although also very simple to implement and widely used, these methods also suffer from some methodological drawbacks (such as treating the imputed data as they were known with certainty, which tends to reduce the variance artificially)
- *Multiple Imputation (MI).* This is a more complex method, essentially based on a 3 stage procedure (1: creation of several datasets with imputation of missing values based on the respective predictive distributions, stage 2: analysis of these datasets, stage 3: pooling of the results to get estimates and confidence intervals that incorporate the missing data uncertainty). The big advantage of these methods is that the confidence intervals and p-values are generally valid because they incorporate uncertainty due to missing data.

In the special case of censored costs data, specific methods are available (methods based on survival techniques or inverse probability weighting methods).

The method used to take into account the missing costs data should be described and justified.

APPENDIX 5: TRANSFERABILITY ANALYSIS

(Welte R, et al. A Decision Chart for Assessing and Improving the Transferability of Economic Evaluation Results between Countries. Pharmacoeconomics. 2004;22(13):857-76.)

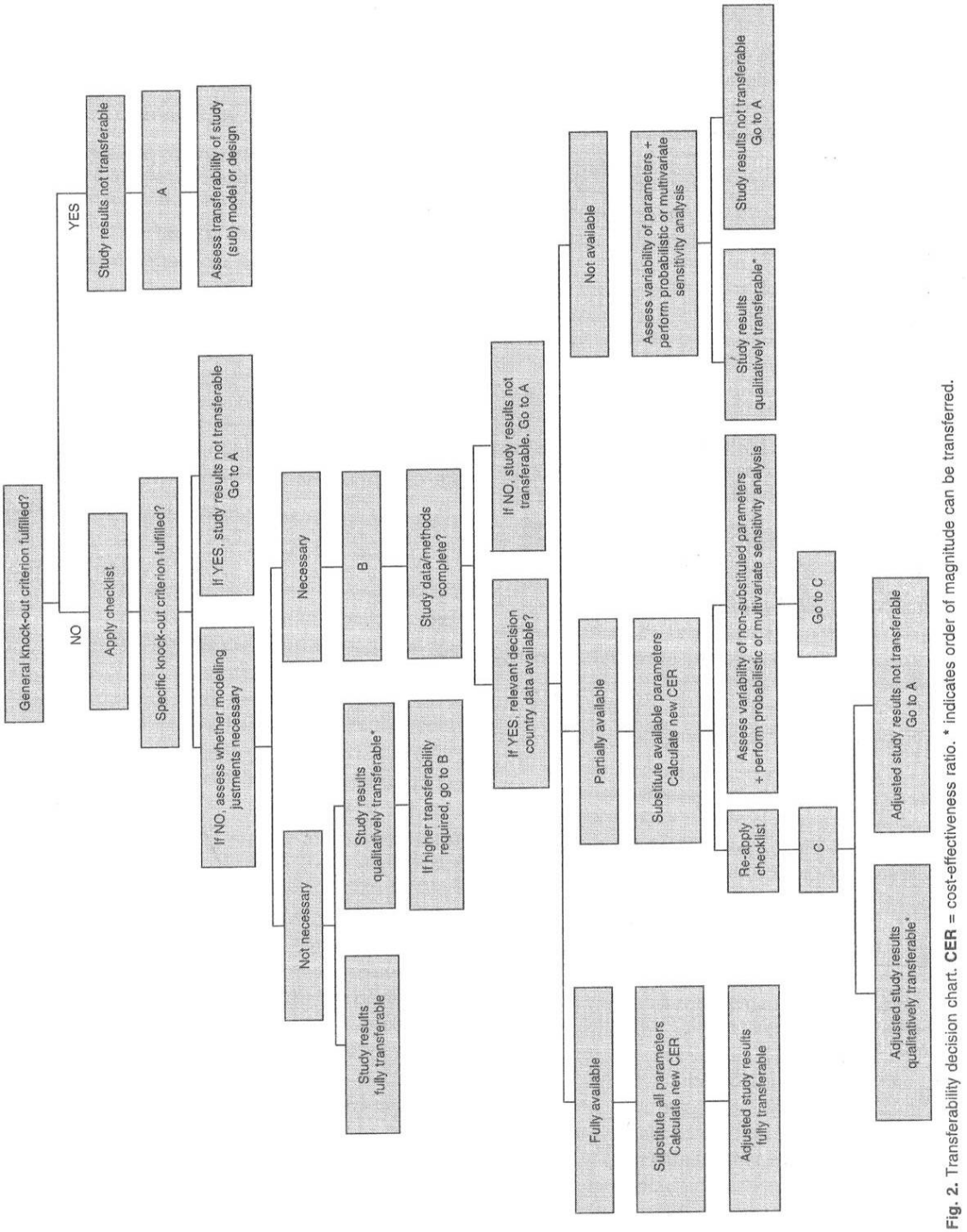

Fig. 2. Transferability decision chart. **CER** = cost-effectiveness ratio. * indicates order of magnitude can be transferred.

General knock-out criteria (factors that preclude transferability to a Belgian context) are:

- incomparability between the evaluated technology and the technology that shall be used in Belgium
- incomparability between the comparator in the study and the comparator that is relevant for Belgium
- bad quality of the study according to the standards required in economic evaluations

In addition to general knock-out criteria, there may also be specific criteria related to the study subject or the information available in the study that make transferability impossible. For example, if the study population is different in terms of age-structure from the Belgian target population, and age is an important factor in the treatment's cost-effectiveness, results may not be transferable.

Adjustments to models may be needed, especially when there are differences in practice patterns, relative prices and prevalence of the disease between the study country and Belgium.

APPENDIX 6: FLEMISH EQ-5D INDEX VALUES

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

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

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 1 - les révisions individuelles comme décrites dans l'A.R. du 21/12/2001
- des demandes initiales pour les classes 1 et 2, lors d'études concernant « expérience avec le produit », comme décrit dans les recommandations pour l'introduction d'un dossier classe 1 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 :
    - le concept, l'exécution, l'analyse et la rédaction de rapports des études conformément à leurs procédures opérationnelles standards (POS).
    - 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.eu.int/pdfs/human/ich/013595en.pdf)

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.

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 Modeling 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

http://www.afigp.fgov.be/New/FR/Departements/essais%20cliniq.htm

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

APPENDIX 8: METHODOLOGICAL REFERENCES BY TOPIC

GUIDELINES

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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. April 2004 (http://www.nice.org.uk/page.aspx?o=114264)

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

Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 2nd edition. Oxford: Oxford University Press, 1997.

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Modeling

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

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HANDLING MISSING COST DATA

General

Manca A, Palmer S. Handling Missing Data in Patient-Level Cost-Effectiveness Analysis alongside Randomised Clinical Trials. Appl Health Econ Health Policy. 2005;4(2):65-75.

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5. Evaluation des risques préopératoires. D/2004/10.273/10.
6. Validation du rapport de la Commission d'examen du sous financement des hôpitaux. D/2004/10.273/12.
7. Recommandation nationale relative aux soins prénatals: Une base pour un itinéraire clinique de suivi de grossesses. D/2004/10.273/14.
8. Systèmes de financement des médicaments hospitaliers: étude descriptive de certains pays européens et du Canada. D/2004/10.273/16.
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13. Traitement endovasculaire de la sténose carotidienne. D/2005/10.273/10.
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18. Utilisation des itinéraires cliniques et guides de bonne pratique afin de déterminer de manière prospective les honoraires des médecins hospitaliers: plus facile à dire qu'à faire.. D/2005/10.273/20
19. Evaluation de l'impact d'une contribution personnelle forfaitaire sur le recours au service d'urgences. D/2005/10.273/22.
20. HTA Diagnostic Moléculaire en Belgique. D/2005/10.273/24, D/2005/10.273/26.
21. HTA Matériel de Stomie en Belgique. D/2005/10.273.28.
22. HTA Tomographie par Emission de Positrons en Belgique. D/2005/10.273/30.
23. HTA Le traitement électif endovasculaire de l'anévrysme de l'aorte abdominale (AAA). D/2005/10.273.33.
24. L'emploi des peptides natriurétiques dans l'approche diagnostique des patients présentant une suspicion de décompensation cardiaque. D/2005/10.273.35
25. Endoscopie par capsule. D2006/10.273.02.
26. Aspects médico-légaux des recommandations de bonne pratique médicale. D2006/10.273/06.
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