Voorlopige richtlijnen voor farmaco-economisch onderzoek in België

KCE reports vol. 28A

Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
2006

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Voorlopige richtlijnen voor farmaco-economisch onderzoek in België

KCE reports vol. 28A

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2006

KCE reports vol. 28 A

Title :	Voorlopige richtlijnen voor farmaco-economisch onderzoek in België
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Conflict of interest :	Geen gemeld.
Disclaimer:	De experts en validatoren werkten mee aan het wetenschappelijk rapport maar werden niet betrokken in de aanbevelingen voor het beleid. Deze aanbevelingen vallen onder de volledige verantwoordelijkheid van het KCE.
Lay-out :	Nadia Bonnouh, Dimitri Bogaerts

Brussel, juli 2006 (2de editie, 1e editie : mei 2006)

Studie : 2005-06
Domein : Health Technology Assessment (HTA)

MeSH : Economics, Pharmaceutical ; Guidelines

NLM classification : QV 736

Taal : Nederlands, Engels
Format : Adobe® PDF™ (A4)

Wettelijk depot : D2006/10.273/10

Hoe refereren naar dit document?
Cleemput I, Crott R, Vrijens F, Huybrechts M, Van Wilder P, Ramaekers D. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de gezondheidszorg (KCE); 2006. KCE reports 28A (D2006/10.273/10)

Voorwoord

Vooruitgang in de gezondheidszorg wordt in belangrijke mate gestuurd door onderzoek van de geneesmiddelenindustrie. Het is vanuit hun standpunt dan ook evident dat zij het gebruik van hun producten zo veel mogelijk stimuleren en naar een snelle terugbetaling streven.

Niet alle ontwikkelingen in de sector hebben echter een even belangrijke maatschappelijke meerwaarde. Voor de overheid is het noodzakelijk om die 'added value' van een product af te wegen tegen de kosten ervan, zodat zij in staat is om haar middelen efficiënt te verdelen. In België werd in 2002 met de oprichting van de Commissie voor Tegemoetkoming van Geneesmiddelen de evaluatie van de kosten-effectiviteit van geneesmiddelen een belangrijk element in de beslissing voor de terugbetaling.

De bewijslast van kosten-effectiviteit ligt bij de producent. De regels voor het aantonen van de relatieve kosten-effectiviteit zijn echter vaag en laten veel ruimte voor betwistbare methodologische keuzes. Een gebrek aan transparantie en consistentie in de dossiers is het gevolg.

Naar aanleiding hiervan hebben het RIZIV en het KCE de koppen bij elkaar gestoken. Wat nu voorligt is, in analogie met andere landen, een set van richtlijnen voor de indiening van farmaco-economische evaluaties voor de terugbetaling van een geneesmiddel. Door middel van farmaco-economische richtlijnen kan de transparantie en kwaliteit van de dossiers verbeteren, wat ook de evaluatie van de dossiers ten goede zal komen. Een speciaal woord van dank gaat naar de leden van het bureau van de CTG, die naast de externe experten, valabele input gaven voor dit project.

De ontwikkeling van de richtlijnen vormde een eerste fase van een tweedelig project. In een tweede fase zullen de richtlijnen worden geëvalueerd tijdens een pilootproject waarbij de indieners de toepasbaarheid van de richtlijnen uittesten. De richtlijnevaluatie moet uiteindelijk leiden tot definitieve en bindende richtlijnen voor alle nieuwe dossiers.

Dit rapport handelt over economische evaluaties van geneesmiddelen. In deze sector zijn economische evaluaties ondanks nog belangrijke methodologische problemen ondertusssen gemeengoed geworden. In de toekomst zullen soortgelijke gezondheidseconomische evaluaties in andere sectoren zoals bvb. die van de implantaten, hulpmiddelen en diagnostische onderzoeken aan impact winnen.

De eerste reeks van Health Technology Assessments van het KCE toont alvast de dringende behoefte hiertoe aan in deze vooralsnog grotendeels braakliggende domeinen. Gezondheidseconomie lijkt dan ook een goede carrièrekeuze voor jonge economisten, tenminste in gezondheidszorgsystemen die budgettair onder druk komen te staan.

Jean-Pierre Closon
Adjunct algemeen directeur

Dirk Ramaekers
Algemeen directeur

Samenvatting van de richtlijnen

Dit rapport ontwikkelt richtlijnen voor farmaco-economische evaluaties die worden ingediend in de context van een aanvraag tot terugbetaling van farmaceutisch producten waarvoor een farmaco-economische evaluatie hetzij verplicht hetzij zinvol is. Het zijn voorlopig nog preliminaire richtlijnen. Ze zullen worden getest tijdens een pilootfase en vervolgens gefinaliseerd. De pilootfase zal verschillende maanden duren. De finale richtlijnen zullen in 2007 worden gepubliceerd.

De richtlijnen zijn opgebouwd aan de hand van een vast referentiekader dat de aanbevolen methodologie voor elke component van de economische evaluatie definieert. Elk farmaco-economisch dossier moet tenminste een analyse bevatten die is uitgevoerd in overeenstemming met de methodologie aanbevolen in het referentiekader. Bijkomende analyses zijn toegelaten maar kunnen de referentie-analyse geenszins vervangen.

Richtlijn 1: Literatuuroverzicht

Elke farmaco-economische evaluatie moet gepaard gaan met een systematisch overzicht van de bestaande klinische en economische studies over de interventie, ook niet gepubliceerde of met negatieve resultaten. De zoekstrategie voor de literatuur moet reproduceerbaar zijn en de selectiecriteria en procedures voor selectie duidelijk. Het overzicht moet alle *evidence* voor de klinische doeltreffendheid en de kosten-effectiviteit van het product weergeven. De *evidence* moet kritisch worden geëvalueerd, de kwaliteit ervan beoordeeld en de concrete gegevens voorgesteld in tabelvorm. Er moet een duidelijke maar beknopte synthese worden gegeven. Lopende studies dienen vermeld.

Richtlijn 2: Perspectief van de evaluatie

In farmaco-economische evaluaties die worden ingediend voor de aanvraag tot terugbetaling van een farmaceutisch product, mag de referentie-analyse enkel directe gezondheidszorgkosten bevatten vanuit het perspectief van de betaler voor gezondheidszorg. Deze omvatten zowel de betalingen uit het gezondheidszorgbudget van de overheid als de eigen betalingen door de patiënt. Gezondheidseffecten moeten worden gewaardeerd vanuit een maatschappelijk perspectief.

Richtlijn 3: Doelpopulatie

De patiëntenpopulatie waarop de farmaco-economische evaluatie van toepassing is, moet consistent zijn met de patiëntenpopulatie gedefinieerd in het klinisch deel van het terugbetalingsdossier. Als de impact van het geneesmiddel op de doeltreffendheid en/of kosten verschilt tussen subgroepen, moeten afzonderlijke subgroepanalyses worden uitgevoerd. Subgroepanalyses moeten (statistisch) gerechtvaardigd worden. Indien beschikbaar, moeten de epidemiologische gegevens voor België worden voorgesteld voor de volledige doelpopulatie alsook voor de relevante subgroepen.

Richtlijn 4: Comparatoren

Het geneesmiddel moet worden vergeleken met de meest relevante alternatieve behandelingen voor de voorgestelde indicatie van het geneesmiddel. De meest relevante alternatieve behandeling is ofwel de behandeling die met de meeste waarschijnlijkheid zal vervangen worden door de nieuwe behandeling of, in geval van behandelingen die bovenop een bestaande worden gegeven, de huidige behandeling zonder de nieuwe. Indien deze behandeling niet kan worden geïdentificeerd, moet de standaardbehandeling volgens de Belgische richtlijnen voor goede medische praktijk worden gebruikt als comparator. Soms zullen meerdere behandelingen in aanmerking moeten worden genomen als comparator.

De comparatoren kunnen medische of niet-medische behandelingen zijn.

De keuze van de comparator(en) moet altijd worden verantwoord.

Indirecte vergelijkingen zijn enkel toegelaten onder specifieke voorwaarden: de keuze voor een indirecte in plaats van een directe vergelijking tussen de studiebehandeling en de comparator moet worden verantwoord en de beperkingen van de indirecte vergelijkingen, die onder meer te maken hebben met de beperktere conclusies die men kan trekken uit dergelijke vergelijkingen, moeten duidelijk worden omschreven.

Richtlijn 5: Analytische techniek

Kosten-nutsanalyse moet worden toegepast als de behandeling een voor de patiënt significante impact heeft op gezondheidsgerelateerde levenskwaliteit of als er meerdere klinische parameters zijn die belangrijk zijn voor de patiënt die niet in dezelfde meeteenheden kunnen worden uitgedrukt (bijv. vermijden van complicaties van de ziekte versus bijwerkingen van het product).

Kosten-effectiviteitsanalyse moet worden toegepast als het hoofddoel van de behandeling is om de levensverwachting te verbeteren en dit ook de belangrijkste uitkomst is voor de patiënt of als er een duidelijk geïdentificeerde dominerende klinische parameter is die relevant is voor de patiënt (bijv. vermijden van complicaties) en er geen andere patiëntrelevante resultaten zijn die worden uitgedrukt in andere meeteenheden.

Gezien de continue controverse over de geschikte methodologie voor kosten-batenanalyse worden kosten-batenanalyses niet aanvaard als een referentietechniek voor farmaco-economische submissies.

Resultaten moet worden uitgedrukt in termen van een incrementele kosten-effectiviteitsratio of kosten-nutsratio.

Richtlijn 6: Studiedesign

Farmaco-economische evaluaties moeten tot op zekere hoogte altijd steunen op observationele gegevens van rechtstreekse vergelijkingen (gerandomiseerde gecontroleerde studies (RCT's) of niet-interventionele studies) tussen het studieproduct en een relevante comparator. Als modellering nodig is omdat de klinische studies onvoldoende informatie verschaffen voor de economische evaluatie, moet het aantal aannames dat niet gebaseerd is op krachtig klinisch bewijs, tot een minimum worden herleid.

Richtlijn 7: Berekening van de kosten

De identificatie, het meten en de schatting van de kosten moeten overeenstemmen met het perspectief van de Belgische zorgbetaler. Er moeten relevante bronnen worden gebruikt voor eenheidskosten. Kosten die geen rechtstreeks verband hebben met gezondheidszorg, mogen niet opgenomen worden in de referentieanalyse.

Bij ontbrekende kostengegevens in longitudinale RCT's of observationele studies, moet er informatie worden gegeven over welke gegevens er ontbreken, wat de redenen zijn voor het ontbreken van deze gegevens en welke methoden men heeft gebruikt om hiermee om te gaan in de analyses.

Richtlijn 8: Schatting en waardering van de resultaten

Resultaten van farmaco-economische evaluaties moeten worden uitgedrukt in termen van finale eindpunten in plaats van intermediaire parameters. Duidelijk gedefinieerde uitkomstenmaten, waarvoor weinig discussie bestaat over de meetmethoden, zijn aanbevolen.

Voor kosten-nutsanalyses moet het aantal gewonnen QALYs worden berekend. Levensverwachting moet worden geschat op basis van Belgische leeftijdsafhankelijke overlevingstabellen. De waardering van de gezondheidsgerelateerde levenskwaliteit moet steunen op observationele gegevens, verkregen via een beschrijvend systeem voor gezondheidstoestanden waarvoor reeds maatschappelijke preferentiewaarden bestaan of recent werden verzameld bij het algemene publiek. Het gebruik van Belgische preferentiewaarden wordt sterk aanbevolen .

Voor kosten-effectiviteitsanalyses moeten de resultaten worden uitgedrukt in termen van gewonnen levensjaren voor chronische aandoeningen of in termen van een relevant resultaat op korte termijn voor acute aandoeningen die geen lange termijngevolgen hebben. Schattingen met betrekking tot levensverwachting moeten zich baseren op leeftijdsafhankelijke overlevingstabellen voor België.

Richtlijn 9: Evaluatietermijn

De meest geschikte evaluatietermijn hangt af van het natuurlijk verloop van de ziekte. Chronische ziekten zullen een langere evaluatietermijn nodig hebben dan acute aandoeningen zonder lange termijngevolgen. Voor chronische ziekten en acute aandoeningen met gevolgen op lange termijn dient men een levenslange evaluatietermijn toe te passen.

Richtlijn 10: Modellering

Modellering moet worden overwogen als de beschikbare observationele gegevens onvoldoende zijn om een volledige evaluatie van de kosten-effectiviteit of de kosten-utiliteit van een product toe te laten. De keuze voor modellering moet altijd worden gerechtvaardigd en de structurele hypotheses, aannames en informatiebronnen moeten op een duidelijke en transparante manier worden voorgesteld. Basisgegevens en oorspronkelijke informatiebronnen die men heeft gebruikt om de waarden van de gebruikte inputparameters te definiëren, evenals het oorspronkelijke computermodel, moet ter beschikking worden gesteld van de Commissie voor Terugbetaling van Geneesmiddelen op eenvoudige aanvraag van deze Commissie.

Richtlijn 11: Omgaan met onzekerheid en het testen van de betrouwbaarheid van de resultaten

Ongeacht het studiedesign moet de onzekerheid rond de schattingen voor kosten-effectiviteit of kosten-utiliteit worden geanalyseerd met behulp van correcte statistische technieken. Het geschatte interval moet voor elke onzekere parameter in de economische evaluatie worden weergegeven. Alle verschillende aspecten van onzekerheid in de evaluatie moeten aan bod komen. Voor modellen moet een probabilistische sensitiviteitsanalyse worden uitgevoerd.

Richtlijn 12: Discontovoet

Toekomstige kosten moeten verdisconteerd worden aan 3% en toekomstige effecten aan 1.5% in de referentieanalyse. Om de gevoeligheid van de resultaten tegenover de gebruikte discontovoet te bepalen, moet men verschillende scenario's voorstellen:

0% voor effecten en 3% voor kosten,

0% of 3% of 5% voor zowel effecten als kosten en

0% voor effecten gecombineerd met 5% of 3% voor kosten.

Richtlijn 13: Gebruik van gegevens uit andere landen

Als gegevens uit andere landen worden gebruikt, moet men een overdraagbaarheidanalyse uitvoeren. De analyse moet alle variabelen die eventueel de overdraagbaarheid naar België hinderen opnemen in een lijst en van commentaar voorzien. De studie moet overeenstemmen met de vereisten die worden opgelegd aan de referentieanalyse of op zijn minst aanpassingen toelaten waardoor de analyse conform de referentieanalyse wordt.

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 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.

[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.)

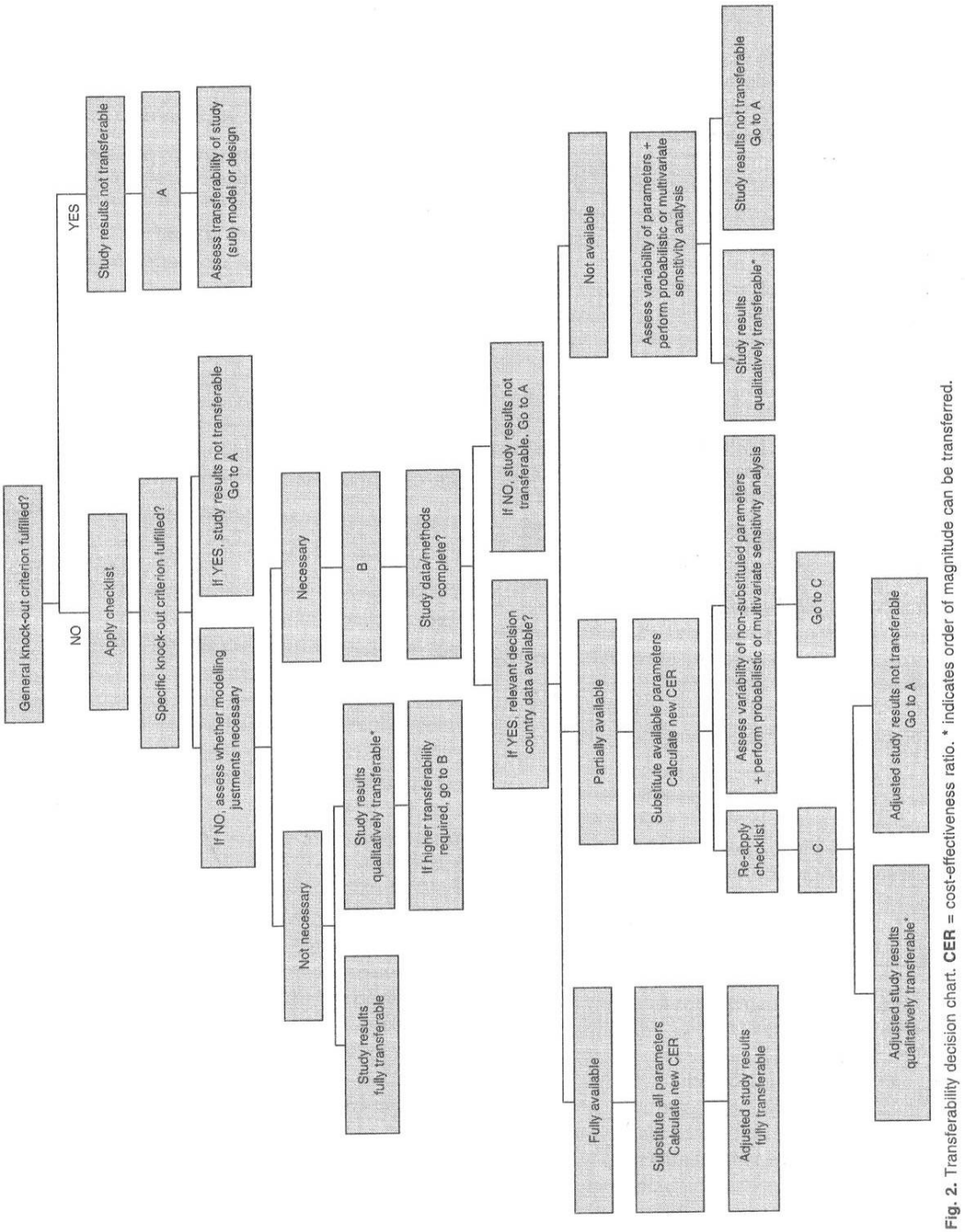

Fig. 2. Transferability decision chart. **CER** = cost-effectiveness ratio. * indicates order of magnitude can be transferred.

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

CTG-AABEVELING OMTRENT NIET-INTERVENTIONELE STUDIES

1. Inhoudstafel

2. Executive summary

Waarom een aanbeveling rond niet-interventioneel onderzoek

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

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

Doel van de aanbeveling rond niet-intervenioneel onderzoek

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

Toepassingsgebied

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

Meer in het bijzonder is ze van toepassing op :

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

Opbouw

De aanbeveling omvat volgende secties:

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

Sleutelelementen van de aanbeveling

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

Aan deze aanbeveling werkten mee

Eerste fase / groep van deskundigen:

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

Tweede fase / Commissieleden:

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

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

3. Introductie

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Niet-interventionele studies zijn dus geen alternatief voor interventionele klinische studies.

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

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

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

Ze omvat:

- een zeer beknopt overzicht van methodologische beschouwingen en gangbare studiedesigns in dit domein: dit is enkel ter illustratie om de mogelijkheden binnen het niet-interventioneel studiegebied te schetsen .
- een uitgebreid overzicht van de noodzakelijke elementen voor kwaliteitscontrole die bij iedere niet-interventionele studie in overweging dienen te worden genomen, en dit bij
    - het opstellen van de onderzoeksvraag
    - het vastleggen van de studiedesign
    - de uitvoering van de studie
    - de gegevensverwerking en de statistische analyse als bij
    - de rapportering van de studieresultaten

4. Toepassingsgebied :

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

Meer in het bijzonder is ze van toepassing op :

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

5. Methodologische beschouwingen en gangbare studiedesigns

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

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

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

Doelstellingen van niet- interventioneel onderzoek:

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

Keuze van design type

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

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

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

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

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

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

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

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

6. Kwaliteitscriteria

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

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

ICH Guideline on Good Clinical Practice (GCP) (http://www.emea.eu.int/pdfs/human/ich/013595en.pdf)

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

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

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

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

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

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

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

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

6.1. Aanvraag tot individuele herziening

In het kader van de klasse-1 herzieningen, kan de Commissie zich tot de aanvrager richten om bijkomende studies op te zetten en uit te voeren, die een antwoord moeten bieden aan de op het moment van het initiële voorstel tot tegemoetkoming nog aanwezige vragen omtrent de therapeutische en/of economische waarde van het betrokken geneesmiddel.

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

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

6.2 Uitvoering van niet-interventionele studies

6.2.1 Protocol

Elke studie moet een schriftelijk protocol bevatten.

Het protocol moet minstens volgende elementen bevatten:

1. Een beschrijvende titel en identificatie van de versie (bv. datum);
2. De namen, titels, graden, adressen van alle verantwoordelijke partijen en hun organisaties;
3. De naam en het adres van elke opdrachtgever en zijn afgevaardigde(n);
4. Een opsomming van de onderzoeksdoelstellingen, specifieke studiehypothesen (a priori en a posteriori) en –eindpunten (met hun prioriteit) evenals de rationale voor het onderzoek;
5. Een beschrijving van de onderzoeksmethodes, met inbegrip van;

- onderzoeksdesign met argumentatie om het voorgestelde studiedesign te kiezen
- De populatie die moet worden bestudeerd
- De populatie wordt gedefinieerd in termen van personen, plaats, tijdsperiode en selectiecriteria. De rationale voor de inclusie- en exclusiecriteria en de impact ervan op het aantal personen die beschikbaar zijn voor analyse moet worden beschreven.
- De gebruikte methode voor de steekproeftrekking
- Bepaling en definiëring van de eindpunten van de studie waarbij zoveel mogelijk gevalideerde meetinstrumenten worden gebruikt
- Methodes voor gegevensbeheer met o.a.;
- Beschrijving van de gegevensbronnen
- Procedures voor gegevensbeheer, van inzameling tot goedgekeurde database
- Procedures om inconsistenties of fouten te corrigeren, het inbrengen van waarden of het wijzigen van ruwe gegevens
- Methodes voor gegevensanalyse met o.a.;
- Geplande omvang van de studie, statistische precisie en de basis voor de bepaling hiervan
- Voorstelling van de te gebruiken statistische methoden en hun rationale
- Bespreking van statistische technieken om te corrigeren voor bias

- Bespreking van de studie beperkingen inzake design, verloop en analyse.
- Er moet minstens rekening worden gehouden met eventuele tekortkomingen op statistisch, epidemiologisch, therapeutisch en/of economisch vlak en een bespreking van hun impact op de interpretatie van de verwachtte resultaten.

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

Dit hoofdstuk moet informatie bevatten over

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

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

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

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

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

6.2.2 Verantwoordelijkheden

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

De taken en verantwoordelijkheden moeten duidelijk zijn afgebakend tussen de opdrachtgever van de studie en de contractant(en) inzake opzet en uitvoering van de

verschillende aspecten van de studie waaronder het eigendom en de archivering van de gegevens.

Personeel

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

Bescherming van personen

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

6.2.3 Studieverloop

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

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

Gegevensinzameling, gegevensbeheer en gegevenscontrole

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

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

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

Analyse

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

Studieverslag

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

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

Het eindverslag moet hierbij minstens het volgende omvatten:

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

Communicatie

Er bestaat een ethische plicht om bevindingen die een potentieel wetenschappelijk belang of een belang voor de volksgezondheid hebben, te verspreiden; studieresultaten zullen worden kenbaar gemaakt door publicatie in de wetenschappelijke literatuur, bij voorkeur in een 'peer-reviewed' tijdschrift. De auteurs van studieverslagen moeten de richtlijnen volgen die zijn opgesteld door het International Committee of Medical Journal Editors (http://www.icmje.org/). Alle auteurs moeten beantwoorden aan de criteria voor auteurschap en alle mensen die hieraan voldoen moeten auteur zijn. Potentiële belangenconflicten moeten aan het licht worden gebracht. Het akkoord om deze richtlijnen na te leven moet in het protocol worden beschreven.

Meedelen van ongewenste gebeurtenissen (adverse events)

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

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

Archivering

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

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

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

6.2.4 Materiaal te overhandigen aan de Commissie

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

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

- lijst van de deelnemende centra, met inbegrip van de hoofdonderzoekers en co-onderzoekers;
- de aantallen gescreende en geregistreerde patiënten per centrum;
- lijst van alle contractanten, meewerkende instellingen en andere relevante studiesites;
- het studieprotocol en de eventueel bijgewerkte versies;
- een kopij van de blanco formulieren voor gegevensinzameling;
- het eindverslag van de studie;
- een kopie van de gevalideerde gegevensbank in een voor analyse toepasselijk formaat;

7. Bijlagen

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

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

Longitudinale data:

8 Verbeke, G. and Molenberghs, G. (2000). Linear Models for Longitudinal Data. New York: Springer Verlag. 568 pages. ISBN 0-387-95027-3
9 Fahrmeir L. and Tutz G. (2001) Multivariate Statistical 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

Algemeen naslagwerk:

11 Ström "Pharmacoepidemiology" Wiley, third edition 2000

Bijlage 2: Extract uit Wet van 7 mei 2004:

«**klinische proeven**»: elke onderzoek bij proefpersonen dat bedoeld is om de klinische, farmacologische en/of andere farmacodynamische effecten van één of meer experimentele geneesmiddelen vast te stellen of te bevestigen, en/of eventuele ongewenste effecten van een of meer experimentele geneesmiddelen aan te tonen en/of de absorptie, de distributie, het metabolisme en de eliminatie van een of meerdere experimentele geneesmiddelen te bestuderen, teneinde de veiligheid en/of de werkzaamheid ervan vast te stellen;

«**proef zonder interventie**»: studie binnen het kader waarvan het of de geneesmiddel(en) op een gebruikelijke manier zijn voorgeschreven, conform de in de toestemming om op de markt te worden gebracht bepaalde voorwaarden. De aanwijzing van de patiënt voor een gegeven therapeutische strategie is niet bij voorbaat vastgelegd door een proefprotocol, doch maakt deel uit van een courante praktijk, terwijl de beslissing om het geneesmiddel voor te schrijven volledig losstaat van deze die het opnemen van de patiënt in de studie betreft. Geen enkele bijkomende procedure inzake diagnose of bewaking moet op de patiënt worden toegepast, terwijl epidemiologische methodes worden gebruikt om de ingezamelde gegevens te analyseren.

Bijlage 3 : Volledige basistekst van externe experten

/ enkel na specifieke aanvraag

Bijlage 4 : Wet van 7 mei 2004

/ via internetadres

http://www.afigp.fgov.be/New/NL/Afdelingen/r-d/klinische_studies.htm

Bijlage 5 : ISPE aanbeveling van aug 2004

/ via internetadres

http://www.pharmacoepi.org/resources/guidelines_08027.cfm

Bijlage 6 : ICH GCP document E6

/ via internetadres

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

Bijlage 7 : Cochrane Reviewer's handbook:

bias definitions / via internetadres

http://www.cochrane.org/admin/manual.htm

APPENDIX 8: METHODOLOGICAL REFERENCES BY TOPIC

GUIDELINES

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

CES. French Guidelines for the Economic Evaluation of Health Care Technologies. Sept. 2004.

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)

GENERAL

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.

STUDY DESIGN

Trial-based economic evaluations

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

Evans C et al, Data collection methods in prospective economic evaluations: how accurate are the results ?, Value in Health vol 3, issue 4, pp 277-286, July 2000.

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

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

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

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

HANDLING UNCERTAINTY

Overview

Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technology Assessment. 1999;3(2).

Confidence Interval around the ICER

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

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

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

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.

Allison P.D. 2002 Missing Data, Sage University Paper 136, Sage Publications Inc, THOUSAND OAKS, USA.

Schafer, J.L. (1997) Analysis of Incomplete Multivariate Data. Chapman & Hall, London.

Methods for Censored Costs data

O'Hagan A, Stevens JW. On estimators of medical costs with censored data.J Health Econ. 2004 May;23(3):615-25.

Etzioni RD, Feuer EJ, Sullivan SD, Lin D, Hu C, Ramsey SD. On the use of survival analysis techniques to estimate medical care costs.J Health Econ. 1999 Jun;18(3):365-80.

Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data.Stat Med. 2005 Jan 15;24(1):131-45.

Lin DY. Regression analysis of incomplete medical cost data.Stat Med. 2003 Apr 15;22(7):1181-200.

Willan AR, Lin DY, Cook RJ, Chen EB. Using inverse-weighting in cost-effectiveness analysis with censored data. Stat Methods Med Res. 2002 Dec;11(6):539-51.

Multiple Imputation Methods

Oostenbrink JB, Maiwenn J. Al The analysis of incomplete cost data due to dropout, Health Economics Volume 14, Issue 8 , Pages 763 – 776

Rubin DB, Multiple imputation for non-response in surveys, Wiley, N-Y, 1987

Rubin, D.B. (1996) Multiple imputation after 18+ years (with discussion). J Am Stat Ass, 91, 473-489.

Schafer JL. 1999. Multiple imputation: a primer. Statistical Methods in Medical Research 8: 3-15.

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Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. Health Technology Assessment. 2005;9(26).

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

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

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

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Wettelijk depot : D/2006/10.273/10

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1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.