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



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADH – HJA	Hospital Day-care Anonymous Hospital Stays (Anonieme Dag Hospitalisaties – Hospitalisations de Jour Anonymes)
AIC	Akaike's Information Criterion
AMCP	Academy of Managed Care Pharmacy
APR – DRG	All Patient Refined-Diagnosis Related Group
AZV – SHA	Hospital Inpatient Anonymous Hospital Stays (Anonieme ZiekenhuisVerblijven – Séjours Hospitaliers Anonymes)
BCFI – CBIP	Belgian Centre for Pharmacotherapeutic Information (Belgisch Centrum voor Farmacotherapeutische Informatie – Centre Belge d'Information Pharmacothérapeutique)
BFM – BMF	Budget of Financial Means (Budget Financiële Middelen – Budget des Moyens Financiers)
BIA	Budget impact analysis
BIC	Bayesian Information Criterion
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CCA	Cost-consequences analysis
CDA – AMC	Canada's Drug Agency / l'Agence des médicaments du Canada
CDSR	Cochrane Database of Systematic reviews
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CMA	Cost-minimization analysis
COMET	Core Outcome Measures in Effectiveness Trials
CPI	Consumer price index
CTG – CRM	Commissie Tegemoetkoming Geneesmiddelen – Commission de Remboursement des Médicaments (Drug Reimbursement Committee)
CTIIMH – CRIDMI	Commission for Reimbursement of Implants and Invasive Medical Devices (Commissie Tegemoetkoming voor Implantaten en Invasieve Medische Hulpmiddelen – Commission de remboursement des implants et des dispositifs médicaux invasifs)
CTR	Clinical Trials Regulation
CUA	Cost-utility analysis
DALYs	Disability-adjusted life years

EMA	European Medicines Agency
EPS	Permanent Sample (Echantillon Permanent – Permanente Steekproef)
EQ-5D	EuroQol 5 dimensions questionnaire
EQ-5D-3L	EQ-5D three-level version
EQ-5D-5L	EQ-5D five-level version
EQ-5D-Y	EQ-5D youth version
EU	European Union
EU HTA Regulation	European Union Health Technology Assessment Regulation
EUnetHTA	European Network for Health Technology Assessment
EVPI or EVPPI	Expected value of perfect or partially perfect information
FDA	Food and Drug Administration
FPS (FOD – SPF)	Federal Public Service (Federale Overheidsdienst – Service Publique Fédéral)
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAS	Haute Autorité de santé
HDA	Health Data Agency
HICP	Harmonised Index of Consumer Prices
HIQA	Health Information and Quality Authority
HIS	Health Improvement Scotland
HTA	Health Technology Assessment
HTACG	Member State Coordination Group on HTA
HRQoL	Health-related quality of life
HUI	Health Utilities Index
IC	Incremental costs
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICHOM	International Consortium for Health Outcome Measurement
ICMJE	International Committee of Medical Journal Editors
IE	Incremental effects
IMA – AIM	Intermutualistic Agency (Intermutualistisch Agentschap – Agence Intermutualiste)
INAHTA	International Network of Agencies for Health Technology Assessment
iPCQ	iMTA Productivity Cost Questionnaire
IPD	Individual patient data
IQWiG	Institute for Quality and Efficiency in Health Care
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
KCE	Belgian Health Care Knowledge Centre
KM	Kaplan-Meier
LY	Life year
LYG	Life year(s) gained
MDC	Major diagnostic category
MDR	Medical Device Regulation
MZG – RHM	Minimale Ziekenhuis Gegevens – Résumé Hospitalier Minimum
NCDB	National Cancer Database
NCPE	National Centre for Pharmacoeconomics
NICE	National Institute for Health and Care Excellence
NoMA	Norwegian Medicines Agency
OCMW – CPAS	Openbaar Centrum voor Maatschappelijk Welzijn – Centre Public d'Action Sociale
OECD	Organization for Economic Cooperation and Development
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PFS	Progression-free survival
PHARMAC	Pharmaceutical Management Agency
PICO(S)	Patient, intervention, comparator(s), outcomes (& study design)
PPP	Purchasing power parity
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
QWB	Quality of Well-Being
RCT	Randomised controlled trial
RIZIV – INAMI	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering – Institut National d'Assurance Maladie-Invalidité (National Institute for Health and Disability Insurance)
RoB	Risk of Bias
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
RVV – BIM	Rechthebbende op verhoogde verzekeringstegemoetkoming – Bénéficiaire de l'intervention majorée
SD	Standard deviation
SF-6D	Short-Form 6 Dimensions

SG	Standard gamble
SOI	Severity of illness
TCT	Technical Cell (Technische Cell – Cellule Technique)
TSD	Technical Support Document
TTO	Time-trade off
VAS	Visual analogue scale
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
YHEC	York Health Economics Consortium
ZIN	Zorginstituut Nederland

SCIENTIFIC REPORT

1 BACKGROUND

Since 2002, a request for reimbursement of a class 1 pharmaceutical product by a pharmaceutical company has to be accompanied by an economic evaluation (Royal Decree of 21 December 2001[1]). Over the years, this Royal Decree has been updated, but the core has remained the same: a pharmaceutical product is ranked as a class 1 drug only if a therapeutic added value compared to existing therapeutic alternatives has been demonstrated. Otherwise, it is categorised as a class 2 or class 3 drug (art. 5 §1-2 of the Royal Decree of 1 February 2018).[2] Reimbursement requests are evaluated by the Drug Reimbursement Committee (CTG–CRM) based on the preparatory assessments conducted by the experts of the RIZIV–INAMI administration (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering – Institut National d'Assurance Maladie-Invalidité (National Institute for Health and Disability Insurance)). If a pharmaceutical product is ranked in class 1 by the applicant, five criteria will be used in the assessment of the reimbursement request (art. 4 and art. 6 of the February 2018 Royal Decree):[2] [a]

- The therapeutic value, taking into account the efficacy, effectiveness, side effects, applicability and user-friendliness of the product,
- The price of the pharmaceutical product and the reimbursement rate proposed by the applicant,
- The importance of the pharmaceutical product in medical practice as a function of therapeutic and societal needs,
- The budgetary impact for the National Health Insurance,
- The cost-effectiveness of the product from the perspective of the National Health Insurance.

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

The definition of therapeutic value used in the Royal Decree is wider than the notion of safety or effectiveness, as frequently used in clinical and economic literature. Besides morbidity, mortality and health-related quality of life (HRQoL), it encompasses social and practical components such as applicability of the product and comfort of use (art. 1, 23° of the February 2018 Royal Decree[2]). This broader definition has implications for the assessment of the cost-effectiveness of a product. While usual outcome parameters in economic evaluations are morbidity, mortality and/or HRQoL, additional reflections and analyses may be necessary to describe the therapeutic (added) value of a product.

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

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[a] An overview of the basic regulations on medicines under the compulsory health insurance is available on the RIZIV-INAMI website: https://www.riziv.fgov.be/nl/publicaties/basisreglementering-over-geneesmiddelen.
The Royal Decree of 1 February 2018 specifying the procedures, deadlines and conditions regarding the reimbursement of the compulsory insurance for medical care and pharmaceutical products is available here: https://www.ejustice.just.fgov.be/eli/besluit/2018/02/01/2018010896/justel.

The procedure for the reimbursement of implants and invasive medical devices is similar. The rules and procedures are stipulated in the Royal Decree of 25 June 2014.[3] [b] The assessment criteria are the same as for pharmaceutical products and their applicability also depends on the class of the device. This is determined by the device's therapeutic or health economic (added) value that is claimed in the reimbursement request file: class 1: demonstrated added value compared to existing therapeutic alternatives; class 2: equivalent therapeutic value but no demonstrated *added* therapeutic value compared to existing alternatives (art. 17 of the March 2014 Royal Decree[3]). For class 1 devices, the same five criteria previously described for pharmaceutical products are used in the assessment (art.16 and art. 18 of the March 2014 Royal Decree[3]).

For several other types of health interventions (e.g. medical procedures), economic evaluations are not a strict requirement for reimbursement decisions. Nevertheless, even in these cases, economic evaluations are useful to assess whether reimbursement of these interventions entails efficient use of limited healthcare resources.[c] Therefore, these guidelines are useful for all types of health interventions, such as pharmaceutical products, devices, surgical procedures, vaccines, disease prevention strategies, screening programmes, health promotion activities, psychotherapy, physiotherapy, health care delivery initiatives, etc.

1.1 Rationale for the update of the guidelines for economic evaluations and budget impact analyses

In 2008, the Belgian Health Care Knowledge Centre (KCE) published a first set of guidelines for pharmacoeconomic evaluations in Belgium.[4] In 2012, a second edition was published with a minor update in 2014.[5] This second edition extended the guidelines to all medical interventions and included guidelines for both economic evaluations and budget impact analyses. These guidelines have been used for over a decade now by multiple stakeholders from governments, universities, the industry, consultants, and other for-profit and not-for-profit entities. Based on their experience, questions and feedback and (national and international) evolutions in the field (e.g. regarding the growing use of real world data, and the introduction of the European Union Health Technology Assessment Regulation (EU HTA Regulation)), an update was considered timely.

Important amendments relate to the use of the most recent Belgian value sets for quality of life (part 5.10.2), the recently published guidance documents developed to support the implementation of the EU HTA Regulation (part 5.10.1 and 5.10.3), raising awareness of the importance of timely consideration of economic evaluations (i.e. when setting up clinical research protocols) (part 4.2.3), the role and use(fulness) of real-world data (part 4.2.4), more explicit indication of the reference case, including the base case and mandatory scenarios, and the possibility for complementary analyses (part 4.2.6), etc.

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[b] The Royal Decree of 25 June 2014 specifying the procedures, deadlines and conditions regarding the reimbursement of the compulsory insurance for medical care and cost of implants and invasive medical devices is available here: https://www.ejustice.just.fgov.be/eli/besluit/2014/06/25/2014022305/justel.

[c] The NICE guidelines manual (https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness), states: "*guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.*" For the assessment of whether the (extra) cost per patient is acceptable for the (extra) benefits the intervention provides, an economic evaluation provides valuable information.

KEY POINTS

- In Belgium, cost-effectiveness is one of the five criteria to evaluate reimbursement requests for class 1 drugs and medical devices, i.e. products for which the manufacturer claims an added therapeutic value and for which a higher price can be requested. Budget impact is a reimbursement criterion for all reimbursement requests.
- Although cost-effectiveness is not a formal reimbursement criterion for *all* types of health interventions in Belgium, the current guidelines are applicable to a broad range of interventions such as surgical procedures, vaccines, disease prevention strategies, screening programmes, health promotion activities, psychotherapy, physiotherapy, health care delivery initiatives, etc.
- An update of the existing guidelines for health economic evaluations and budget impact analyses appeared timely, following multiple comments, questions and feedback from users of the former guidelines and national and international evolutions in the field.

2 OBJECTIVES

The objective of this study was to update the methodological and reporting guidelines for economic evaluations and budget impact analyses of health interventions, that is, pharmaceutical, medical device or other interventions, submitted to expert committees at the RIZIV–INAMI, advising the health minister about reimbursement. An economic evaluation is defined as a comparative analysis of at least two health interventions in terms of their costs and health consequences. A budget impact analysis (BIA) is defined as a tool to predict the potential financial impact of the adoption and diffusion of a new technology into a healthcare system with finite resources.[6, 7] The aim of a BIA is to measure the impact of a (possible) policy decision concerning a specific intervention on the healthcare budget.

Any intervention for which a health economic evaluation or a BIA is required by the RIZIV–INAMI for reimbursement, should be assessed by following these guidelines which present the requirements for a reference case. Companies are strongly recommended to follow these guidelines for every economic evaluation and BIA submitted in the context of a reimbursement request. Any deviation needs a clear and detailed justification (see part 4.2.6).

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

These guidelines will assist both the developers and assessors in conducting and assessing/appraising economic evaluations and BIAs. Furthermore, they may assist researchers in identifying relevant outcomes that should be included in their study protocols in order to produce robust economic evaluations and budget impact analyses (see part 4.2.3).

KEY POINTS

- **The aim of the guidelines is to increase the relevance, methodological quality, transparency and uniformity of economic evaluations and budget impact analyses of health interventions in Belgium.**
- **Working in a common framework, the guidelines assist both those conducting economic evaluations and budget impact analyses and assessors. They also support researchers in gathering the necessary data to be able to perform robust economic evaluations and budget impact analyses.**

3 METHODS

The update of the guidelines was based on evolutions in the research field, identified through review of the guidelines of other Health Technology Assessment (HTA) institutes, evolutions in the European collaboration on HTA and specific feedback from Belgian stakeholders on the previous guidelines, based on their experience.

First, guidelines from other countries were reviewed. Guidelines for economic evaluations and Budget Impact Analysis of healthcare interventions used in European countries, US, Canada, Australia and New Zealand, were searched in July 2024. Only guidelines issued since 2012, i.e. the year of the previous version of the Belgian guidelines, were considered. The guidelines used to inform this update were mainly from Ireland (Health Information and Quality Authority, HIQA), the Netherlands (Zorginstituut Nederland, ZIN), Canada (Canada's Drug Agency, CDA[d]) and the UK (National Institute for Health and Care Excellence, NICE). An overview of the search strategy and identified guidelines is available in Appendix 1.

Secondly, guidance documents relating to the joint clinical assessments (JCAs) and joint scientific consultations (JSCs), as developed under the EU HTA Regulation, were carefully considered and taken into account when there were implications for the economic evaluations at national level.

Finally, several stakeholder meetings were organised with external experts experienced in applying the guidelines, including experts from the RIZIV–INAMI assessing reimbursement requests for the Drug Reimbursement Committee (CTG–CRM) and the Commission for Reimbursement of Implants and Invasive Medical Devices (CTIIMH–CRIDMI), experts working for the pharmaceutical industry (invited through Pharma.be), experts working for the device industry (invited through BeMedTech), professors in health economics from Belgian universities and private consultants. Additionally, the guidelines were also discussed internally with KCE experts. A draft version of the updated guidelines with track changes was delivered to all stakeholders after which comments could be provided to the KCE team. The KCE authors of this report took responsibility for formulating the final guidelines.

The core text of the guidelines is deliberately brief, especially for items for which there is little discussion about the most appropriate methodology. The guidelines are not intended as a textbook for every item that is mentioned. It is assumed that readers have basic knowledge about economic evaluations and budget impact analyses.

In Chapter 4, a brief overview of the guidelines (part 4.1) and some general remarks directly or indirectly related to (performing) economic evaluations are presented (part 4.2). The guidelines for the economic evaluations and budget impact analyses are presented in Chapters 5 and 6, respectively. A general discussion is provided in Chapter 7. The appendices provide supportive documentation, and elaborate on some technical aspects of the guidelines. A vocabulary list is also presented.

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[d] In December 2023, it was announced that Canada's Drug Agency (CDA) would be built from the Canadian Agency for Drugs and Technologies in Health (CADTH): https://www.cda-amc.ca/news/cadth-now-canadas-drug-agency.

4 BRIEF OVERVIEW OF THE BELGIAN GUIDELINES AND GENERAL REMARKS

4.1 Overview of the Belgian guidelines

The reference case defines the elements of an economic evaluation or BIA and the recommended methodology for each component. The reference case consists of a base-case analysis with all mandatory sensitivity and scenario analyses for specific components. We are aware that discussion about the appropriateness of the recommended methodology is possible. Such discussion may relate to value judgements (e.g. the discount rate to reflect the time preference for health benefits), technical aspects (e.g. the choice of the uncertainty analysis) or other issues. Therefore, provided that there is a strong justification, the reference case *can* be complemented (but not replaced) by an analysis that deviates from the recommended reference case methods on one or more aspects. The justification should be supported by scientific evidence. The reference case methods for economic evaluations and BIAs are briefly presented in Table 1 and Table 2, respectively. For full details we refer to Chapters 5 and 6.

Table 1 – Reference case methods for economic evaluations

Component of an economic evaluation	Reference case	Guideline
Current situation & research question	Clear description of the disease and the current standard of care. Clear description of the decision problem, specifying the PICO elements.	1
Literature review	Systematic review of up-to-date clinical and economic literature following methodological standards: reproducible search strategy, transparent selection criteria, critical appraisal. The approach for searching information for specific elements of the economic evaluation (e.g. HRQoL) or BIA (e.g. epidemiological data) also needs to be transparent.	2
Perspective of the evaluation	Costs: Health care payers (federal government + communities (or other local authorities) + patients). Outcomes: Patients for measurement of outcomes; Society for valuation of outcomes. (HRQoL – health states should be described by patients on a generic utility instrument. Health state valuations for these states should come from the general public) (see guideline 10).	3
Target population	Consistent with the clinical part of the reimbursement request. Clinically relevant subgroups need to be defined. (Post-hoc) subgroup analyses only in case of appropriate statistical proof of differences in safety, effects, costs or heterogeneity in baseline risk.	4
Intervention	A clear description of the intervention should be provided, including actions required to use the intervention.	5
Comparator	Economic relevant comparisons are performed on the efficiency frontier, calculating ICERs for non-dominated interventions. This might include both “current practice”, as well as other more cost-effective alternatives. The latter may include an evidence-based off-label intervention.	6
Analytic technique	Preference for cost-utility analysis (CUA) if HRQoL is of importance. The choice for cost-effectiveness analysis (CEA),	7

Component of an economic evaluation	Reference case	Guideline
	cost-minimization analysis (CMA) or cost-consequences analysis (CCA) should be justified.	
Study design	Economic evaluation based as much as possible on data from head-to-head RCTs between the study intervention and the comparator(s). Most of times some modelling is needed.	8
Calculation of costs	Direct health care costs paid by the federal government, the communities (or other local authorities) and the patients. Focus on incremental costs. Mandatory scenario analyses applying price discount scenarios for the comparator(s) and other relevant treatments reimbursed under confidential contracts.	9
Valuation of outcomes	CUA: QALYs gained, with HRQoL weights based on empirical data obtained with a generic utility instrument such as the EQ-5D-5L for adults for which public preference values from the Belgian population exist. CEA: life years gained (LYG) for interventions with an impact on mortality. Recommended to use head-to-head RCTs with final patient-centred endpoints (if possible). Indirect comparisons may be accepted. Validity of estimates for treatment efficacy/effectiveness should be assessed. Where surrogate endpoints are used, evidence supporting the validity of the surrogates needs to be provided.	10
Time horizon	The appropriate time horizon for the economic evaluation depends on the duration of the impact of the study intervention on relevant outcomes as compared to the comparator intervention. When modelling a long time horizon, mandatory scenario analyses applying shorter time horizons.	11
Discount rate	3% for costs and 1.5% for outcomes. Mandatory scenario analyses applying an equal discount rate for both costs and effects of 0%, 3% and 5%.	12
Equity weighting	None (weight all outcomes equally regardless of the characteristics of people impacted by the intervention or comparator).	13
Modelling	Based as much as possible on data from clinical studies comparing the study intervention and the comparator(s), data from validated databases and/or data from literature. Clear presentation of model structure, input variables, (extrapolation) assumptions and sources of information. Both internal, external and face validity should be checked. Mandatory scenario analyses applying different extrapolation assumptions.	14
Handling uncertainty	Probabilistic sensitivity analyses for parameter uncertainty. Scenario analyses for structural and methodological uncertainty.	15
Reporting	Transparent reporting, allowing replication and critical assessment. An overview of all input variables should be provided.	16

Component of an economic evaluation	Reference case	Guideline
	Presentation of uncertainty around the incremental costs (IC), incremental effects (IE) and ICERs by means of confidence intervals. Results presented using the cost-effectiveness plane, cost-effectiveness acceptability curve, and tornado diagram.	

BIA: budget impact analysis; EQ-5D: EuroQol 5 dimensions questionnaire; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; PICO: patient, intervention, comparator(s), outcomes; QALY: quality-adjusted life year; RCT: randomised controlled trial.

Table 2 – Reference case methods for budget impact analyses

Component of a BIA	Reference case	Guideline
Literature review	See economic evaluation guideline.	2
Perspective of the evaluation	See economic evaluation guideline.	3 & 17
Target population	See economic evaluation guideline. Calculate the annual budget impact up to the steady state. The size of the population may vary over time.	4 & 18
Comparator	The current situation that might change if the intervention under consideration is introduced in the healthcare system. Also consider the budget impact of more cost-effective alternatives (based on the results of the economic evaluation).	19
Calculation of costs	See economic evaluation guideline (inclusive mandatory scenario analyses applying price discount scenarios for the comparator(s) and other relevant treatments reimbursed under confidential contracts). Transfers of budgets between different levels of governments and/or patients should be considered.	9
Costs of health outcomes	The cost consequences of the treatment effect, side effects and other short- and long-term consequences should be included in the BIA.	20
Time horizon	The time needed to reach a steady state budget impact, with a minimum time horizon of 3 years (if the steady state is already reached in the short-term).	21
Discount rate	No discounting.	22
Modelling	See economic evaluation guideline. Consistent with the clinical and economic assumptions in the economic evaluation.	14 & 23
Handling uncertainty	See economic evaluation guideline. Deterministic sensitivity analysis for (expert-based) assumptions, including best- and worst-case scenarios.	15 & 24
Reporting	Transparent reporting, allowing replication and critical assessment.	25

BIA: budget impact analysis.

Before presenting the guidelines, some general remarks follow about economic evaluations and BIAs of medical interventions.

4.2 General remarks

4.2.1 Access to all clinical evidence

KEY POINTS

- **Having access to all clinical evidence is essential to perform a balanced assessment of the intervention. This includes both studies with positive results and studies with negative results, as well as discontinued studies for which the reason for discontinuation must be stated.**
- **Data on clinical trial outcomes should be available at all times. "Academic in confidence" redactions should be avoided.**

Full access to relevant study results should be pursued and facilitated. In the HTA regulation, the dossier specifications for medicinal products and medical devices and in vitro diagnostic medical devices stipulate that the dossier should include "*all up-to-date published and unpublished information, data, analyses and other evidence as well as study reports and study protocols and analysis plans from studies with the [intervention] for which the health technology developer was a sponsor and all available information on ongoing or discontinued studies with the [intervention] for which the health technology developer is a sponsor or otherwise financially involved, and corresponding information about studies by third parties if available, relevant to the assessment scope …, including the clinical study reports and clinical study protocols if available to the health technology developer*".[8] This should support the completeness of clinical study information at the point of performing the Joint Clinical Assessment (JCA).

For interventions that fall out of the scope of this HTA regulation, there is no legal framework that obliges the health technology developer to provide all relevant evidence, e.g. both positive and negative trial results. Nevertheless, in line with the HTA regulation, it is desirable that the health technology developer submits a list of all clinical studies involving the intervention under consideration and provides transparency about the status of these studies and study results (or e.g. the reason why a specific study was stopped). This is also in line with the 2024 revised Declaration of Helsinki that states that, "*researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human participants and are accountable for the timeliness, completeness, and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.*"[9] Access to all evidence is essential to perform a balanced assessment of the intervention.

The 2024 revised Declaration of Helsinki also states that "*medical research involving human participants must be registered in a publicly accessible database before recruitment of the first participant.*"[9] This ethical standard has been partially implemented in a number of laws. The US Food and Drug Administration (FDA) requires for instance all submitted trials involving FDA-regulated drug, biological, or device products (excluding Phase 1 trials and small feasibility studies) to be registered no later than 21 days after enrolment. Results of those trials should also be submitted, in general, no

later than 1 year after the study's primary completion date.[e] Prospective registration of all trials (regardless of the phases and study interventions) and submission of the results is applied when the clinical trials are funded by the US National Institute of Health.[f] In the EU, prospective registration of clinical trials and submission of the results is more fragmented (where there are two separated legislation for clinical trials with drugs and for clinical investigation with medical devices). In general, clinical trials involving drugs or devices should be registered[g] and a summary of results must also be uploaded within one year of the end of the trial.[h] For clinical trials not covered by the Clinical Trials Regulation (CTR) or the Medical Device Regulation (MDR), the registration and result submission requirements are national. Generally, regulatory authorities use the existing guidelines. For instance, the WHO Joint statement on registration of clinical trials and public disclosure of results from clinical trials.[i]

These obligations allow assessors to check the completeness of submitted evidence. The International Committee of Medical Journal Editors (ICMJE) has stated that results or data contained in assessment reports published by HTA agencies, medical regulators, medical device regulators, or other regulatory agencies will not be considered to be duplicate publications.[10] This removes the rationale behind "academic in confidence" redactions.[11] Data on clinical trial outcomes that are of importance to patients, clinicians, researchers and assessors should be available at all times. It should be explicitly stated if companies are not able or willing to provide the requested information.

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e Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (https://clinicaltrials.gov/policy/fdaaa-801-final-rule). For more information, we refer to the following link: https://clinicaltrials.gov/policy/faq#resultsInfoSubDeadline.

f For more information, we refer to the following link: https://clinicaltrials.gov/policy/reporting-requirements.

g For clinical trials with medicinal products, from 31 January 2025, all ongoing clinical trials in the European Union (EU) fall under the Clinical Trials Regulation (CTR) and should have been submitted to the Clinical Trials Information System (CTIS). With this platform, the registration of all concerned clinical trial becomes automatic and part of the information becomes accessible (not the early phases clinical trials) before the start of the trial (see art. 80 CTR). A similar obligation exists for some clinical trials with medical devices, but due to delays in the implementation of the platform (EUDAMED), sponsors must register their clinical investigations in another platform to be compliant with section 5.4 of ISO14155. SE MDCG 2024-3 Guidance (https://health.ec.europa.eu/document/download/690de85a-ac17-45ea-bb32-7839540c25c4_en?filename=mdcg_2024-3_en.pdf).

h EU: Article 37.4 of the Clinical Trials Regulation. In principle, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. See also article 77.7 of the MDR for medical devices (available to the public when the device comes on the market). Result-related information should be posted within the timeframes set out in the Regulation (EC) No 1901/2006 and the guidelines referred to under Section 1, i.e. (relating to paediatric clinical trials) within six months and otherwise within one year of the end of the trial (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52012XC1006(01)).

i https://www.who.int/news/item/18-05-2017-joint-statement-on-registration.

4.2.2 Performing an economic evaluation in the context of weak or non-existing evidence

KEY POINTS

- **The fact that an intervention targets a rare disease is not an argument for not conducting an economic evaluation.**
- **Uncertainty regarding evidence, due to issues related to rareness of a condition, should always be taken into account in economic evaluations.**
- **The reliability and validity regarding the estimated treatment effect will influence the reliability and validity of the economic evaluation. If no or only weak evidence is available, the model can at most be considered hypothetical.**

In general, it is recommended to always request/perform an economic evaluation if an added value is claimed and the intervention will cost more than the comparator (or vice versa if an intervention is less effective and less costly). This also applies to interventions for rare diseases. It is recognized that in rare indications, the evidence might be weak or non-existent and there may be more uncertainty about the estimated treatment effect. For example, in cases where there are only single-arm or non-randomised studies, the evidence might be insufficient for estimation of the relative treatment effectiveness.[12] This will lead to the conclusion that the economic evaluation is hypothetical or cannot provide reliable results. The same argument also applies to medical devices, screening, lifestyle interventions, etc. If there is no reliable evidence on the magnitude of the treatment effect, it becomes difficult to perform a reliable economic evaluation.

In line with the Guidance on the validity of clinical studies for joint clinical assessments regarding uncertainty, we emphasise that "*the certainty of results is independent of the medical context of the PICO question. It is methodologically inappropriate, for example, to take the rareness of a disease or the impossibility of blinding as a justification to ignore the resulting uncertainties in the clinical evidence.*"[13] Evidence regarding treatment effectiveness and its related uncertainties should be used as input for the economic evaluation.

In addition, there might be fundamental problems with the (quality of the) evidence supporting the added value claims. For example, as indicated in the methodological guidance document; "*For some interventions, single-arm or non-randomised evidence may be the only evidence available for consideration. However, it may well be that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA.*"[12] If the health technology developer cannot develop an economic evaluation due to the lack of evidence, they can state this explicitly. Where an economic evaluation is performed in the context of a lack of evidence of the relative treatment effect, the assessor may conclude that the economic evaluation is hypothetical or does not provide reliable results and therefore focus on other assessment criteria when reviewing the reimbursement request.

4.2.3 Think about the economic evaluation in due time

KEY POINTS

In economic evaluations, the focus is on the incremental impact on both costs and effects. When setting up clinical trials and writing research protocols, researchers should already think about a possible future economic evaluation to select relevant endpoints and appropriate outcome measures.

In economic evaluations, the focus is on the incremental impact on both costs and effects, i.e. the elements that are different when comparing the intervention with its relevant comparator(s). Both positive and negative impacts in the short- and long-term should be included. When designing a

research protocol for a clinical trial, it is important to think about these potential incremental impacts and how these can be measured. For example, if researchers set up an RCT and indicate there might be a large effect on productivity, it is important to think about how to measure this effect and include an appropriate instrument in the research protocol (see part 5.9.3.9). Similarly for quality of life, if this is considered relevant, including a generic utility instrument to complement a disease-specific instrument(s) in the RCT research protocol is recommended (see part 5.10.2). Hence, the guidelines for economic evaluations are important not only for those who carry out or assess such evaluations, but also for researchers involved in conducting research since the guidelines provide support for the information needs. Including the relevant endpoints and appropriate measurements can support the conduct of an economic evaluation and improve its quality when the trial is completed.

There are several possible sources to assist in selecting appropriate outcomes, e.g. relying on patient experience or existing core outcome sets. There are the International Consortium for Health Outcome Measurement (ICHOM) or Core Outcome Measures in Effectiveness Trials (COMET) initiatives.[j] However, the recommendations from these sets are not always fit for use in economic evaluations and, for example, to calculate QALYs.[14] Hence, it is recommended that protocols should also take into account the suitability of outcome measures for conducting economic evaluations.

Finally, it may be interesting to link data from randomised patients to information from existing administrative databases. For example, for survival, after the end of the trial follow-up, it is generally possible to track the long-term survival of the randomised (Belgian) patients via the Crossroads Bank for Social Security. This may be important if more mature data (i.e. longer follow-up) are requested. In theory, it is also possible to make a link with information on e.g. the incidence of a specific type of surgery that can be identified through the nomenclature. The relevance and reliability of the administrative data, as well as the ability to access them, should be considered first. If making a link with such information is possible, then it is necessary to include this in the study protocol, seek deliberation from the Information Security Committee to the extent its legally necessary, and inform the patient at the moment of study participation.[k] This approach can be considered because, in comparison with active collection of this information within a study, it may allow access to relevant information in a very efficient way without increasing (or even decreasing) the cost of a randomised study.

4.2.4 Data sources: the place of real-world data, models and expert opinion

KEY POINTS

- **The appropriateness of specific data sources depends on the intended use of the data.**
- **RCTs (and meta-analysis) are the best source for estimates of the relative treatment effects.**
- **Real-world data is useful for specific variables for an economic evaluation applicable to Belgium (e.g. costs, baseline risk for specific events, etc.).**
- **Data from expert panels is not accepted for key input variables (e.g. the relative treatment effect). If such data is used, the model should be labelled as hypothetical.**

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j https://www.ichom.org/ & https://www.comet-initiative.org/.

k We recommend checking the legal basis for possible future linkage before finalising the research protocol.

Real-world data, e.g. observational data from registries or administrative databases, is under usual circumstances[l] unsuitable to provide valid and reliable evidence on the added therapeutic benefit of an intervention because of the absence of a randomised comparison group.[m] It is, however, useful to value specific variables needed for an economic evaluation relevant to the Belgian context. Real-world data might provide information for the following non-exhaustive list of elements:

- The number of patients in the target population (~budget impact)
- A description of the characteristics of the real-world target population (~external validity)
- The intervention(s) used in the real-world target population (~identification of relevant comparator)
- The natural history and care pathway of the specific disease
- The baseline risk for specific events (~baseline risk adjustment)
- The context-specific costs related to the intervention (if already applied in the real-world), comparator(s), or specific events (e.g. adverse events or rehospitalisations), including information on e.g. the average treatment duration or length of hospitalisation
- Long-term adverse events
- Adherence/compliance and/or persistence in the target population[n]

Modelling studies can be performed to combine the information from randomised and non-randomised real-world data (see part 5.8.2).

Expert opinion is the lowest form of evidence.[16] Evidence generated by expert opinion elicitation, either using structured or unstructured methods, is subject to risk of bias and high uncertainty.[17] In any case, researchers should always firstly try to identify appropriate data sources to inform parameter estimates.[18] While using expert opinion to obtain information about a determining variable (such as the relative treatment effect) is not recommended, expert opinion can be used for e.g. checking the face validity of the results of a model, identifying the conditions in which an intervention is used and the potentially relevant comparators. "*Data derived from expert panels are not generally acceptable, especially for key effectiveness or safety variables. However, this approach may be reasonable for other variables.*"[19] The approach used to elicit expert opinions should be specified and should be used in combination with extensive sensitivity analyses. If expert opinion is used for key variables such as the relative treatment effect, the model should be labelled as hypothetical.

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l In the case of large treatment effects, non-randomised studies may already demonstrate the impact of an intervention. For example, if before the use of an intervention for a given indication, no patient survives longer than 3 months, but after the introduction of this intervention, a large proportion of this population are still alive after one year without any indication that something else in the patient population or the treatment pathway has changed. However, for most interventions the treatment effect is not that large and it is important to have a reliable estimate of both the direction as well as the relative and absolute size of the treatment effect. Randomised studies are the gold standard for estimating the relative treatment effect.

m Note that real-world data from registries or administrative databases can sometimes be used to generate real-world evidence from RCTs, through the application of an appropriate study design that allows for appropriate comparisons between different types of health interventions for the same indication (e.g. registry-based RCTs or pragmatic RCTs).

n It is important to consider whether adherence/compliance and/or persistence are important for the technology under evaluation and whether these are different in the real world in comparison with the situation in trial(s).[15] If they are different, this might have a substantial impact on effectiveness and/or safety and thus an intervention's cost-effectiveness. The impact of e.g. (poor) adherence should be quantified based on appropriate evidence. The impact of changing assumptions related to adherence should be explored in sensitivity analyses.

4.2.5 Access to public data

KEY POINTS

Access to good quality Belgian data for the measurement and valuation of resource use should be facilitated to allow for economic evaluations with higher relevance for health care policy makers.

Data requirements for good economic evaluations and budget impact analyses are high. Although good quality data for Belgium are often available at the company's level or at the governmental level, these data are not always easily accessible. For example, companies may find it difficult to estimate the average costs of treating a specific complication in Belgium without access to individual data on health care expenditures; similarly, governmental agencies may find it difficult to perform or verify economic evaluations of medical interventions without access to complete datasets from all relevant clinical trials. Confidentiality, secrecy and publication bias hamper the quality of economic evaluations and budget impact analyses in Belgium as well as their relevance for reimbursement decisions. Access to essential public data for the measurement and valuation of resource use for those performing economic evaluations, including companies, their subcontractors for the economic evaluation and other experts is often limited. In Appendix 2, we refer to a number of useful databases, as well as access opportunities for various stakeholders.

4.2.6 The reference case and flexibility

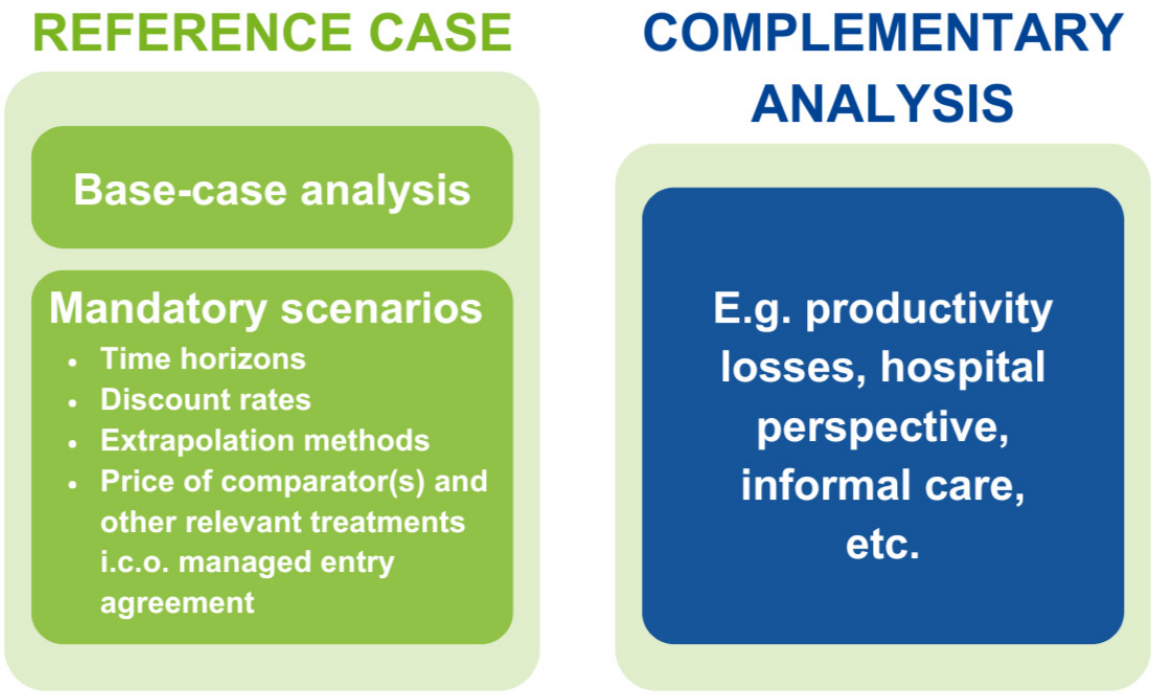
KEY POINTS

- **The guidelines for economic evaluations and budget impact analyses specify a reference case to increase transparency and uniformity, facilitating comparisons across disease areas and over time.**
- **Deviations from the reference case should be justified. Non-reference case analyses should be presented as additional analyses.**

For most methodological aspects of economic evaluations and budget impact analyses, different approaches exist. To improve transparency and consistency in future reimbursement requests, these guidelines focus on describing a "reference case", including the essential elements for each economic evaluation or BIA together with the most appropriate methodology. The Drug Reimbursement Committee (CTG–CRM), the Commission for Reimbursement of Implants and Invasive Medical Devices (CTIIMH–CRIDMI), or other expert committees could request an economic evaluation and/or a BIA according to these "reference case methods", facilitating comparisons across disease areas and over time.

The reference case consists of a base-case analysis with a number of mandatory scenarios. Besides these base-case analyses, complementary analyses are allowed. These might include non-mandatory scenario analyses or deviations from the reference case, as presented in Figure 1.

Figure 1 – Reference case versus complementary analyses



Non-reference case analyses cannot replace the reference case but can be highly relevant. The appraisal committee, however, will decide how much weight it attaches to the additional analyses.

It is recommended to think ahead when designing the (clinical) studies and clearly define upfront the elements that are important for the reference case and/or non-reference case economic evaluations, as well as the ways to gather evidence for these elements (e.g. measuring the impact on productivity with validated instruments, see part 5.9.3.9). This can support the relevance and reliability of these analyses.

5 GUIDELINES FOR HEALTH ECONOMIC EVALUATIONS

5.1 Guideline 1: Description of the current situation and research question

Each economic evaluation should include an adequate description of the disease and the current standard of care.

The research question should be clearly described, specifying at least the target population, the intervention(s) and the comparator(s) studied.

5.1.1 Description of the disease and current standard of care

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

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

5.1.2 Description of the research question

A clear and relevant research question should be established to set the context of the economic evaluation.[18, 20] Aspects that should be addressed in defining the research question include the target population (and potentially relevant subgroups) (see part 5.4), the intervention under evaluation (see part 5.5) and relevant comparator(s) (see part 5.6). Further details reflecting the setting in which the intervention is used, the study perspective (see part 5.3), the time horizon (see part 5.11), etc. can be provided.

5.2 Guideline 2: Literature review

A systematic review of the relevant clinical literature should be performed. The inclusion and exclusion criteria supporting the study selection should reflect the research question. The review should report up-to-date evidence for safety and clinical effectiveness of the intervention relative to its appropriate comparator(s). Results of both published and unpublished studies should be included (or the lack of information related to unpublished studies should be explicitly mentioned). Stopped studies and ongoing studies should also be included in the review.

A review of economic studies is useful to identify relevant input parameters and possible structures for the economic model, as well as to support the assessors.

If an additional search strategy is performed for specific elements (e.g. QoL or epidemiological data), this search strategy should be reported transparently.

The medical and economic search strategies should be reproducible and selection criteria and procedures clearly presented. The evidence should be critically appraised, its quality assessed and data presented in summary/evidence tables. A clear and concise synthesis, substantiated with references, should be provided.

5.2.1 Literature review: safety and efficacy/effectiveness

The validity and reliability of an economic evaluation crucially depends on the completeness, validity and reliability of the evidence it is based upon. As mentioned before, having access to all evidence is essential to perform a balanced assessment of the intervention. For a full overview of the clinical effectiveness of a medical intervention, it is crucial to start with a thorough and systematic literature review on the safety and efficacy and/or effectiveness of the interventions. The review should be based on the best available up-to-date evidence for clinical effectiveness of the intervention and the comparator(s). Besides published literature, an overview of ongoing studies should be provided. Studies that were stopped (e.g. for safety issues) should also be described.[o] Unpublished studies can be identified by searching clinical trial registries.[p] Results of these studies should also be included (e.g. by contacting the principal investigator) or the lack of availability of trial results should be explicitly stated.

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

5.2.2 Literature review: economic evaluations

A review of the economic literature can be carried out for several purposes. First of all, it is possible that an existing economic evaluation applicable to the Belgian context has already been carried out. In most cases, no such study will yet have been published. Even then, conducting a review of economic evaluations is still valuable. It is useful e.g. to identify relevant input parameters or the structure of the model. Being aware of other economic evaluations and the applied models with their similarities, differences, strengths and weaknesses can also help researchers avoid duplication of effort when tackling the same decision-making problem.[18] This can provide support to both those who set up a context-specific economic evaluation as well as the assessors (e.g. identifying critical points of attention discussed in previous evaluations). The results of existing economic evaluations can also be used to validate results, e.g. comparing the number of life years gained (LYG) or quality-adjusted life years (QALYs).

When analysing the results of economic evaluations, the presence of significant publication bias should be noted. An analysis based on a registry of 8192 cost-effectiveness analyses identified a significant and systemic bias due to sponsorship that was present across a range of diseases and study designs, with industry-sponsored studies more often reporting lower incremental cost-

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[o] It is a misconception that stopped studies should not be included because study results would not be published. There is a big difference between e.g. a study that is stopped because of problems with inclusion of patients versus a study that is stopped because of safety issues. This kind of information is needed to perform an appropriate assessment of all evidence.

[p] Examples of trial registries are:

- The EU Clinical Trials Register (https://www.clinicaltrialsregister.eu), which provides a search of clinical trials in European Union member states and the European Economic Area.
- ClinicalTrials.gov (https://clinicaltrials.gov), providing access to summary information about ongoing and completed clinical studies.
- The International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/clinical-trials-registry-platform; https://trialsearch.who.int/), which provides access to a central database containing the trial registration data sets provided by about 20 clinical trial registries.

effectiveness ratios (ICER).[21] Stakeholders with a conflict of interest will be reluctant to publish economic evaluations that are not in favour of their intervention and vice versa. Therefore, calculating an average ICER based on published economic evaluations makes no sense.

5.2.3 Search strategies

The methodology for conducting systematic reviews should be used to search for the best available up-to-date evidence. For more information about conducting systematic reviews of clinical and economic literature we refer to:

- the guidance for undertaking reviews in health care of the Centre for Reviews and Dissemination (CRD),[q]
- the NICE process and methods guideline for identifying evidence,[r]
- KCE's process note "Search for evidence".[s]

In general, the review should be transparent about the search strategy, study selection criteria and procedures used to select studies, study quality assessment, data extraction sheets, etc.

A literature review is an iterative process. A first search might reveal the existence of a high-quality systematic review. In that case, the literature review can be limited to an update of the existing review to include more recent primary studies. The approach to find HTA reports will be the same for both the clinical and economic search strategy. It is advised to search the international HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA).[t] This is an open access, publicly available, bibliographic database, with references provided voluntarily by INAHTA's members. In addition, since this database is not complete, a search of the websites of HTA institutes is also recommended. For the clinical search strategy, the Cochrane Database of Systematic reviews (CDSR)[u] should also be searched.

Next, after searching for existing systematic reviews and HTA reports, different databases and search strings should be used to retrieve primary clinical and economic studies. Databases searched for clinical evidence should include at least:

- Medline,
- Embase and,
- The Cochrane Central Register of Controlled Trials (CENTRAL[v]).

The economic search strategy should include searches in Medline and Embase.

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q https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. This guidance document was published in 2009. It provides general information about search strategies. However, to identify up-to-date literature databases, we refer to the more up-to-date NICE process and methods guideline for identifying evidence and KCE's process note.

r https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission.

s Formulation of the review questions, study location, study selection, critical appraisal and data extraction: https://processbook.kce.be/search-evidence-gcp-hta.

t https://database.inahta.org/.

u https://www.cochranelibrary.com/cdsr/about-cdsr.

v https://www.cochranelibrary.com/central.

The methodology used for the literature search should be clear and reproducible. Selection of articles is part of the review process. The selection criteria include specification of the population, the intervention, the comparator(s), the outcomes and the study design(s) (PICOS: Population, Intervention, Comparator, Outcome, Study Design). With respect to the outcomes,[w] consideration should be given to (1) disease-specific outcomes, (2) adverse events, (3) overall survival and (4) quality of life, for both the intervention and the comparator. The selection criteria could also relate to the years of publication, population size, language, etc. The main requirement is transparency in selection criteria and justification as to why certain selection criteria were applied. Therefore, exclusion of articles is not problematic *per se* once the reasons for exclusion are well-justified.

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

The search algorithm should be presented, including date of search and search terms used for each database. It is possible to use existing search filters[x] extended with relevant search terms from the PICO. It is recommended to show the number of hits per line. A PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram,[y] specifying the yield and exclusions (with the reason for exclusion) should be presented.

An overview of the selected studies (based on the defined selection criteria) should be provided. For the excluded studies, a summary table, stating the reason for exclusion, should be included in the appendix. A synthesis of the evidence found should be provided.

5.2.4 Critical assessment is more than following a (reporting) checklist

Both clinical and economic literature should be critically appraised. For the economic literature, both checklists (e.g. Appendix 3) and data extraction sheets can be useful tools to collect the relevant data from the selected literature. Appendix 4 provides an example of a data extraction sheet for economic studies.

The statements and data presented in the literature review should always be accompanied by the references from which they are derived. The external validity of study results included in the review, and their applicability to Belgium, should be assessed, especially if these results are used in the subsequent economic evaluation.[13] In this context it is worth noting that clinical practice guidelines can be but are not necessarily evidence-based. Issues affecting external validity of RCTs are discussed by Rothwell.[24] They relate to the setting of the trial, selection of patients, characteristics of selected patients (e.g. baseline risk), differences between the trial protocol and routine practice, outcome measures, follow-up, and adverse effects of treatment. A full list of the issues highlighted by Rothwell[24]

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w GRADE requires a clear specification of the relevant setting, population, intervention, and comparator. It also requires specification of all important outcomes--whether evidence from research studies is, or is not, available.[22]

x Several search filters are available, e.g.: https://www.sign.ac.uk/using-our-guidelines/methodology/search-filters/ or https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home. Remark: The economic studies filter used by SIGN is available for both Medline and Embase. For Medline, only the OVID version of the search filter is provided. The query language in PubMed is different. We refer to a research article[23] for an overview of these differences and a PubMed translation of the OVID economic studies filter.

y https://www.prisma-statement.org/.

is found in Appendix 5. The analysis of the external validity and hence the relevance of study results for Belgium is mainly descriptive in nature.

If stakeholders wish to make use of the results of existing economic evaluations, it is important to check to what extent the inputs and assumptions applied correspond to the most up-to-date clinical evidence and whether they are applicable to the Belgian context. This exercise is more than just checking whether all inputs have been transparently reported (e.g. according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist) and requires a critical assessment of the input parameters used.

5.2.5 Input from other studies in modelling

If modelling is used for the primary economic evaluation, all (clinical) studies used to derive the input parameters should be described in detail (including methodology used, assumptions, results). This also applies to inputs from other economic evaluations used in the primary economic evaluation. It should be clear what the underlying reference or methodology is or if these inputs are assumptions only. Relevance and appropriateness should be discussed in detail. While the use of unpublished material in an economic evaluation is allowed, the material should be sufficiently described to allow evaluation of its appropriateness.

It is possible that a (targeted) search strategy may be implemented for specific input variables of the primary economic model. This may be the case, for example, when searching for epidemiological data, specific utilities or costs associated with the occurrence of a particular adverse event. As with a systematic search strategy, it is important to be transparent about how this (targeted) search strategy was carried out (which search terms in which database) so that it is reproducible.

5.3 Guideline 3: Perspective of the evaluation

The reference case analysis should only include direct health care costs from the perspective of the public and private health care payers. This includes payments out of the federal government's and the communities' health care budget (or other local authorities) as well as patients' co-payments. Health outcomes should be measured in patients but health state values should come from the general public.

Analyses from another perspective are allowed, if justified, and should be clearly distinguished from the reference case.

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

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

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

To be of interest to the decision maker the calculation of the ICER should be based on the aggregated costs of the health care payers, i.e. the patients, the federal government *and* the communities, as well as other local authorities. An ICER for either the government or the patient only does not make much

sense as its value will depend on the level of reimbursement of the product. Therefore, the ICER should be based on the aggregated costs of *all* health care payers.

For the health care policy makers, it is nevertheless useful to report costs for the different categories of health care payers also in disaggregated form, i.e. as the costs borne by the different categories of payers (see part 6.10).

Outcomes included in the analysis should be relevant for the patient population involved in the treatment and valued from a societal perspective. If HRQoL is used as an outcome measure, health states should be described by patients but values of HRQoL should be values allocated to these states by the general public (see part 5.10.2).

This does not mean that consequences of a treatment relevant from a broader perspective cannot or will not be taken into account in resource allocation decisions. Other considerations, such as impacting the patient's absence from work (absenteeism) or the functioning at work (presenteeism) linked to illness or medical conditions, may be important factors in determining the value of a therapy. Other examples might relate to (levels of) education or school attendance, impact on informal caregivers' productivity, impact on addiction, organizational impact, etc. If researchers argue the impact of these elements is important, then it is essential to accurately measure the impact of the intervention on these elements. Elements that are difficult to translate into monetary terms or utilities can at least be included by describing the impact in e.g. a cost-consequences analysis (see part 5.7.4). Attention should be paid to double-counting, e.g. including time sacrifices which are already considered in changes in HRQoL.[18]

If these consequences are expected to be important for a specific treatment, additional analyses can be presented. However, these complementary analyses cannot replace the reference case analysis. For example, if it is indicated that the intervention allows a patient to return to work sooner, then an analysis from a societal perspective can be presented, in addition to the analysis from the health care payers' perspective.

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

5.4 Guideline 4: Target population

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

If the intervention's effectiveness and/or costs differ between clinically relevant subgroups (e.g. based on pre-specified analysis), separate subgroup analyses should be performed. A scientific justification for subgroup analysis should always be provided.

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

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

5.4.1 Description of the target population

The target population should be clearly defined. Parameters to define the target population can refer to different elements, such as: 1) baseline demographic characteristics, e.g. age and/or gender; 2) disease characteristics, e.g. stage or severity, presence of comorbidities and/or risk factors; 3) treatment setting, e.g. primary care or hospital setting; 4) the context of past treatment, e.g. non-responders, treatment relapse, non-adherence and/or poor tolerance.[20] The target population could refer to a patient population for which the intervention is approved, as well as to off-label use.[18]

The target population may also be broader than the originally targeted population for the intervention. Consider for instance the impact on informal caregivers or spill-over effects. As stated in the French guidelines: "*The population concerned can be extended to include other individuals when their health is affected by the interventions studied, even though they were not targeted. Examples include: the positive effect of a vaccination programme for persons who are not vaccinated but are nevertheless protected; the negative effect of antibiotic therapies if antibiotic resistance develops.*"[25] The Irish guidelines go a step further and also refer to impact on future cohorts: "*Consideration should be given to modelling multiple cohorts where population or patient characteristics are expected to differ between current and future incident cohorts, between incident and prevalent cohorts, or where there may be shared effects between cohorts. For example, effects may be shared where vaccination of the current cohort will have implications for disease transmission in future cohorts, thereby impacting on cost effectiveness.*"[20] It is also important to have reliable evidence for this impact. If there is doubt about the (size of the) impact, we recommend presenting the situation with and without this impact and/or different sizes of this impact.

5.4.2 The (real-world) target population and subgroup analyses

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

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

Choices related to post-hoc subgroup analyses should be justified. Ad hoc data mining in search of subgroups with significant results is not acceptable. There should be a clear rationale behind the choice of subgroups and an answer should be provided to the question of why a differential effect is

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[z] Coincidentally observed differences in relative effectiveness between subgroups are not sufficient for post-hoc subgroup analyses, because it is impossible to say whether the differences observed are true differences if the study was not designed to observe such subgroup differences in effectiveness.

expected. In addition, it is important that the defined subgroups are clinically relevant, meaning that they should be clearly defined groups that *can* be identified in real-life. For the policy maker, it is of utmost importance that the subgroups are identifiable based on objective criteria. If not, it is impossible to apply specific reimbursement rules to the subgroups. The application of objective selection criteria might be difficult. In that case, this should be explicitly discussed in the economic evaluation and BIA. Outliers can therefore never be considered as a separate subgroup, as they are not a clearly identifiable homogenous group of patients with specific characteristics. Separate analyses on outliers are not acceptable.

Post-hoc subgroup analyses always entail certain assumptions, e.g. about the treatment effect in the different clinically relevant subgroups. It is essential to use an assumption of constant relative treatment effect if the subgroups were not defined a priori and included as such in the clinical trial design. This means that the relative effectiveness in the different post-hoc subgroups is assumed to be equal to the relative effectiveness found in the complete sample of the clinical trial(s), while the baseline risks between the subgroups are different.[aa] [26] Other assumptions cannot be justified in the absence of clinical effectiveness data for the different subgroups.[bb]

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

In conclusion, two reasons for (post-hoc) subgroup analysis are acceptable:

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

To provide the policy makers with transparent information, the cost-effectiveness should be presented separately for these subgroups. The size of these subgroups should be taken into account if results are aggregated. Unweighted aggregation is not acceptable.

5.4.3 Epidemiological data

Epidemiological data for Belgium for the target population or relevant subpopulations is part of the clinical submission. The size of the target population and subgroups should be provided in absolute numbers. If epidemiological data are not available for Belgium, data from other European countries should be presented and well described. In this case, the relevance of these data to Belgium should be assessed.

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

bb "*If the risk of an event substantially differs among the control groups of the studies included in a meta-analysis, an assessment of whether the relative risk is constant over different baseline risks should be undertaken. This is especially important when the relative risk is to be used within an economic decision model and the baseline rate in the model is very different to the control event rates of the studies in the meta-analysis.*"[17, 27]

5.4.4 Baseline risks in the target population

The absolute treatment effect is determined by applying the relative effect of the intervention on an event (compared to the comparator) to the baseline risk of that event. This baseline risk can be derived from real-world data. As such, the strengths of both randomised and real-world data can be combined by determining the relative treatment effect from (a meta-analysis of) randomised studies and the baseline risk from reliable real-world data.[17, 26] The combination of a lower baseline risk for a certain event and a similar relative treatment effect will result in a lower absolute benefit (and vice versa).

The relative effectiveness of an intervention should always be assumed equal in post-hoc subgroup analyses, unless justified according to an appropriate analysis.[bb] The validity of this assumption should be checked by considering, for instance, the face validity of the outcomes of the model when applying this assumption. This is important to avoid modelling an unrealistic absolute treatment effect based on an RCT with a selective population that is not representative of the actual target population. For example, a relative mortality risk reduction in a patient group of a specific age with severe co-morbidities cannot lead to a lower overall mortality risk than in the healthy population of that age. In general, the modelled avoided number of events can never exceed the baseline risk for that event in the target population in the reimbursement file.[26] Adjustments for the baseline risk on the event of interest is necessary (see also part 5.10.1.2).

When using real-world data to identify baseline risks, it is important to assess the reliability of the data. It is also important that the methods for identifying appropriate baseline data for the purpose of subgroup analysis are provided in enough detail to allow replication and critical appraisal.[17]

5.5 Guideline 5: Intervention

The intervention should be described in sufficient detail. This also includes, if applicable, all other actions required to use the intervention.

It is important to describe the intervention in sufficient detail. This includes the regulatory status for which the intervention was approved and the application for which the intervention is being evaluated. Depending on the intervention, this includes e.g. dose, frequency, route of administration, duration of use, version of the medical device (or other features to distinguish it from other medical devices), number of treatment sessions, etc.[20] If the intervention is part of a particular treatment sequence, it is important to clearly describe the sequence. It should also be indicated if the intervention is already used in the Belgian setting. This information can be used e.g. to better estimate the context-specific cost for this intervention.

It is also important to describe, if applicable, all resources required to use the intervention, for example, the use of associated diagnostic or prognostic tests, and other specific investments or tools. If additional or fewer actions are required to use the intervention, it is important to state this explicitly as this may involve additional or less costs or have an impact on the implementation of the intervention in practice.

5.6 Guideline 6: Comparators

For the identification of the appropriate comparator, the efficiency frontier should be constructed. This involves the identification of all relevant treatments for the targeted indication and population, the removal of dominated or extendedly dominated interventions from the list of relevant comparators, and the calculation of the ICERs of all interventions compared to the next best alternative. In practice, this means that next to the current practice, other more cost-effective comparators should also be included in the analysis.

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

The inappropriate inclusion of interventions that are not cost-effective and the inappropriate exclusion of interventions that are more cost-effective must be avoided since this can have a significant impact on the calculation of incremental costs and effects and thus the cost-effectiveness of an intervention.

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

In the reference case, high-quality RCTs directly comparing the intervention with the relevant comparator are preferred. The choice for an indirect rather than a direct head-to-head comparison between the study treatment and the comparator should be explained, together with the limitations of the indirect comparison.

5.6.1 Working on the efficiency frontier

The choice of the comparator in the economic evaluation is of crucial importance for the relevance of this evaluation for decision makers. It has a major impact on the incremental costs and effects, and hence an intervention's cost-effectiveness.

In order to avoid the mistaken improvement of the cost-effectiveness ratio of an intervention by comparing it to a non cost-effective intervention, comparisons and thus calculations of ICERs should be performed on the efficiency frontier.[28] The efficiency frontier is the line on the cost-effectiveness plane connecting the non-dominated treatment alternatives (see Appendix 6). It can be constructed as follows:

3. Make a comprehensive list of all possible therapeutic strategies for the target indication and population.
4. Exclude interventions that are dominated by other interventions with lower costs and greater therapeutic benefits.[cc]
5. Exclude extendedly dominated alternatives, which means that linear combinations of other strategies can produce the same (or greater) benefit at lower (or the same) cost.
6. For the remaining alternatives, calculate the cost-effectiveness by comparing each strategy with the previous less costly and less effective intervention.[29]

In theory, "*to achieve maximum generalisability and transparency, a HTA needs to consider all available comparator technologies.*" However, "*the technical difficulty of doing this, as well as the*

[cc] This does not mean that the ICER has to be calculated firstly. If it can be clearly demonstrated that the incremental costs are not lower and the effects are less good, or the incremental costs are higher and the effects are not better, then for reasons of dominance this intervention can be excluded. This might not be easy, e.g. in cases where confidence intervals of incremental costs and/or effects overlap. The supporting arguments must be presented transparently (see part 5.6.3).

additional time and resource implications required, could make this hugely burdensome and inefficient."[20] To perform a relevant and practically feasible selection, we recommend distinguishing between identifying possible comparators (part 5.6.2) and selecting those that are relevant for performing a correct incremental analysis (part 5.6.3).

5.6.2 Identification of relevant alternatives

The possible comparators can be very diverse. It can be a medical or non-medical treatment, best supportive care, watchful waiting or doing nothing. Note that the "doing nothing" approach is usually not associated with zero costs and effects. The list of potential comparators is not limited to a specific type of intervention. When considering a pharmaceutical product or device, the best comparator may also be a non-pharmaceutical or non-device comparator, e.g. a lifestyle intervention. The list of relevant alternatives might also include non-licensed treatments and non-proprietary (generic) medicines and biosimilars. Also different configurations of the same basic interventions might be within scope.[20] For example, a different mode of administration, treatment duration and/or dose, treatment sequence or combination, screening interval, etc.

It is also important, if relevant, to refer to a possible background or supportive therapy for a specific disease or condition. It is essential to indicate whether this background therapy is given for both the intervention and the comparator, as this may affect both incremental costs and effects.

Several sources can support the identification of possible comparators. Clinical practice guidelines, for instance, might recommend a range of different treatment options. However, as clinical practice guidelines usually do not consider cost-effectiveness, the recommended intervention in the guidelines might not necessarily be on the efficiency frontier. Therefore, guidelines should be considered as a source to identify possible comparators. When relying on (inter)national practice guidelines, note that standard care may depend on the country and/or region. We note that the comparator may also be different depending on the subpopulation under evaluation. For example, in inoperable patients, the comparator may be drug treatment, while it might be surgery for the operable patients.

Real-world data can sometimes also provide information on relevant comparators, by indicating which interventions are currently used and could potentially be displaced in the relevant target population. The availability and reliability of such data should be considered. For example, it may be difficult or impossible to identify off-label use of certain interventions in the target population.

5.6.3 Selection of comparator(s)

It is not necessary to perform an incremental evaluation for all possible alternatives. However, it is necessary to identify the comparators that determine the calculation of the cost-effectiveness of the intervention being evaluated. From a practical point of view, we recommend the following:

- The intervention to be assessed should be compared with the standard or usual care in Belgian practice.
- If this is not the most cost-effective intervention in Belgium, then the most cost-effective intervention should also be included as a comparator.[16, 18]

Just as inappropriately including alternatives that are not cost-effective has a significant impact on an intervention's cost-effectiveness, inappropriately excluding more cost-effective interventions is also an important concern (see Appendix 6.3). It is possible that the current treatment approach is not cost-effective itself, e.g. because it received a positive reimbursement decision in the past for reasons that now no longer apply (e.g. because at that time no other treatment was available for that indication or economic considerations were not taken into account). Striving to make calculations on the efficiency frontier avoids situations in which interventions appear to be cost-effective by comparing them with non-cost-effective alternatives, further stimulating non-efficient use of limited resources. The appropriate economic approach compares every alternative with the previous most cost-effective alternative. In practice, this means that next to the current treatment situation, alternative more cost-

effective comparators should be included in the analysis. This can be a generic product, lifestyle adoptions (e.g. smoking cessation), the previous standard of care, or a new evidence-based intervention that has shown to be more cost-effective than the current treatment practice.

Off-label used pharmaceutical products can also be used as valid comparators in a pharmacoeconomic evaluation if they are used in routine practice[20, 25, 27] or if evidence is available about the clinical safety and efficacy of the off-label use, e.g. from government sponsored trials. For the Drug Reimbursement Committee the existence of an "off-label" used product can sometimes be a consideration in its advice to the minister. Therefore, if available, it is necessary to present the evidence on off-label used products in the literature review, thereby strengthening the transparency of the dossier. The same applies to non-pharmaceutical interventions used beyond their described indication.

Absence of evidence for the routine off-label use might jeopardize the reliability of the economic evaluation. In such a case, it might even be impossible to perform an economic evaluation. Still, it may be important to point out the absence of evidence to e.g. encourage further research. In contrast, evidence-based off-label use can be included in the reference case. Even if it is currently not routinely applied in Belgium, it might be relevant for policy makers as it may indicate how efficient use of resources can be stimulated. If e.g. more cost-effective alternatives are currently not registered or reimbursed, then pointing this out could have an impact on regulations, reimbursement decisions, or demonstrate the need for further research.[dd]

The selection of comparators should be conceptually driven and should not be determined by the availability of data.[18] The selection of relevant comparators should not be restricted to interventions supported by the manufacturer. The relevant comparator may thus be different from the comparator in the clinical studies.[27]

In conclusion, we recommend including routine care and the alternatives with the highest probability of being more cost-effective than current standard of care as relevant comparators in the economic evaluation. The latter is definitely relevant if the cost-effectiveness of current practice can be questioned. Justification for the chosen comparators should be provided and the selected comparators should be sufficiently described. A reference to 'routine practice' or 'standard of care' is not sufficiently detailed and needs further clarification.

5.6.4 Moving target and (in)direct comparisons

High-quality RCTs directly comparing the intervention with the relevant comparators provide the most valid evidence of relative safety and efficacy. If available, the reference case should be presented including the results of such direct comparisons. However, in some cases, the choice of the comparator will be difficult due to, for instance, changes in prescription behaviour and therapeutic insights over time. The comparator defined at the time of the clinical trials may no longer be the relevant comparator at the time of the economic evaluation. In this case, (anchored) indirect comparisons and/or modelling may be required. Indirect comparisons are associated with higher levels of uncertainty and therefore are only accepted if no single trial of appropriate quality or relevance to the Belgian target population has been performed and the analyses are conducted under specific conditions. Appropriate statistical techniques must be used for indirect comparisons. For more information, we refer to the methodological[12] and practical guidelines[31] about direct and indirect comparisons, and the guidance on the validity of clinical studies[13] developed in the context of the EU HTA Regulation[8] (see part 5.10.1.1).

Comparators for which no direct or indirect evidence is available cannot be included in the economic evaluation. All other interventions for which evidence is available can be included in the analysis. Evidence about the relative effectiveness of the two treatments is required for an economic evaluation.

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dd For more details, we refer to the KCE report 'Towards a better managed off-label use of drugs'.[30]

Without such evidence, an economic evaluation will not be informative for the health care decision maker. Nevertheless, identifying an evidence gap is also of interest to the decision maker. Therefore, in the absence of reliable evidence about the relative safety and efficacy in comparison to relevant comparators, it is recommended to explicitly indicate this as the underlying reason why no reliable, or only a hypothetical, economic evaluation can be performed.

5.7 Guideline 7: Analytic technique

Cost-utility analysis (CUA) should be used in the reference case. Outcomes of CUA should be expressed in euro per quality-adjusted life year (QALY) gained. It should be justified if another type of analytic technique is used.

Cost-effectiveness analysis (CEA) should be used if there is an impact on life expectancy. Outcomes of CEA should be expressed in euro per life year gained (LYG). Also in this case, to support comparability, the CUA remains the reference case and the CEA is provided to complement.

Cost-minimisation analysis (CMA) can be used if there is proof of equivalence between the interventions being compared in terms of all relevant health outcomes. If there is doubt about the equivalence, CUA reflecting the uncertainty on important outcomes (e.g. adverse events) should be used in the reference case.

Cost-consequences analysis (CCA) can be presented if it is not possible to link important outcomes to QALYs or LYs or if important patient needs addressed by the intervention are not covered by QALYs or LYs. However, the CCA should never replace the CUA or CEA analyses if such an analysis can be performed.

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

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

A full economic evaluation is described as an analysis comparing both costs and effects of an intervention with the comparator. There are five common types of economic evaluations:[18]

- "Cost-effectiveness analysis [CEA]: a comparison of costs in monetary units with outcomes in quantitative non-monetary units (for example, reduced mortality or morbidity).
- Cost-utility analysis [CUA]: a form of cost-effectiveness analysis that compares costs in monetary units with outcomes in terms of their utility, usually to the patient, measured in quality-adjusted life years (QALYs).[ee]

[ee] Other outcomes such as disability-adjusted life years (DALYs) are also possible. DALYs are related to a specific disease or disability. However, there is no standardized approach in the DALY weights for simultaneous consideration of comorbidities within an individual or population. An intervention that causes e.g. adverse events or has an impact on symptoms without providing cure can also not be captured within the DALY framework. In contrast, QALYs are not intrinsically related to a disease or disability. Instead, QALYs are related to measures of important domains of HRQoL. This allows description and valuation of the impact of e.g. adverse events or comorbid conditions. For these reasons, and to improve comparability, it is recommended to measure HRQoL and calculate QALYs instead of using DALYs.

- Cost-minimisation analysis [CMA]: a determination of the least costly among alternative interventions that are assumed to produce equivalent outcomes.
- Cost-consequence analysis [CCA]: a form of cost-effectiveness analysis that presents costs and outcomes in discrete categories, without aggregating or weighting them.
- Cost-benefit analysis [CBA]: a comparison of costs and benefits, both of which are quantified in common monetary terms."[32]

A table classifying the different types of economic studies is provided in Appendix 7.The report should specify which of the above types is used. Justification for the choice of analytic technique should be provided.

The result of a CEA or CUA is expressed as an incremental cost-effectiveness ratio (ICER). The ICER reflects the additional (incremental) cost per additional unit of outcome achieved, being LYG or QALYs gained. If the effectiveness of an intervention is better and the costs are lower than the comparators', the ICER is negative. In that case, the intervention is dominant (and the comparator is dominated), which should be stated, and the ICER should not be presented and vice versa, if the intervention is dominated. Independent of the sign of the ICER, separate reporting of incremental costs and incremental effects, with their respective confidence intervals (see part 5.16.2), is always required.

5.7.1 Cost-utility analysis

In these guidelines, the term CUA is used for economic evaluations that include HRQoL in the assessment of treatment outcome.[ff] A CUA is appropriate if:

- The treatment has an impact on HRQoL 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).
- As this is the case for most interventions, it is recommended to use a CUA in the reference case analysis.

The CUA should use the quality-adjusted life years (QALY) gained as the preferred outcome.[ee] The QALY combines changes in both the length and quality of life. Measuring HRQoL is much more subject to variation according to the measurement methods than measuring survival. This might influence the comparability of different CUAs. Therefore, it is recommended to use, where possible, evidence emanating from the application of a standardised generic utility instrument like the EQ-5D-5L, for which a utility value set for Belgium has been established (see part 5.10.2). Generic utility instruments have the advantage of enabling comparisons across interventions for patients with different diseases. It can also detect the impact of both expected and unexpected positive or negative effects related to an intervention (e.g. adverse events).[33] Generic utility instruments also allow the description of a health state to be translated into a utility, needed to calculate QALYs. If researchers expect that an intervention will have an impact on a patient's quality of life, including this instrument in the study protocol should be strongly encouraged, complementary to possible disease-specific instruments. This is in line with the European Network for Health Technology Assessment (EUnetHTA) guideline on HRQoL and utility measures.[33]

To increase the usefulness of a CUA for health care decisions, the applicant must provide sufficient detail about the methods used for valuing utilities (see part 5.10.2.2).

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

5.7.2 Cost-effectiveness analysis

In cost-effectiveness analyses the outcome should be expressed in terms of LYG. The choice of the outcome measure should be consistent with the objectives of the treatment and the impact on patient-relevant outcomes. However, CEAs expressing the effectiveness in another natural unit, e.g. number of reinterventions avoided or unit reduction in systolic blood pressure, preclude comparisons with other economic analyses.[20] As a result, these are less informative for decision makers.

If there are multiple patient-relevant clinical outcomes that are expressed in different units (e.g. life years gained and complications avoided), CEA is less appropriate. For example, a CEA of an intervention that prolongs life expectancy significantly at a high cost in terms of adverse events, should present its results in terms of QALYs to encompass the full impact of the intervention, including its adverse events. This shall be considered as the base-case. However, because of the significant impact on life expectancy, the cost per life year gained should also be presented to provide the most complete information to the decision maker.

5.7.3 Cost-minimisation analysis

Cost-minimisation analyses (CMA) are used if the effects (safety and efficacy) of two treatments are identical. Hence, cost-minimisation analysis can only be justified by proof of equal outcome. In such cases, comparing costs between the intervention and comparator(s) is sufficient. This analytic technique is not recommended within the scope of a reimbursement request in which an added value is claimed but could be considered for e.g. generics.

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 CUA or CEA, during which it becomes clear that health outcomes are identical. In this sense, a CMA can be interpreted as a special case of CUA or CEA with equal outcomes. Nevertheless, if there is uncertainty about the equivalence, e.g. because there might be small differences in adverse events, performing a CUA to include this uncertainty is required.[18]

5.7.4 Cost-consequences analysis

Cost-consequences analyses (CCA), i.e. descriptions of costs and consequences without calculation of an incremental cost-effectiveness ratio, can complement the reference case CUA when relevant outcomes are not captured in the QALY or LYG-estimate. This can relate, for instance, to aspects of therapeutic value (e.g. applicability or user-friendliness) or aspects related to unmet health-related patient or societal needs that are not covered by generic HRQoL or life expectancy.[34] Additionally, the impact of the intervention on other relevant outcomes, e.g. school attendance or addiction, might be difficult to include in a CUA or CEA. The results of a CCA can be difficult to interpret if different consequences go in opposite directions (one outcome is positive, another is negative). It is the responsibility of the decision maker to weight and consider the different types of outcomes and make a judgement on the final overall benefit. In exceptional circumstances, a CCA may provide results that are easily interpretable by the policymaker, e.g. when all consequences are positive and incremental costs are neutral or negative.

A CCA can also be presented if it is not possible to link important outcomes to QALYs gained or LYG. However, a CCA should never replace a CUA or CEA if there is an impact on quality of life and/or survival.

5.7.5 Cost-benefit analysis

Unlike CEA, CUA, and CCA, cost-benefit analyses express all outcomes in monetary terms. The monetary valuation of clinical and non-clinical outcomes has long been debated. Due to the difficulty of expressing the effects in monetary terms, cost-benefit analyses have not been used frequently. Given the challenges associated with this technique, cost-benefit analysis is not acceptable as a stand-alone reference case analysis. However, it may be presented as an additional analysis to cost-effectiveness, cost-utility, or cost-consequences analysis to illustrate societal benefits accruing from non-health impacts.

5.8 Guideline 8: Study design

Whenever possible, estimates of the relative treatment effect on safety and efficacy outcomes should be based on data from head-to-head RCTs comparing the study intervention and a relevant comparator. However, some modelling will almost always be needed. The number of assumptions in the economic models not based on clinical evidence should be reduced to a minimum and be fully justified.

Economic evaluations can be performed alongside a clinical trial (e.g. piggy-back economic evaluations) or an observational study, or can be based on an economic 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.

5.8.1 Trial-based economic evaluations

The weaknesses of an economic evaluation performed alongside a clinical trial are directly related to the purposes of the clinical trial. Clinical trials are not set up for economic evaluation but rather for evaluating treatment efficacy. For economic evaluations, information is needed on the effectiveness in routine practice. As a consequence, the information provided in clinical trials is often insufficient for the economic evaluation. Some of the potential weaknesses of clinical trials for the purpose of economic evaluations are:

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

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

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

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

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

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

5.8.2 Modelling

In general, also for trial-based economic evaluations, modelling is likely to be needed for different reasons: extension of time horizons, extrapolation of intermediate outcome parameters to final outcome parameters, modelling of comparators which have become more relevant in practice since completion of the trial, consideration of externalities associated with a treatment, translation of foreign data to the Belgian context, pooling data from multiple trials, including adjustments to reflect the baseline risk for the Belgian target population, etc. Health economic models allow the analyst to combine information from a variety of sources and to link these data to outcomes of interest to decision makers. Computer based models also allow the simulation of various policies. In such models, data from different sources are combined and assumptions have to be made (e.g. about the comparability of the data derived from different sources, the representativeness of the study population and observed resource use for Belgium, etc). The arguments to use a modelling approach should be set out clearly and sources for input variables and assumptions should be presented. The strength of a model mainly depends on the reliability of the underlying input.

A separate guideline is devoted to modelling (see part 5.14).

5.9 Guideline 9: Calculation of costs

In the reference case, the identification, measurement and valuation of costs should be consistent with the perspective of the Belgian health care payers, being government (RIZIV–INAMI, FOD–SPF, communities or other local authorities) and patients. The reference case should only include direct health care costs.

Direct costs outside the health care sector, productivity costs and health care costs associated with unrelated diseases should not be included in the reference case, but may be reported in a separate complementary analysis. In this case, the impact of the intervention on these elements should be demonstrated by means of hard data. Validated sources should be used for the unit costs.

Economic evaluations focus on incremental costs. The level of effort and precision for both the measurement and valuation of resource use depends on the importance of this element in the total incremental costs.

It is recommended to work with mean costs, i.e. including information from outliers.

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

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

Confidential price discounts *for the comparator(s) and/or other relevant treatments* impacting the incremental costs should be included in the reference case by developing price discount scenarios for these treatments reimbursed under a confidential contract. *For the intervention under assessment*, the official list price should be used in the reference case and price discounts can be included in 'classic' scenario analyses.

In the reference case, the perspective for the cost calculation is that of the health care payers (government and patients). Health care costs borne by the government (RIZIV–INAMI, Federal Public Service (FPS, FOD–SPF), communities or other local authorities) and costs borne by the patients, as far as available, should be reported both separately and aggregated. Valuation of resource use in monetary units must be consistent with the perspective of the analysis.

The focus is on the incremental impact, i.e. the identification of costs (or savings) that differ between the intervention and the relevant comparator(s). This includes not only the costs of the intervention itself, but also all costs (or savings) resulting from the introduction of this intervention (e.g. preparatory examinations and tests, companion diagnostics,[gg] etc.), as well as all short-term (e.g. monitoring, follow-up examinations) and long-term consequences (e.g. reinterventions) of introducing the intervention (both positive and negative). This includes both the impact within the targeted health condition and the impact on other health conditions (e.g. due to (avoided) adverse events). Focussing on the incremental impact means that not all costs of a disease or treatment need to be estimated. "*In certain circumstances, cost and resource consumption that are common to all the technologies being compared may be excluded from the economic analysis. The cost and resource consumption must be equal in terms of quantity, timing, and duration. The process of omitting resources should be clearly described and justified.*"[20] For example, if a comparison is made between two types of stents (e.g. a drug-eluting or a bare-metal stent), and there is no impact on the initial surgery, then the cost of this surgery is not incremental and can be disregarded in the economic evaluation.

The required level of effort and precision for both the measurement and valuation of resource use depends on the importance of this element in the total incremental costs.[20, 25, 36] For example, in a non-reference case analysis from a societal perspective, the one-off cost of transport to a reference centre might be very small compared to the cost of a very expensive surgical procedure or intravenous treatment performed at this centre. A rough estimate of the travel costs could then be included in the analysis, while the costs of the treatment should be measured in much more detail. If an element has a significant impact on incremental costs, then sufficient effort must be put into the correct measurement and valuation of this element to include it in the analysis.

Primary and secondary sources can be used to collect cost information.[36] In primary data collection, relevant information can be collected during, for example, a clinical trial or an observational study. The method used to collect this data should be described. Secondary data collection uses existing data sources, such as patient records or financial databases.[36] Administrative databases are a potentially useful source of information for measuring and valuing resource use. They can provide cost information that reflects real-world conditions in the Belgian context. It should be checked whether the information from such administrative databases can provide reliable data that are fit for purpose.

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gg The sensitivity and specificity of the companion diagnostics have a major impact on the ICER of a targeted treatment.[35] Therefore, it is recommended that companion diagnostics should be co-evaluated during reimbursement decisions of targeted therapy. The demonstrated clinical sensitivity and specificity of the approved companion diagnostic should be identical or highly similar to the one used in the trials demonstrating the efficacy of the pharmaceutical product. For more information, we refer to KCE report 240.[35]

Appendix 2 provides an overview of administrative databases in Belgium and the access possibilities for different stakeholders.

Cost data often have a right-skewed distribution, where outliers cause the mean resource use and costs to be higher than the median. For example, after surgery, a minority of patients may experience severe adverse events leading to a prolonged length of stay and much higher treatment costs. Outliers are also part of reality and should also be taken into account in economic evaluations.[15] Therefore, it is recommended to work with the mean and not the median.

5.9.1 Cost categories

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

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

	Health care costs	Non-health care costs
Direct costs	*Included.* e.g. health services, medicines, devices, hospitalisations, outpatient care, examinations, consultations, etc.	*Not included.** e.g. travel expenses to and from hospital, informal care, invalidity/incapacity allowances, social services, etc.
Indirect costs	*Not included.** e.g. health care costs in life years gained (unrelated health care costs)	*Not included.** e.g. productivity losses patient or informal caregiver

*This report uses this classification although other cost classifications exist. * Not included in the reference case. Flexibility to apply complementary analyses.*

The reference case should only include direct health care costs. These encompass costs directly related to the disease or the treatment of the disease (also including adverse events) 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, other non-health care costs and/or unrelated health care costs are deemed important for a specific treatment, they may be presented in a separate analysis.

5.9.2 Measurement of resource use

Measurement of resource use should be based on observational data or be derived from literature. Observational data 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, (administrative) databases, patient charts, etc.

Use of expert panels for resource use measurement is subject to specific conditions (Appendix 8.1). Expert panels are preferably only used as a complementary source of information rather than the sole source of information on resource use. If they are used, it is essential to provide a description of the way experts are selected.

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

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

For the measurement of mean length of hospital stay per All Patient Refined Diagnosis Related Group (APR-DRG), data can be found on the website of the Technical Cell (TCT, Technische Cel voor de verwerking van de gegevens met betrekking tot de ziekenhuizen – Cellule Technique de traitement de données relatives aux hôpitaux)[hh], under the heading "Financiële Feedback per pathologie – Feedback Financier par pathologie". The database also provides distributional parameters for each APR-DRG. This information can be used in the sensitivity analysis of the economic evaluation. Other databases can be used, provided that they are compliant with legal requirements about privacy and provided that the data in the database are validated, for instance against the data of the TCT. An overview of health care related databases in Belgium can be found in Appendix 2.

For any information extracted from these databases, the reliability and appropriateness of the information should be checked (e.g. can the relevant intervention be correctly identified, is the degree of detail sufficient, etc.). Each database has its weaknesses, such as the cross-sectional nature of the data, discrepancies in the computation of length of stays, imperfect registration, etc. These weaknesses can generally not be remedied without some assumptions. It is recommended to discuss these weaknesses and their potential impact on the cost estimates.

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

5.9.3 Valuation of resource use

5.9.3.1 General principles of cost estimation

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

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

The values should reflect Belgian prices/costs for each resource input rather than foreign prices converted to euros. Valuation of resource use by means of simple currency conversion of values found in literature or in studies from other countries is not recommended but can be used in specific cases (e.g. when the cost item is of relatively minor importance for the total incremental cost, or when there are no reliable data available for Belgium). If foreign data are used, the conversion is done in line with the recommendations in the Dutch and Irish guidelines.[20, 36] When transferring costs from another country, the inflation should be calculated using the consumer price index (CPI) for the local currency of that foreign country, before converting to the Belgian equivalent in euros using purchasing power parity (PPP) indices. The international CPIs and PPPs are available on the website of the Organization

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hh https://tct.fgov.be/etct/index.html.

for Economic Cooperation and Development (OECD).[ii] Several CPIs are available. None of them are specific for interventions or services in the health care sector.[jj] To support consistency, it is recommended to apply the Harmonised Index of Consumer Prices (HICP).[kk] An example is provided in Appendix 8.2. The result of the indexation approach should be checked for appropriateness to the Belgian context, at least by checking its face validity (especially when using data from non-EU studies), and is subject to extensive sensitivity analysis.

All costs should be expressed in values for the current (or most recent) year, e.g. by using current prices. If this is not possible and costs from past years are used, these costs should be indexed using the HICP, if relevant. In some cases, indexation will not be appropriate for particular products or services. For example, the reimbursement basis of pharmaceutical products is not necessarily indexed and might even decrease for products entering the reference price system.

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

5.9.3.2 Valuation of health care services

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

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

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ii CPI: https://www.oecd.org/en/data/indicators/inflation-cpi.html (for consistency: choose 'Eurostat Harmonised index of consumer prices (HICP)). PPP: https://www.oecd.org/en/data/indicators/purchasing-power-parities-ppp.html.

jj We refer to the glossary for a definition of the CPI, the health index and the HICP.

kk The HICP is a European harmonised consumer price index used to compare inflation rates in the EU member states. To this end, the applied expenditure approach and methods have been coordinated as much as possible and laid down in European regulations (https://statbel.fgov.be/en/themes/consumer-prices/harmonised-index-consumer-prices-hicp).

ll In 2021, the coverage of the global medical record, i.e. the percentage of people who have a global medical record with their general practitioner, was 83.3% (Source: https://www.healthybelgium.be/en/health-system-performance-assessment/quality-of-care/continuity-of-care#QC-1).

mm https://webappsa.riziv-inami.fgov.be/Nomen/nl/search.

5.9.3.3 *Valuation of pharmaceutical products*

Unit prices (reimbursement basis and the patients' share) for reimbursed pharmaceutical products are publicly available on the RIZIV–INAMI website.[nn] Unit prices for reimbursed and non-reimbursed (e.g. over the counter) pharmaceutical products are available on the website of the Belgian Centre for Pharmacotherapeutic Information (BCFI–CBIP).[oo]

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

CONFIDENTIAL PRICE DISCOUNTS

Pharmaceutical products might be reimbursed under a managed entry agreement including confidential price discounts. The list of pharmaceutical products that are reimbursed under a contract is published on the website of the RIZIV-INAMI.[pp] It is possible that the relevant comparator(s) and/or disease-related treatments (e.g. administered after disease progression) are reimbursed under such a confidential contract. Because of the confidential nature of the managed entry agreements, the price discounts are by definition unknown for the researchers performing the economic analysis. Cases of uncertainty are usually handled in economic evaluations by means of sensitivity or scenario analyses. Because of the high probability that a price discount applies to a product under contract, ignoring this in the economic evaluation would most certainly result in an underestimation of the incremental costs. For example, based on the list prices, an intervention costing €100 000 seems cheaper than a comparator with a list price of €150 000, while the comparator could be under a contract where the actual paid price is €75 000. In reality, the new treatment is then €25 000 more expensive. Therefore, we recommend developing price discount scenarios for the comparator(s) and other relevant treatments reimbursed under confidential contracts as part of the reference case. The policy maker, who knows the confidential price discount, can then choose the scenario that most closely reflects the actual discount.[qq]

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nn https://webappsa.riziv-inami.fgov.be/ssp/ProductSearch.

oo https://bcfi.be/.

pp https://webappsa.riziv-inami.fgov.be/ssp/Contracts.

qq This is in line with the NICE guideline: "*Reference-case analyses should be based on prices that reflect as closely as possible the prices that are paid in the NHS for all evaluations. Analyses should be based on price reductions when it is known that some form of price reduction is available across the NHS. Sources of prices may include: patient access schemes, commercial access agreements, […] the drugs tariff or through negotiated contracts such as Commercial Medicines Unit (CMU). When judgement on the appropriate price is needed, the committee should consider the limitations around the price source in its*

The stakeholder submitting a reimbursement request may use the *official list price of the intervention* in the reference case. At the time of submitting a reimbursement request it has not yet been decided whether a discount will be granted. If considered relevant, the discount on the intervention under assessment can then be performed in a 'classic' scenario analysis.

WASTAGE AND COMPLIANCE

Medicine wastage may arise due to e.g. patient non-compliance, when a package contains medicine for a longer treatment period than necessary, when the unused part of the preparation cannot be used later (e.g. injection preparations), or when storage requirements are not met.[20, 37] In the reference case, the cost of medicine wastage should be included in the costs.

If there is evidence that there is a difference in compliance between the underlying clinical trials and the real world, it is incorrect to only adjust the incremental costs without including the impact on the incremental effects. It is recommended to use the evidence from the trial in the reference case and reflect the impact of non-compliance on both incremental costs and effects in a scenario analysis.

5.9.3.4 Valuation of implants and invasive medical devices

The list and prices (reimbursement basis and patients' share, interpretation rules, etc.) of reimbursed implants and invasive medical devices (per category) is published on the RIZIV–INAMI website.[rr] Both the list and implants and invasive medical devices listed on the so-called "nominative lists", are also available in the searchable sIMPL database of implants and invasive medical devices on the RIZIV–INAMI website.[ss]

5.9.3.5 Future changes in costs

It is possible that costs related to an intervention will be different in the future. For pharmaceutical products, the reference analysis is performed using prices that reflect the real actual situation. In case of patent expiry, consideration should be given to the implications of the introduction of a generic or biosimilar product.[38] Furthermore, it is possible that costs related to an intervention will be lower in the future due to e.g. learning effects (which may lead to e.g. shorter hospitalisation duration after a specific surgery) or scale effects. If there is no evidence yet that this will actually be the case, we recommend using the current estimate of costs in the reference case. A possible decrease in costs can be included in a sensitivity analysis.[25] Similarly, if certain resources will not be required anymore in the longer term (e.g. short-term impact on necessary facilities, equipment, staff training costs, etc.), then an analysis with and without these costs can be made. In general, in the reference case, costs are included reflecting the actual situation.

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deliberations. This should consider transparency to the NHS and the period for which the prices are guaranteed. Any uncertainty should be acknowledged and explored."[17]

rr https://www.riziv.fgov.be/nl/professionals/individuele-zorgverleners/verstrekkers-van-implantaten/implantaten-en-invasieve-medische-hulpmiddelen-lijst-van-de-verstrekkingen-en-nominatieve-lijsten-van-de-individuele-hulpmiddelen.

ss https://webappsa.riziv-inami.fgov.be/simpl/. Remark: not all reimbursements have a corresponding nominative list.
Note: There is also a separate search application (CT MedDev) in which lists of reimbursed products from bandaging, orthopaedic technology and hearing aids can be searched: https://webappsa.riziv-inami.fgov.be/ctm/.

5.9.3.6 *Valuation of per diem hospitalization prices*

Belgian per diem hospitalization prices (in euro) are published on the RIZIV–INAMI website.[tt] [uu] The publicly available Excel files are updated every six months and contain the per diem prices per hospital. They also include the type of hospital stay: acute (A), burns (BRA), geriatrics (G), palliative (PAL), psychiatric (P) and specialized stays for chronic conditions (Sp). This break-down per type of hospital stay is the one used in the Belgian hospital financing law. A description of how 100% per diem hospital prices are computed in Belgium is provided in Appendix 8.3.

The publicly available Excel list contains the 100% hospital stay price for all hospitals in Belgium, including hospital name and address. Based on this published list of per diem prices, a *mathematical* average across hospitals can be computed to derive Belgian average per diem prices per type of hospital stay. However, this method does not account for the volume effect of each hospital such that large hospitals with more hospitalization days and higher per diem prices would have the same weight as smaller hospitals with lower per diem prices. Calculating a *weighted* average per diem price, accounting for disparities in the case mix (i.e. different levels of activity) of the hospitals, is only possible if data on the number (volume) of stays per hospital are available. Since these data are not publicly available, a practical and feasible approach is to use the simple mathematical average of the per diem prices. This should include sufficient consideration of the selected hospital(s), e.g. one specific hospital, all university or non-university hospitals, one particular type of hospital, etc. It is recommended to reflect daily practice (e.g. which (type of) hospitals perform the intervention). The choice should be adequately justified.

5.9.3.7 *Valuation of lump sums for pharmaceutical products, medical imaging and clinical biology in hospitalized patients*

Over the last two decades, lump-sum payments have been introduced in the Belgian hospital payment system, e.g. lump sums for laboratory tests and medical imaging and a (separate) case-based system for a subset of inpatient pharmaceutical specialities. Although this system of prospective payment aims at a more efficient use of public resources, it makes it difficult to assess the healthcare resources used as it does not reflect actual consumption.

If the intervention being evaluated is not covered by a prospective lump sum, it is recommended that no conversion is made from the lump sum to the real consumption cost. For individual patients, adjusting for actual consumption would result in hospital costs being higher in some cases (i.e. those who actually received a pharmaceutical product, medical imaging or clinical biology and for whom only a lump sum was charged) and lower in others (i.e. those for whom a lump sum was charged, even though they did not 'consume' the products or services). At the population level, these effects are expected to be balanced.

If the intervention being evaluated is covered by a prospective lump sum, adjustments should be made to obtain 100% of the cost of that intervention, otherwise the cost would be underestimated. Appendix 8.4 describes the appropriate methods for adjustment.

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tt https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/wat-het-ziekenfonds-terugbetaalt/verzorging-in-ziekenhuizen/verpleegdagprijzen-ziekenhuizen.

uu The per diem hospital price covers only a part of the total hospital stay costs. All other costs incurred, e.g. related to the use of intensive care, medicines, procedures, physician fees, etc. should be added.

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

Transport costs[vv] are not direct health care costs and as such should not be included in the reference case. For some interventions (e.g. dialysis), however, it may be important to quantify the travel expenses incurred by the patient or the RIZIV–INAMI for travel to and from the caring institution or physician. These expenses may then be reported as a complementary analysis, *separate from the reference case*. It is important to consider beforehand whether these costs are expected to affect the incremental costs, and therefore whether they are sufficiently significant to include in the economic evaluation.[36]

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

- Transport costs are based on the cost allowance per kilometer for federal government employees. This is an official tariff that is revised quarterly by circular letter and published in the Moniteur Belge, giving the advantage that it is up-to-date and publicly available.[ww] As an example, for the period January-March 2025, this cost allowance was €0.4290 per kilometer. We recommend using the most recent information. No adjustment is made for the type of transport (personal car, public transport…) and the number of kilometers is limited to a maximum of 15 per journey (i.e. 30 kilometers per day).[xx]

Although these standard costs contribute to reducing some price differences between studies, deviations from the values are allowed if the researcher can demonstrate that the values relevant for his/her study differ considerably. This may be the case, for example, if a limited number of centres offer a particular treatment and the average distance to these reference centres is longer.

5.9.3.9 *Valuation of productivity costs (societal perspective)*

Productivity costs are not categorised as direct health care costs and as such should not be included in the reference case. If relevant, indirect productivity costs can be presented in a complementary analysis, *separately from the reference case*. In any case, the impact of the medical intervention on the level of productivity must be supported by evidence and well documented. Appropriate consideration should be given to the age distribution of the patient population and the consequent potential impact on productivity losses. In older, generally retired, patient populations, it is inappropriate to account for productivity losses.

Productivity costs are costs arising from production losses due to:

- Unfitness to work/sick leave (in the case of treatment/illness),
- Early retirement/incapacity to work (in the case of long-term illness or disability),
- Premature death.

Productivity costs are divided into paid and unpaid work (i.e. voluntary job, housekeeping…).

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vv Ambulance transport is an exception and is included in the category of direct health care costs.

ww https://bosa.belgium.be/nl/themas/werken-bij-de-overheid/verloning-en-voordelen/toelagen-en-vergoedingen/vergoeding-voor-0.

xx Statbel, the Belgian statistical office, publishes information on the proximity of essential infrastructure to Belgian citizens. Based on January 2024 population figures, 58% of the Belgian population lives within a radius of 5 km of a hospital. This percentage rises to 87% for 10 km and 99% for 20 km (https://statbel.fgov.be/nl/themas/datalab/geografische-indelingen).

Short-term[yy] lost productivity during ***paid work*** should be valued using the Human Capital Approach. The human capital approach values the time during the whole period of work inactivity due to sick leave, early retirement (potentially up to retirement) or premature death (up to retirement). Productivity costs in the Human Capital Approach are to be computed by multiplying the total number of days of work absenteeism by the national average labour cost per day. Labour costs include employee wages and/or salaries and employers' social security contributions. The Belgian average labour cost per working hour was estimated at €47.1 (costing year 2023; Source Eurostat, labour costs annual data).[zz]

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

The amount of production lost due to disease depends on the length of this friction period. Productivity costs are then calculated by multiplying the labour costs per hour (i.e. €47.1 or, applying an 8-hour working day, €376.8 per day, see above) with the duration of the friction period. Researchers determined the friction period for thirty countries (EU 27 + UK, Switzerland and Norway).[39] For these 30 countries, over the period 2008-2018 and depending on the calculation approach, the average friction period was 65 or 86 calendar days. For Belgium, this was 102 or 111 calendar days.[39] We recommend applying the average of 107 calendar days (~3.5 months).

In the Dutch guidelines, the length of the friction period is increased by 4 weeks, to account for the period assumed to be used by employers to open a vacancy to replace the employee who has to take sick leave.[36] Since no information is available for Belgium, we recommend adopting the same assumption as in the Dutch guidelines. As a result, it is recommended to take into account a total friction period of 135 calendar days. An example is provided in Appendix 8.5.

There is no consensus on the best instrument or approach to measure this impact. Available tools are the Work Productivity and Activity Impairment (WPAI) questionnaire and the iMTA Productivity Cost Questionnaire (iPCQ).[aaa] To measure the impact on productivity of a caregiver, e.g. a parent staying home from work to care for his/her child, an adapted version of the WPAI is also available, i.e. the WPAI-CG. We recommend that the suitability of the questionnaire(s) for the specific study is verified (e.g. if absenteeism and presenteeism are important and need to be measured or rather the time until someone can return to work).

If the impact on absenteeism is measured directly in e.g. an RCT, then the impact of the proportion of the included population that is employed or not (e.g. linked to age), the number of days this population works, etc. is automatically taken into account since, e.g. in the iPCQ and WPAI, participants are asked whether they are employed (paid work) and how many days or hours they were absent from

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yy This should be interpreted as people being absent from work for a couple of days or weeks due to illness.

zz Information retrieved from Eurostat (https://ec.europa.eu/eurostat), through the following link: Data – Database – Population and social conditions – Labour market – Labour costs – labour costs annual data. We recommend using the most recent information.

aaa WPAI: https://www.reillyassociates.net/wpai_general.html. The WPAI is available for free in more than 80 languages, There are versions available for specific diseases, a General Health (GH) version, as well as a version that can be adapted to a specific health problem (SHP). There is also a caregiver version (CG) to measure e.g. the effect of a child's specific health problem on the parent's work productivity. For more information we refer to the website.

iPCQ: https://www.imta.nl/questionnaires/ipcq/. The iPCQ is available in 18 languages. For non-commercial studies, the questionnaire can be used free of charge. For more information we refer to the website (https://www.imta.nl/questionnaires/ipcq/faq/).

work during a given period because of their health problems. However, if it is measured how much earlier or later a patient can return to work, this entire duration may not be fully counted as productive days since the impact of full-time or part-time work, the presence of weekends or holidays, etc. is not taken into account. This would lead to an overestimation of the impact on productivity. If only the impact on 'time to return to work' and no information on the actual impact on productivity is gathered, we recommend taking into account the average number of working hours in Belgium as published by the OECD for the active population.[bbb] This was 1535 hours per year for Belgium in 2022. Spread over 365 days, whether these are working days or not, this equates to an average of 4.2 hours per day which can be counted for the days that one returns to work sooner or later.

For presenteeism, if relevant, we recommend presenting the evidence related to efficiency losses as a consequence (e.g. in hours worked less efficiently), without converting this into a monetary value.

Unpaid work such as voluntary work, housekeeping or caregiving tasks can be considerable, especially in those with chronic diseases. It is recommended to present the incremental number of unpaid working days. The Dutch guidelines recommend asking how much time would be needed if all activities not performed by the patient were taken over by someone else. This avoids limiting the loss of unpaid work to activities actually performed by others.[36] As there is currently no consistent method to value unpaid working days, it is recommended not to include them in the cost estimates and only provide the impact on the volume of unpaid work.

5.9.3.10 Valuation of informal care costs

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

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

If relevant, informal care related to the disease/intervention under study can be taken into account in a complementary analysis, *separate from the base-case*. For reasons of consistency with unpaid work, informal care should only be measured (i.e. in number of days spent caring) but not valued. As mentioned in the Dutch in-depth cost manual, "*a problem in measuring the volume of informal care is that in some cases it is not easy to arrive at an unambiguous determination of the amount of time spent. For example, an informal carer may indicate that she/he provides informal care 24 hours a day, by always keeping an eye on and, if necessary, assisting. However, during that time the informal carer can often perform other, normal activities, such as housework or watching TV. How much of that time is effectively spent on informal care is then difficult to say. It can also be difficult to indicate what is and what is not informal care. For example, if a housewife or husband has always cooked dinner and now does the same for her/his sick partner, this does not qualify as informal care. However, if she/he has to cook something special that takes extra time or has to help her/his partner eat due to illness,*

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bbb https://www.oecd.org/en/data/indicators/hours-worked.html. Definition OECD: "*Hours worked is the total number of hours actually worked per year divided by the average number of people in employment per year. Actual hours worked include regular work hours of full-time, part-time and part-year workers, paid and unpaid overtime, hours worked in additional jobs. Hours excluded include time not worked because of public holidays, annual paid leave, own illness, injury and temporary disability, maternity leave, parental leave, schooling or training, slack work for technical or economic reasons, strike or labour dispute, bad weather, compensation leave and other reasons. The data cover employees and self-employed workers. … This indicator is measured in hours per worker per year.*" We recommend using the most recent information.

this can be called informal care."[36] One solution to accurately record informal care is to ask about the actual time spent on informal care and the tasks performed through self-reporting. This is specifically the time that could normally be spent on something else, but now has to be allocated to informal care.[36] The Dutch guideline refers to the iMTA Valuation of Informal Care Questionnaire.[ccc] The suitability of the questionnaire needs to be verified.

Costs of informal care that are not related to the intervention/disease in life years gained (indirect non-health care costs) should not be measured or valued.

5.9.3.11 Valuation of other outcomes relevant from a societal point of view

It is possible that, in comparison with a comparator, an intervention may have an impact on certain elements that have not yet been described. These include elements that might be important from a societal point of view, such as education (e.g. increased school absenteeism or need for specific support), justice (e.g. addiction problems), etc. In general, it is important to measure the incremental impact first. If no valuation is possible in monetary terms, the consequence(s) can still be transparently reflected in a cost-consequences analysis. Elements beyond direct health-related costs can be presented in a separate non-reference case analysis.

Transfer costs or payments, e.g. pensions, sickness and invalidity allowances as well as unemployment benefits, are financial flows from one part of society to another, that do not consume resources but simply transfer the power to use resources from one person or sector to another.[40] Transfer payments can be a cost to the paying government, but a financial gain to another sector or a patient. Therefore, because they do not use or create resources, transfer payments are typically not considered when estimating economic costs using a societal perspective.[41, 42]

Furthermore, as suggested by CADTH and ZIN,[18, 36] we recommend that lost leisure time is not included as a cost in the evaluation. Lost leisure time would be partly captured by the QALY, as part of the preference of a health state.[18, 36]

5.10 Guideline 10: Estimation and valuation of outcomes

Outcomes in economic evaluations should be expressed in terms of final endpoints instead of intermediary outcomes. Clearly defined patient-relevant outcome measures are recommended.

For cost-utility analyses (reference case), QALYs should be calculated. For cost-effectiveness analyses, outcomes should be expressed in terms of life years gained.

Data on survival and HRQoL should be presented separately.

Direct versus indirect comparisons:

- **The most robust evidence on comparative effectiveness comes from RCTs with low risk of bias. Companies should consider the organisation of such an active control study with the relevant comparator(s) in the pre-marketing authorisation phase to increase the reliability of the economic evaluations when submitting a reimbursement request.**
- **Both the internal and external validity of the estimated treatment effect, be it based on direct and/or indirect comparisons, need to be assessed.**
- **Acceptability of an indirect comparison for the assessment of the comparative effectiveness in an economic evaluation, must be judged on a case-by-case basis.**

[ccc] www.imta.nl/questionnaires/ivicq.

Efficacy versus effectiveness

- **Efficacy results can be transposed to effectiveness results by performing baseline risk adjustments under the assumption of an equal relative treatment effect.**

Health-related quality-of-life weights should be based on empirical data, obtained in patients using a descriptive system for health status for which corresponding preference values exist from the general public. Therefore, in adults, the EQ-5D-5L is recommended. In addition, the use of Belgian preference values is recommended.

Description of health states by proxies should be avoided as long as patients in the target population are able to complete a survey themselves or can be interviewed.

Scenarios with disease-specific measures for HRQoL and scenarios including effects on caregivers' HRQoL can be presented as complementary analyses but are not acceptable in the reference case.

It is recommended to use final patient-centered outcomes. Where this is not possible, evidence for the association or correlation of effects on the surrogate and the final outcome needs to be provided. If such evidence is not available, this needs to be stated explicitly.

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

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

5.10.1 Effectiveness evaluation in cost-effectiveness analysis

For cost-effectiveness analyses, the outcomes should be consistent with the results of the clinical file. The estimated effectiveness should be based on all-cause mortality in the reference case analysis. Effectiveness estimates based on disease-specific mortality can be presented in complementary analyses.

5.10.1.1 Direct versus indirect treatment comparisons

The key input in an economic evaluation of an intervention for which added value is claimed is the assessment of that added value. The estimation of the relative and absolute impact on safety and efficacy/effectiveness of an intervention relative to its comparator(s) is intrinsically linked to the economic evaluation. How a critical assessment of this clinical component is performed is outside of the scope of this guideline. For this, the guidance as prepared under the HTA regulation to support JCA activities should be followed.

Article 9 of the HTA Regulation[8] stipulates that a JCA shall contain a description of the scientific analysis:

- Of the relative effects of the health technology as assessed on the health outcomes against the chosen parameters which are based on the assessment scope [i.e. the PICO elements] …;
- Of the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence.

To support this scientific analysis, guidance documents were developed which are available under the following link: https://health.ec.europa.eu/health-technology-assessment/key-documents. In this section, we refer to the following guidance documents:

- Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons[12]
- Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons[31]
- Guidance on the validity of clinical studies for joint clinical assessments[13]

The research design and the reliability of the estimate for the relative treatment effect are inherently related. "*Randomised controlled trials (RCTs), provided they are well designed and have low risk of bias, are the gold standard for informing estimates of treatment effectiveness and should be used for evidence synthesis when possible.*"[12] Indirect comparisons are not banned. However, strengths and weaknesses are associated with different methods. Some key points from the Methodological Guideline for Quantitative Evidence Synthesis - Direct and Indirect Comparisons include:[12]

"*In situations where no direct RCT evidence on a comparison of interest is available or where multiple treatments must be compared simultaneously, indirect comparisons may be used. In general,* ***direct comparisons are preferable*** *to comparisons based on indirect evidence alone because the latter are associated with greater uncertainties.* ***If indirect comparisons are required, in general only anchored indirect comparisons respecting randomisation are appropriate****, which requires that the evidence network is connected.*"[12]

"*Anchored indirect comparisons of aggregate data require the* ***assumption of exchangeability across studies****. The properties of similarity, homogeneity and consistency should be assessed and reported as a means of assessing the validity of this assumption.* ***If any of these properties do not hold, the results of an anchored indirect comparison are unlikely to provide a meaningful estimate of the treatment effect****.*"[12]

"*In any situation with* ***non-randomised data, such as observational evidence and single-arm trials, or in the case of disconnected networks****, complete access to the IPD [individual patient data] is required in order to apply methods that can adequately adjust for confounding. Again, these methods require that a set of all covariates (confounders, prognostic variables, or effect modifiers) relevant for adjustment are measured. However,* ***this is often unverifiable and unattainable****. Therefore, it is imperative that the model and covariate selection strategies for adjustment are prespecified and based on transparent criteria. Use of propensity scores is a method frequently applied. The assumption of conditional exchangeability needs to be met and can be assessed by investigating positivity, overlap, and balance. If conditional exchangeability is not met, an adequate analysis is not possible and the results from the corresponding analysis are unlikely to provide a meaningful estimate of treatment effectiveness. If a propensity score approach is applied, the final target population has to be described in detail, especially if trimming or truncation methods are used.* ***Owing to the greater uncertainty associated with non-randomised data, a sufficiently large treatment-effect estimate is required****…*"[12] [ddd]

This connection between uncertainty and study design is also reflected in the Guidance on the Validity of Clinical Studies, requiring any effectiveness result in a JCA report to be accompanied by a description of its certainty. This refers to three concepts: "*internal validity (i.e., the extent to which a study is free from bias [also called systematic errors], a concept analogous to Risk of Bias [RoB]); external validity (i.e., the extent to which study results provide a basis for generalisation to the target population, a concept which encompasses generalisability and applicability); and statistical precision (i.e., the uncertainty associated with study results due to random sampling variability).*"[13]

Concerning the internal validity, the guidance document refers to suitable RoB assessment tools: for outcomes with evidence coming from RCTs, RoB should be assessed using the Cochrane RoB 1 tool; for outcomes with evidence coming from comparative non-RCTs, this is the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions). Uncontrolled clinical trials, e.g. single-arm trials,

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[ddd] We refer to Appendix 8.6 to provide further information about the problems with propensity score analyses to provide estimates of the relative treatment effect.

do not allow relative effectiveness assessment. Therefore, the guidance states: "*Since uncontrolled trials per se are of very limited value for performing relative effectiveness assessment, RoB assessment is in general not required.*"[13]

Concerning the external validity, the guidance document states the following: "*a lack of external validity of clinical evidence threatens the overall certainty of results if, because of relevant effect modification, the effect in the population of interest could be different from the effects in the clinical studies.*" Problems with the external validity are referred to as the PICO mismatch: *"Limitations to the external validity of the evidence can occur if: (i) the study population (based on eligibility criteria or actual recruitment) differs from the intended target population; (ii) the experimental intervention, control interventions and/or subsequent interventions differ from the target setting; or (iii) the study outcomes (e.g., surrogate outcomes) do not give information about the outcomes of interest.*"[13]

For more details, we refer to the full guidance documents.

Whether an indirect comparison is acceptable for an economic evaluation or not and, in the case where it is acceptable, whether it is of sufficient quality, will have to be assessed on a case-by-case basis.

5.10.1.2 Efficacy versus effectiveness

For relative treatment effects there is a strong preference for high-quality randomised controlled trials (RCTs).[12, 17] However, RCTs often provide information on efficacy (i.e. the treatment effect under ideal circumstances), while information about an intervention's effectiveness is requested (i.e. the treatment effect under usual circumstances). Information about the experience with an intervention in routine care is as such insufficient due to the absence of a comparator group. Efficacy results are often transposed to the real life target population to estimate effectiveness in an economic evaluation. This is acceptable, as long as adjustments are made for baseline risk in the real life target population.[26] This is done under the assumption of an equal relative treatment effect, unless otherwise justified according to an appropriate analysis (see part 5.4.4).

Such an adjustment is not needed if an RCT is set up as a pragmatic trial or if comparison with real-world data provides support for the external validity of trial results. In contrast, if the probability of the event of interest in a trial is very different from the probability of this event in the actual target population treated with the same intervention (e.g. if in an RCT a large number of patients in the comparator group receive a re-intervention, while in the target population in the real-world, receiving the same intervention, a much lower percentage of patients undergo such a re-intervention).

5.10.2 Utility assessment in cost-utility analysis

In cost-utility analyses, the valuation methods for HRQoL should be the same for all comparators. Data on survival and HRQoL should be presented separately. As weights that represent distributional preferences of the general public according to the populations affected are not available, QALYs should not be weighted in the economic analysis. This means that in submitted economic evaluations a QALY is a QALY, regardless of to whom it accrues (see part 5.13).

Quality-of-life assessment for specific health states, needed for the calculation of QALYs, should be conducted in two steps. The first step is to obtain patients' description of health states (5.10.2.1). Health states should be described on a standardised descriptive system such as the EQ-5D. The second step consists of assigning a value between 0 (= value for dead) and 1 (= value for perfect health) to these health states (5.10.2.2).[eee]

[eee] A direct choice-based valuation method such as the Time Trade-Off (TTO) and Standard Gamble (SG) can also be used to reveal preferences. However, due to the complexity and cost associated with directly measuring health utilities,[18] this approach is not recommended.

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

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

In a population, HRQoL is negatively affected by ageing.[43] In general, it is recommended to measure HRQoL directly within the comparative study. If an age-related adjustment for HRQoL is deemed necessary (e.g. in the extrapolation period),[fff] it is possible to make use of Belgian age-and gender specific population-based HRQoL estimates. The EQ-5D-5L has been included in the Belgian Health Interview Survey,[ggg] providing Belgian population norms for the EQ-5D-5L by sex and age.[43, 44] We recommend to use the most recent index value set available.[hhh]

5.10.2.1 Health state description

In the reference case, a generic health-related quality-of-life measure should be used for the description of health states. The health state description should be made by patients on a generic descriptive system such as the EQ-5D (for adults) and the EQ-5D-Y (for youngsters) or Short-Form 6D (SF-6D).[iii] If justified by the disease or the intervention (e.g. care for disabled persons, terminal care, etc.), informal caregivers' health states can also be considered in a complementary analysis, but not as part of the reference case. It should then be explicitly stated that the QALY estimates include the effect on caregivers' HRQoL. Other instruments than the EQ-5D or SF-6D exist, e.g. the Health Utilities Index (HUI) or Quality of Well-Being (QWB) scale, but these have not been validated in Dutch or French for Belgium. Health state descriptions with the EQ-5D or SF-6D in similar patient populations in other countries may be used, provided that the criteria for valuation as explained in 5.10.2.2 are fulfilled.

The use of a generic utility instrument[jjj] should be considered in the design phase of a clinical study when a future economic evaluation is envisaged (see part 4.2.3). The study protocol should specify which instrument will be used to obtain utility values and when it will be used (e.g. at baseline,

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fff Different approaches exist, e.g. no adjustment in the extrapolation phase (i.e. constant utilities), taking the lowest value (the constant utility versus the age- and sex specific utility based on Belgian population norms), reducing utilities to the same extent as in the age- and sex specific Belgian population norms, etc. The impact of different approaches can be examined in scenario analyses.

ggg https://www.sciensano.be/en/projects/health-interview-survey. https://www.healthybelgium.be/en/health-status/life-expectancy-and-quality-of-life/quality-of-life.

hhh An Excel file is available as a supplementary file under the following link: https://link.springer.com/article/10.1007/s11136-021-02971-6.[43] At the moment of writing this guideline, 'Supplementary file2' contains the most recent information (population norms in 2018). It is recommended to check for updates since the Belgian Health Interview Survey is repeated every 4 to 5 years. Results for the most recent Health Survey (2023) will be published by the end of 2025.

iii The SF-6D consists of a subset of the SF-36. When the SF-36 has been used in a clinical trial, and SF-6D tariff values are available, the SF-36 data can be used to calculate QALYs.

jjj Not all generic instruments can transfer results into utilities. We apply the terminology 'generic utility instrument' to refer to the subgroup of generic instruments that are fit for this purpose and can be used to calculate QALYs (such as the EQ-5D and SF-6D).

prespecified timepoints[kkk] and/or events[lll]). In the reference case, generic health state descriptions should be used. In line with the EUnetHTA guidelines,[33] new studies should preferably always include a generic utility instrument such as the EQ-5D, alongside disease-specific instrument(s) if a disease-specific instrument is considered necessary. This increases the potential usefulness of the data for later economic evaluations.

Applying a generic utility instrument allows the transformation of health states described by patients/participants to utilities. Specifically recommending the use of the EQ-5D improves consistency and facilitates comparability. The EQ-5D is available in different versions: the three-level version (EQ-5D-3L) and five-level version (EQ-5D-5L) for adults, and the EQ-5D-Y-3L (Y – youth) and EQ-5D-Y-5L (since 2024) for children and adolescents. The 5L version was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity and to reduce ceiling effects in comparison with the 3L version. Therefore, the EQ-5D-5L version is recommended for measuring HRQoL in adults. For the youth version, a preference for the 3L-version is expressed, which is related to the current availability of value sets (see part 5.10.2.2).

If it is thought that a generic instrument is insufficiently sensitive to relevant changes in health for a specific disease, additional (disease-specific) quality-of-life results can be described in separate analyses. However, this should not replace the reference case, i.e. if results using the generic utility instrument are available, the calculations based on these results should be presented. Furthermore, it is not acceptable to create an ad hoc disease-specific questionnaire for a single economic evaluation and use this in the reference case analysis to estimate the number of QALYs gained. Such ad hoc created instruments, defined as a set of alleged relevant questions about a disease state and its associated HRQoL, are not sufficiently validated and tested to offer reliable and consistent results. If disease-specific instruments are used, references to publications that document the psychometric properties should be provided.

Description of health states on a generic (utility) or disease-specific quality-of-life instrument by proxies should be avoided as long as patients in the target population are able to complete a survey themselves or can be interviewed. There is evidence that expert opinions are not always close to the descriptions given by patients. Therefore, the use of proxies to describe patients' health states is only accepted if patients cannot describe their health state themselves (e.g. mentally disabled persons, very young children, etc.[mmm]). The reason for using proxies for the description of health states should always be justified with clear arguments.

When used in a mixed population with young participants, adolescents and/or adults, the usefulness of the questionnaire for (the majority of) the studied population should be considered. If possible, it is recommended to use the same questionnaire for the entire sample. This allows applying the same value set to the population in the intervention and comparator group and simplifies the analysis of the results. Other arguments may need to be weighed up. For instance, how long will the population be followed up and from what age is it useful to switch to the adult version of the EQ-5D if children and/or adolescents are followed-up into adulthood. Could the proxy version be used for all children (4-18 years) and this approach validated by also having the children complete the questionnaire themselves

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kkk In general, it is recommended to collect HRQoL information longitudinally at different time points. From a practical point of view, these include, for example, time points when other information is also collected for the study, as well as time points when incremental impact is expected (e.g. when there is progression of the condition, re-interventions occur, etc.).

lll If there is a negative impact or disutility of a particular incremental event (e.g. needing a specific surgery), it might be useful to measure its impact on quality of life (e.g. before the intervention is carried out and during hospitalisation) as well as the duration of this impact (e.g. related to the length of hospitalisation).

mmm We remark that for unconscious patients, the Belgian EQ-5D-5L and EQ-5D-3L questionnaires specifically include this health state. Therefore, it is sufficient that the proxy indicates this 'unconscious' health state.

from a certain age (e.g. 8 years) and compare the results with the proxy answers? These considerations should be made when designing the study protocol.

5.10.2.2 Health state valuation

Values assigned to the health state descriptions[nnn] should come from (a representative sample of) the general public. Belgian value sets, also called tariffs, are only available for the EQ-5D. They are available for the EQ-5D-3L (see Appendix 8.8),[45] EQ-5D-5L[46] and EQ-5D-Y-3L[47] questionnaires. The use of these Belgian tariffs is recommended in the reference case. An Excel file is available on the KCE website to convert the health states of the three EQ-5D questionnaires to utilities.[ooo] For other generic utility instruments, like the SF-6D, HUI or QWB, no such Belgian value sets are available. If primary data are not available and HRQoL results from trials from another country are used, index values from that country can be used. In such cases, having information from the same (foreign) value set applied to both the intervention and comparator group should minimize the influence on the incremental impact in comparison with applying the Belgian value set to both groups.

If health states were collected in an international study and the health states are available at the individual patient level, we recommend applying the Belgian value set to the health states of all participants, maintaining the largest possible sample. If another approach is applied, this should be adequately justified and the result which includes the full sample should at least be presented as a sensitivity analysis. If the health states are not available at the individual level, this conversion is not possible and only the foreign valuation can be used.

The EQ-5D questionnaires also contain an EQ VAS (visual analogue scale) which records the respondent's own assessment of their health status. It is not recommended to use the VAS scores in an economic evaluation. Instead, the utilities derived from the health states should be used.

Currently, a Belgian value set is not available for the EQ-5D-Y-5L. As there is currently no research ongoing in Belgium to develop this value set, we recommend using the EQ-5D-Y-3L version for children and adolescents.

Further information on the EQ-5D, the manuals for the different instruments, available versions (language, paper or digital, self-completion, proxy, interviewer administration, telephone, etc.), registration to use and obtain the questionnaire(s) (free for non-commercial use), etc., can be found on the website of the EuroQol group.[ppp]

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

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nnn Different approaches exist for the valuation of health states. For more information, we refer to Appendix 8.7.

ooo https://kce.fgov.be/sites/default/files/2025-05/20250508-EQ-5D-value-sets-Belgium.xlsm.

ppp https://euroqol.org/.

qqq An Excel spreadsheet listing studies mapping to EQ-5D from other patient-reported outcome measures or clinical instruments is available here: https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies. In case mapping is applied, the algorithm and its reference should be reported transparently. It should also be checked and reported whether the underlying population on which this mapping function is based is comparable to the target population in the economic evaluation.

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

Health state values from different (clinical) studies should be treated with utmost caution. Only if measured with the same instrument and in a similar patient population are the values comparable and can they be used in one and the same economic evaluation. Combining different questionnaires and valuation methods may generate a biased picture of the absolute and relative impact on quality of life. Consistency in methodology for the measurement of health states and the valuation of these health states in the economic evaluation should be pursued.

Similarly, combining health utilities and disutilities in cases of multiple adverse events or multi-morbidity should be treated with caution. There are different approaches to combine these: additive (taking the utility for a single health state and applying the marginal disutility for each additional state), multiplicative (multiplying individual health state utilities to derive a single health utility) and minimum (using the lowest utility to represent the joint health state) methods.[18] None of these methods is free of bias. The chosen approach should be justified and appropriate scenario analyses should be performed to assess the impact of alternative plausible assumptions.[18]

5.10.3 Surrogate outcomes

One of the documents prepared under the European HTA regulation to support JCA activities is the "Guidance on outcomes for joint clinical assessments".[48] One of the points of attention for the assessment scoping process is that outcomes relevant for HTA should be long-term or final where possible. Where it is not feasible to measure final outcomes, intermediate or surrogate outcomes[rrr] may be acceptable if there is evidence of a strong association or correlation of effects on the surrogate or intermediate outcome with the effect on the long-term or final outcome.[48]

The controversy with surrogate outcomes is that the validity of these surrogate outcomes has rarely been fully established. For example, studies that have extensively examined the correlation between progression-free survival (PFS) and overall survival (OS) in oncology conclude that there is a low correlation.[53-55] The results are also disappointing for the correlation between PFS and quality of life (QoL).[56]

[rrr] The following description is provided in the HTA guidance:[48] "*A surrogate outcome is an outcome that is intended to replace an outcome of interest that cannot be observed in a specific clinical study.[49] It is a variable that provides an indirect measurement of effect in situations in which direct measurement of a patient-centred effect is not feasible or practical.[50] A surrogate outcome may be a biomarker that is intended to substitute for a patient-centred outcome, or it may be an intermediate outcome. A surrogate outcome is expected to only predict the treatment effect of an outcome that is not observed in a clinical study. A biomarker is a surrogate which can be defined as a characteristic that is an objective measure of an indicator of normal biological processes, pathogenic processes or pharmacological responses to an intervention.[51] Examples of biomarkers used as surrogacy for mortality and/or morbidity and/or disease remission include levels of cholesterol, haemoglobin A1C (HbA1C), and antibody titre after vaccination. An intermediate outcome is a surrogate outcome such as a measure of a function or of a symptom (disease-free survival, angina frequency, exercise tolerance) but is not the long-term or final outcome of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction).[52]*"

Therefore, we make two recommendations relevant for economic evaluations:

- If it is possible to measure a final endpoint in a trial, primary data on the final endpoint should be collected and used in the economic evaluation. For example, if it is possible to measure the impact on QoL, clinical trials should include QoL as an outcome and these data should be used. This is in any case preferred over mapping functions that come with an additional level of uncertainty.
- If surrogate outcomes are used, then, in line with the HTA guidance, evidence supporting the link to the final outcome should be provided. The HTA guidance[48] refers to a correlation of at least 0.85 that is described as 'high' and can be used as a criterion for validation of surrogate outcomes.[54] If this evidence is not present, this should be explicitly stated. Furthermore, it is useful to verify and indicate whether a patient-centred outcome is likely to be available at a later date.[48] This can be done, for example, by longer follow-up of the underlying trial for monitoring the impact on overall survival. These and other considerations are further developed in the HTA guidance document.[48]

5.11 Guideline 11: Time horizon

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

When modelling a long time horizon, it is recommended to apply and present multiple shorter time horizons in scenario analyses, applying the same time horizon to both costs and effects. This is especially relevant in cases where evidence is only available for a relatively short time horizon and most of the longer-term impact is modelled based on assumptions and extrapolations.

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

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

If evidence is only available for a short time horizon and most of the longer-term impact must be modelled based on assumptions and extrapolations, we recommend to not only present results for the lifetime time horizon, but also the impact of applying (multiple) shorter time horizons. The same time horizon should always be applied to both costs and outcomes. A shorter time horizon typically has greater certainty about the incremental impact but may underestimate the total incremental impact by not including longer-term impacts. Vice versa, the analysis with the longer-term horizon potentially suffers from the impact of the large number of assumptions and extrapolations made. Allowing the time horizon to vary shows the sensitivity of the results for the chosen time horizon. This can support the interpretation of the results by e.g. indicating which part of the incremental impact is evidence-

based and which part is still uncertain. This can e.g. support the demand for longer follow-up of a specific trial or the request for gathering more evidence on longer-term impacts.

A particular issue that may be important for some interventions is the rapid development of new interventions. These innovations may not be formally evaluated yet, but may be expected to enter the market in the near future, making the current intervention 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. However, no formal analysis of the likely effect can be performed as the clinical effectiveness of the innovations is still uncertain.

5.12 Guideline 12: Discount rate

Future costs should be discounted at a rate of 3%; future outcomes at a rate of 1.5%.

To assess the sensitivity of the results to the discount rate applied, different scenarios should be presented, including an equal discount rate for both costs and effects of 0%, 3% and 5%.

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

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

Apart from the reference case analysis with a 3% discount rate for costs and 1.5% for effects, the report should present alternative scenarios showing the relative importance of using different discount rates for the final result. Given the prevailing advice for the base-case analysis in many economic guidelines of other countries, a 3% discount rate for both costs and outcomes should be used. Other mandatory scenarios include a 0% and 5% discount rate for both costs and outcomes. Applying a 0% discount rate is important to be able to judge e.g. the modelled life expectancy when comparing it with that of the average Belgian sex- and age-adjusted population based on existing life tables (see part 5.14.6). For the decision makers it is important to keep in mind that, if they wish to compare the ICER of a new product with the ICER of a product for which a decision has already been taken (based on the ICER and other elements), he/she should always compare the ICERs of the reference case analyses of both products.

5.13 Guideline 13: Equity

No equity weights should be applied to outcomes in the reference case. All outcomes (e.g. QALYs) should be weighted equally, regardless of the characteristics of the population receiving or affected by the intervention.

Weighting of health outcomes to account for equity aspects is sometimes suggested. However, there is no standardised way to do this in Belgium (no societal equity weights have been determined). Moreover, equity weights might change over time and with changing governments, depending on priorities defined for healthcare policy.

In line with other national guidelines,[17, 18, 20, 25] equity weights should not be applied to outcomes in the reference case. "*All outcomes should be weighed equally, regardless of the characteristics of people receiving, or affected by, the intervention in question.*"[18] Nevertheless, to allow decision-makers to discuss equity issues during the appraisal of a dossier, the report should stipulate how much QALYs are gained in which target population in a disaggregated way, e.g. highlighting unmet needs of certain disadvantaged groups. In such cases, the potential impact of a technology in addressing this concern should be described.[20]

5.14 Guideline 14: Modelling

Modelling should be applied if the available data are insufficient to allow a full assessment of the cost-effectiveness or cost-utility of an intervention. Models should be based as much as possible on data from clinical studies with the same study intervention and comparator, on data from validated databases and/or data from literature. Modelling should always be justified.

If modelling is performed, the structural hypotheses, input variables, assumptions and sources of information should be justified and presented in a clear and transparent way.

If extrapolations are performed, different extrapolation assumptions should be applied as part of the reference case, including not only optimistic but also pessimistic interpretations (or vice versa). The impact on the results should be presented transparently.

Modelling inputs and outputs should be consistent with existing data. Both internal, external and face validity should be checked.

Primary data and original sources of information used to define the values of input parameters as well as the original computer model should be kept at the disposal of the Expert Committee responsible for the reimbursement advice.

Routine submission of the model is not required. However, the assessor can request a copy of the model.

5.14.1 Need for modelling

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

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

mentioned in part 4.2.3 and 5.10.3, where possible, it is important to include the final outcomes (e.g. QoL and survival) to avoid applying modelling assumptions, which includes an extra level of uncertainty.

Modelling can also be used to simulate the *real life* application of an intervention even if trial data are available. RCTs usually do not reflect real life settings. Adaptations by means of modelling may be useful to assess effectiveness instead of efficacy as presented by the RCTs. This can be done by adjusting for differences in baseline risk between the trial population and the real-world target population.[26] Adjustments for protocol-driven costs or events should also be considered. This may be assessed by comparing protocols in RCTs with relevant clinical practice guidelines or real-world practice patterns (e.g. identified in real-world administrative data).

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

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

Finally, modelling can be used to compare the intervention with the relevant *comparator*. A comparison between interventions that have never been directly compared in a clinical trial may be modelled. For more details about indirect comparisons, we refer to part 5.10.1.1.

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

Guidelines for good general modelling practices have been developed by the modelling task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[sss] Specific guidelines for standardization of economic evaluations of immunization programmes have been developed by the World Health Organization (WHO).[57] [ttt] These guidelines might provide further support whenever a model is built, e.g. on when to use a static or dynamic model. However, if they include other recommendations on e.g. which type of costs should be included, what perspective should be followed in the base case, how results should be presented, etc., the Belgian guidelines should be followed for reimbursement requests submitted in Belgium.

5.14.2 Choice of the model design

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

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

[sss] https://www.ispor.org/heor-resources/good-practices/article/modeling-good-research-practices---overview.

[ttt] https://iris.who.int/bitstream/handle/10665/329389/WHO-IVB-19.10-eng.pdf.

5.14.3 Description of model structure, input variables and assumptions

The model structure should be clearly described. All variables in the model and their sources must be listed and documented in a table (Table 4). Uncertainty around input parameters and distributions for (probabilistic) sensitivity analyses should be presented. These distributions should be presented with the relevant parameters, e.g. Beta distributions should be presented with alpha1 and alpha2.

Table 4 – Description of the variables used in a model: template

Variable	Description	Mean	Distribution – type* and parameters (e.g. SD, 95% CI, α1, α2, etc.)	Source

*SD: Standard deviation, CI: confidence interval. * type: e.g. beta, gamma, lognormal or uniform distribution.*

All assumptions made in the model should be explicitly documented and justified. Assumptions should be tested in the sensitivity analysis and/or scenario analysis to test the robustness of the results (see part 5.15). This does not mean that every variable must be individually adjusted down to the smallest detail. For example, the cost of a hospitalisation may be varied as a whole in a sensitivity analysis instead of all individual costs incurred within this hospitalisation.

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, considered the lowest level of evidence, are not allowed for the assessment of probabilities or outcomes if relevant and reliable data are available. 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 8.1). The use of expert panels should always be well justified. Abstracts and oral presentations usually provide insufficient information to assess the quality of their contents. They should be avoided as a source for input values.

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

5.14.4 Long-term extrapolations

If the clinical evidence contains only short term outcomes and long term outcomes are considered important for the economic evaluation, modelling may be needed. It is recommended to present different scenarios to show the impact of different extrapolation approaches on the results.[58]

Depending on access to data, different methods may be used. Systematic approaches to survival analysis for economic evaluations alongside clinical trials where patient-level data are available have been developed.[59] [uuu] Different approaches are possible, e.g. whether a parametric model is fitted to the entire dataset or whether the dataset is split and a parametric model is fitted to each treatment arm. A variety of methods that can and should be used when assessing the suitability of fitted models are described,[59] such as visual inspection (how closely does the parametric survival model follow the Kaplan Meier curve), the log-cumulative hazard plots or performing the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) tests of the relative fit of alternative parametric models. Concerning the latter, we need to stress that the best fit does not always represent a good fit (see part 5.14.6). Furthermore, these tests are useful to determine whether a model fits the observed data, but do not indicate how suitable a parametric model is for the time period beyond the final trial follow-up.[59] Furthermore, "*when survival data are relatively complete the extrapolated portion may*

[uuu] A series of Technical support documents have been produced in the area of survival analysis: https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis.

contribute little to the overall mean area under the curve and in this case the log-cumulative hazard plots and AIC/BIC test results may be of particular use. However when the survival data require substantial extrapolation it is important to attempt to validate the predictions made by the fitted models by other means."[59] For more information we refer to the NICE Technical Support Document.[59]

If there is no access to the patient-level data, e.g. if published summary measures or presented Kaplan-Meier (KM) curves are relied upon, it is possible to use the published data for the follow-up period of the trial and apply different extrapolations for the longer term.

In the extrapolation phase, assumptions have to be made about the treatment effect, e.g. after treatment discontinuation. A first possibility is to model the following three scenarios:

- 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. This scenario can be further elaborated by applying multiple waning assumptions.

The plausibility of these scenarios and waning assumptions is to be discussed case-by-case. An overreliance on prior appraisals without any justification should be avoided. Similarly, non-intuitive assumptions that might be made when e.g. linking the treatment effect waning and treatment stopping rules should be avoided.[60] Evidence-driven approaches are recommended. Invoking the lack of evidence to only model a lifetime treatment effect is not acceptable. In all situations, scenario analyses should be conducted that consider alternative assumptions relating to the waning of effectiveness.[18]

Another possibility for extrapolation of within trial survival results is to apply the following three scenarios linked to the Belgian age- and gender specific mortality risk:[vvv]

- A scenario in which the mortality risk remains constant over time. This is usually a too optimistic scenario in an ageing population.
- A scenario in which the mortality risk increases with the absolute increase in mortality risk of the general Belgian population of the same age and gender.
- A scenario in which the mortality risk increases with the relative increase in this mortality risk of the general Belgian population of the same age and gender. This is usually a pessimistic scenario in populations with a relatively high observed mortality risk during the trial follow-up since the mortality risk during the extrapolation period might increase relatively fast.

In general, many different extrapolations can be applied. Important here is to include not only optimistic but also pessimistic interpretations (or vice versa) and transparently present the impact on the results. The scenarios are all part of the reference case analysis because the choice of an extrapolation approach is mainly a judgement. By presenting different, sometimes extreme, scenarios, the uncertainty related to the effectiveness of the therapy in the extended period can be assessed.

The presentation of scenarios is the most transparent option to show how robust the results are to the extrapolation approach used. Each scenario should be accompanied by appropriate sensitivity analyses on uncertain parameters as specified in part 5.15.

[vvv] Age- and gender-specific life tables for Belgium are available at the National Institute of Statistics: (http://www.statbel.fgov.be), under the following link: https://statbel.fgov.be/nl/themas/bevolking/sterfte-en-levensverwachting/sterftetafels-en-levensverwachting#figures.

5.14.5 Half-cycle corrections

A model defines health states through which a population or patient can evolve over time. The choice of health states and cycle length are determined by the available data. It is recommended to apply half-cycle corrections, for example to the number of patients alive during a specific cycle. Half-cycle corrections should of course not be applied to events that occur specifically at the beginning of a cycle (e.g. performing surgery or administering a pharmaceutical product at the beginning of the first cycle).

5.14.6 Calibration, internal, external and face validity and cross-validation of a model

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

Specifically for survival modelling and extrapolations, several complementary validation approaches exist, such as comparing the modelled survival curve with the available evidence (e.g. from the presented Kaplan Meier curve) or comparing the evidence-based incremental effect at specific time points with the modelled incremental effect (internal validity), and comparing the (non-discounted) life expectancy of the modelled target population with the (non-discounted) life expectancy of the general population of the same age and gender (external validity). To simplify this task, we recommend presenting a figure of the modelled survival of the intervention and comparator group. This can provide insight into whether certain assumptions are correct or not (e.g. the applied parametric survival curve and the assumption of proportional hazards over time). As noted earlier, the best fit is not necessarily a good fit. A visual inspection might already show that the fitted survival curves do not provide a good presentation of the original KM-curves of the intervention and/or comparator group and thus the incremental benefit. In such cases, points may be extracted at different time points from the KM curve for both the intervention and the comparator to reflect the identified evidence.

The results of the model should be intuitively correct, that is, the model should have face validity. Counter-intuitive results should be examined and explained.[20] The model description should be transparent enough to allow an explanation of the differences with other models for the same interventions (cross-validation).

The presentation of the results of an economic model as a point estimate together with its appropriate uncertainty range is an absolute prerequisite. An economic model is by definition subject to uncertainty. The results are conditional upon the input data and the assumptions applied in the model. Both the uncertainty about the input data and the assumptions generate uncertainty in the outputs. This uncertainty should be appropriately presented, as the level of uncertainty might be an element in the decision making process. For the recommended presentation of the results, see part 5.16.2.

Finally, the outcome of an economic evaluation can be highly dependent on the extrapolation and assumptions made about the treatment effect.[20] In addition to applying different extrapolation scenarios, we have already pointed out that it is also important to display the results for different time horizons (see part 5.11) which allows further reflection on the maturity of data. This can e.g. provide insight into the importance of obtaining longer follow-up data to assess the validity of a model and extrapolation assumptions.

5.14.7 Access to the economic model

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

Regarding access to the model, the intention is to find a balance between transparency and practical feasibility. Different software packages for building economic models are available (e.g. Excel (with add-inn software like ModelRisk or @Risk), DATA/Treeage, R or WinBUGs). While no specific software packages are prohibited, it is important to ensure that the assessors are practically able to validate the model. Therefore, either a generally applied package is used (e.g. Excel) or prior consultation with the assessors about which package can be used or how the model can be delivered to allow for validation is recommended.

Validation of a model should be done in the first place by the author of the model. If additional analysis needs to be performed, the reviewer may request this from the submitter of the reimbursement request. Routine submission of the model is not required. However, the assessor can always ask for a copy of the model.[www] The model version should be the same as the one on which the results in the submission are based. Confidentiality needs to be guaranteed by the Committee. Models shared with assessors may only be used in the context of assessing the specific reimbursement request, unless otherwise stated by the owner of the model.

5.15 Guideline 15: Handling uncertainty and testing the robustness of the results

Irrespective of the study design, the uncertainty surrounding the cost-effectiveness/cost-utility estimates should be analysed using appropriate statistical techniques. Interval estimates should be presented for each uncertain input parameter in the economic evaluation.

The different types of uncertainty should be addressed, i.e. parameter, structural and methodological uncertainty. For parameter uncertainty, probabilistic sensitivity analyses should be presented in the reference case. Structural and methodological uncertainty should be addressed using scenario analyses.

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

- *Variability* refers to the variation or randomness observed within a homogeneous sample of patients. Variation by chance between individual patients is not the primary concern in economic evaluations, given that economic evaluations focus on a specific target population rather than on the individual. Nevertheless, detailed descriptive statistics, showing the distribution and variability of costs and effects data, should be presented.
- *Heterogeneity* refers to observed differences between patients which can, in part, be explained (e.g. differences in age, sex…).[61]
- *Generalisability* refers to applicability of the results to other populations (e.g. non-trial populations with different baseline risk).
- *Transferability* refers to the applicability of the results from other countries. Context-specific studies are, however, preferred.

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www When sharing models, attention should be paid to providing a transparent model, including a 'user guide' describing: the model, input variables, assumptions, calculations, results, etc. Extra information or comments can be provided for e.g. complex formulas or specific choices.

Uncertainty is usually divided into two areas:[61]

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

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

In the case of modelling, sensitivity analysis can help determine the impact of the different model assumptions on the results. Probabilistic sensitivity analyses should be performed on all *uncertain parameters* in a model; i.e. one probabilistic sensitivity analysis where all uncertain parameters are allowed to vary according to a predefined distribution, e.g. by means of Monte Carlo simulations.[xxx] Distributions used for the uncertain modelling parameters should be justified. Appropriate probability distributions should be selected for specific input variables, e.g. beta distributions for transition probabilities or utilities (e.g. avoiding modelling utilities >1), gamma distributions for costs (avoiding negative costs and also allowing to model outliers) or a lognormal distribution for relative risks or hazard ratios. Where sample information is available, the probability distribution can reflect the information from this sample. If such sample information is not available, the upper and lower bounds of the input variable should be plausible and adequately reflect uncertainty in the parameter value. Parameters defined with very narrow confidence intervals may be a cause for concern.[15] Correlations between parameter values should also be taken into account, which should also be reflected in univariate sensitivity or scenario analyses.[15]

For composite measures, such as total costs, the different components with their respective distributions should be included in the sensitivity analysis if applicable. The probabilistic sensitivity analysis should be performed on the reference case and the alternative scenarios such as the scenarios related to the assumed effectiveness of the therapy in extended time periods. It is recommended to present the most important contributors to the uncertainty of the estimated incremental cost-effectiveness/cost-utility ratio (e.g. by means of a tornado diagram).

The central estimate of the ICER results directly from the probabilistic sensitivity analysis as the mean of the simulated ICERs. This is not necessarily equal or close to the ratio of the mean incremental cost and mean incremental effect, which is the deterministic version of the ICER. Such a deterministic ICER can be presented if the Monte Carlo simulations fall in different quadrants of the cost-effectiveness plane. Nevertheless, in these cases, the uncertainty surrounding the incremental costs and incremental effects should still be presented and taken into account when presenting results and conclusions.[yyy]

[xxx] In exceptional cases, best- or worst-case scenarios might also provide clear results and information for stakeholders, e.g. when applying a worst-case scenario for all uncertain input variables still results in cost savings (i.e. better outcomes and lower costs), or vice versa.

[yyy] For example, if the results of the Monte Carlo simulations are somewhat equally spread over the four quadrants of the cost-effectiveness plane, it is possible that the deterministic ICER ends up in e.g. the second quadrant of the cost-effectiveness plane. In such a case, it would be incorrect only to state the intervention is cost-saving. Rather it would be justified also to point at the uncertainty surrounding the incremental costs and effects presenting the confidence intervals for these outcomes.

Furthermore, scenario or univariable sensitivity analyses could be performed on modelling parameters that contribute most to the ICER of the intervention, such as the price of a pharmaceutical product. Also for *methodological uncertainty*, arising for instance from the applied discount rate or the extrapolation method used in models, scenario analyses should be used. Scenario analysis can also be applied if more than one data source is considered to be appropriate for a specific input variable (e.g. the relative treatment effect or impact on HRQoL). This is comparable to one-way sensitivity analysis, where only one parameter is changed (e.g. the discount rate or the assumed effectiveness in the extended time period).

For each scenario a probabilistic sensitivity analysis can be easily performed and hence results can be presented with their 95% confidence interval. Values and distributions of other parameters can be kept as in the reference case analysis for these scenarios. There is no need to present all possible combinations of all scenarios. Hence, if one scenario changes the discount rates and another scenario changes the price of the product, it is not necessary to present a scenario where both the price and the discount rates have been changed compared to the reference case.

The applicant is free to present additional univariable sensitivity or scenario analyses if these are deemed relevant. If deemed relevant, other analysis such as threshold analysis (i.e. determining the value of a variable above or below which the results and/or conclusions of an analysis are likely to change), the incremental net monetary benefit (INMB) or the expected value of perfect or partially perfect information (EVPI or EVPPI) may also be provided.[62] [zzz] The latter might provide suggestions to how decision uncertainty may be reduced, for example through further data collection to improve the precision of parameter estimates or plausibility of model assumptions.[15] Appropriate justification of the additional analyses should be provided.

Finally, in general, shortcomings in the available data and assumptions should be highlighted and discussed. Being aware that a model is an imperfect representation of reality, researchers should be forthcoming in highlighting issues that contribute to uncertainty.[15]

5.16 Guideline 16: Reporting

- **Reporting should be sufficiently transparent so that it allows a critical evaluation of the economic evaluation.**
- **An overview of all input variables should be provided, including: a description of the variable, the mean value, the uncertainty (e.g. 95% CI), the applied probability distribution (if relevant), and the underlying source. Assumptions should also be clearly indicated.**
- **For the presentation of the results of an economic evaluation, uncertainty around the incremental costs, incremental effects and ICERs should be provided by means of confidence intervals. A cost-effectiveness plane and cost-effectiveness acceptability curve should be presented. The most important contributors to the uncertainty of the estimated incremental cost-effectiveness/cost-utility ratio should be shown (e.g. on a tornado diagram).**
- **Belgium does not apply a fixed threshold value for the incremental cost-effectiveness ratio. Referring to (indexed) threshold values applied in other countries or based on previous decisions should be avoided.**
- **Presenting results on the cost-effectiveness acceptability curve (CEAC) facilitates the interpretation of outcomes of economic evaluations by allowing the reader/stakeholder**

[zzz] We refer to the Dutch[63] and ISPOR guidelines[64-66] for more information on Value of Information analyses.

to apply different ICER thresholds and showing the impact on the intervention's probability that it can be considered cost-effective.

- **While consideration of the cost-effectiveness of an intervention is necessary, it is not the sole basis for decision-making.**

The reporting should be sufficiently transparent so that it allows critical evaluation of all aspects (the applied methodology, modelled values of input variables, results and conclusions, etc.). For this purpose, the report should be well structured with information on all elements described in this guideline. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) can be used to support this reporting.[67] [aaaa] The CHEERS statement is primarily intended for researchers reporting economic evaluations for peer-reviewed journals. In an HTA report, there is more space than in a traditional journal article allowing to provide more details. We refer to Appendix 9 for an example of the structure of an economic evaluation as part of an HTA report. Nevertheless, in general, we stress that critically assessing an economic evaluation involves more than checking whether everything was reported transparently.

5.16.1 Reporting data

All parameters used in calculating the effectiveness and cost-effectiveness of an intervention compared with a comparator should be described. It is recommended that, in addition to a general description of all input variables, a summary table is included (see Table 4 in part 5.14.3) presenting each variable's value (with a focus on the mean), the uncertainty (e.g. the 95% CI) the probability distribution applied (and its parameters) for variables included in a probabilistic sensitivity analysis (PSA), and the underlying source. If there is no evidence (i.e. no supporting data) for a specific input variable, it should be clearly noted that an assumption is made.

5.16.2 Reporting results

Results should be presented transparently, both aggregated and disaggregated. This means that results for both the intervention and the comparator(s) are initially presented separately. If QALYs are presented, results without adjustment for QoL should also be presented as LYs (see part 5.7). In addition to the ICER(s), incremental costs and effects are also presented separately. It is recommended to present the uncertainty around these results by means of confidence intervals. Results should be presented in tabular format (see Table 5).

Table 5 – Presentation of the results of an economic evaluation: template

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

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

It is recommended to present the results graphically on the cost-effectiveness plane. If simulations are spread over different quadrants of the cost-effectiveness plane, the percentage of simulations in each quadrant should be reported. In addition, results should also be presented on the cost-effectiveness

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[aaaa] https://www.equator-network.org/reporting-guidelines/cheers/.

acceptability curve to show the probability that the treatment is cost-effective, given varying theoretical threshold values for the cost-effectiveness ratio (see part 5.16.3). The main determinants contributing to the uncertainty of the estimated cost-effectiveness should be presented (e.g. in a tornado diagram). Uncertainty around the incremental costs (IC), incremental effects (IE) and ICERs in scenario analyses can be presented in an analogous table format as the reference case.

5.16.3 The ICER threshold

Belgium does not use an explicit discrete threshold value for incremental cost-effectiveness ratios below which an intervention is considered worthwhile and above which it is not.[68, 69] Referring to such thresholds from other countries or international organizations should be avoided, such thresholds should not be adjusted to the Belgian context or indexed for inflation. A cost-effectiveness threshold – if we assume that it exists and that we can determine this threshold – is very context dependent. It depends, for instance, on the available health care budget and the interventions already financed in a country. Therefore, it does not make sense to refer to a previously stated threshold or a threshold from another country in a Belgian economic evaluation. Comparisons with other currently (non-)reimbursed interventions are difficult to interpret, since it is not clear whether economic or other arguments have been considered or played a decisive role.

The economic consideration in the form of an intervention's cost-effectiveness tries to support the balance between the quality of the health care system, accessibility and financial sustainability. It is not sustainable to systematically use very high ICER threshold values if this creates chronic deficits in the budget and/or if more efficient interventions are replaced as a consequence. The budget constraint affects the optimal cost-effectiveness threshold. In that respect, it is more about what we can pay for within our budgets (ability to pay) rather than what we want to pay (willingness to pay).[70]

Not having an explicit ICER threshold does not mean that the results of economic evaluation are not useful. This would also be unethical as spending resources on one health programme reduces the resources available for others.[69] Striving for efficient use of resources is necessary to create as much health for society as possible with the available resources. Systematically applying too high (implicit) ICER thresholds leads to additional pressure on healthcare budgets and/or not funding other interventions that are more cost-effective, resulting in suboptimal use of available resources.[bbbb]

To allow policymakers to take cost-effectiveness into account without imposing an explicit ICER threshold, it is recommended that the reference case presents the results on the so-called cost-effectiveness acceptability curve (i.e. expressing the probability of the cost-effectiveness of an intervention as a function of varying ICER thresholds – see Appendix 6.1). The implicit threshold that policymakers use might be influenced by other factors, such as whether there is a high unmet need or severity of the disease, the strength of the evidence for both safety, effectiveness and cost-effectiveness, equity considerations, the pressure on healthcare budgets, etc. While consideration of the cost-effectiveness of an intervention is necessary, it is clearly not the sole basis for decision-making.[20]

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bbbb We refer to the publications of Culyer[71, 72] for more information about the ICER threshold, the budget dependence of this threshold, the impact of setting ICER threshold too high or too low, etc. (http://www.york.ac.uk/media/che/documents/papers/researchpapers/CHERP121_Cost-Effectiveness_thresholds_Health_Care.pdf).

6 GUIDELINES FOR BUDGET IMPACT ANALYSES

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

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

- **Guideline 3 (Perspective of the evaluation),**
- **Guideline 9 (Calculation of costs),**
- **Guideline 14 (Modelling),**
- **Guideline 15 (Handling uncertainty).**

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

Target population: Besides the recommendations stated in guideline 4 for economic evaluations, budget impact analyses should estimate the potential size of the population targeted and its potential evolution over time (e.g. shifts in incidence, prevalence, disease severity). The methods used to estimate the population size should be described and justified. The degree of penetration of the intervention in the targeted population (e.g. detection rate, compliance, market share, etc.) needs to be considered and justified.

Comparator: The BIA calculates the predicted financial impact of introducing an intervention compared to the current situation. It is not only relevant to calculate the budget impact for the intervention under consideration given the current situation, but also compared to a more cost-effective alternative (based on the results of the economic evaluation).

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

Confidential price discounts: The presence of confidential price discounts is a special point of attention. In this case, in line with the recommendations for economic evaluations, the certainty of a managed entry agreement (with confidential price discounts) should be taken into account. Scenario analyses should be developed for budget impact analyses where different price discounts are applied for the comparator(s) and/or follow-up treatments in which different price discounts are applied.

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

Discount rate: Future costs and savings should not be discounted in a BIA.

Uncertainty: Similar approach as for economic evaluations. For crucial variables for which there is often no evidence (e.g. market share), it is recommended to perform a deterministic analysis, including best- and worst-case scenarios.

Reporting: The budget impact should be presented at different levels: 1) the intervention; 2) impact on other initial expenditures; 3) other elements within the healthcare payer's perspective; 4) possibility to include elements outside the healthcare payer's perspective.

6.1 Similarities and differences between economic evaluations and budget impact analyses

Economic evaluations assess the value for money of an intervention. In contrast, budget impact analyses (BIA) help to determine if we can afford a specific intervention, i.e. do we have the budgets to implement and/or reimburse the intervention. Table 6 provides an overview of similarities and differences between guidelines for economic evaluations and BIA. More details on similarities are provided in the previous sections. In the BIA guidelines we focus mainly on the differences.

Table 6 – Similarities and differences between economic evaluations and budget impact analyses

	CEA	BIA
Research question	Acceptability (value for money)	Affordability
Perspective	Health care payers	
Target population	Consistent with reimbursement request	
	Closed *	Open
Comparator	On the efficiency frontier	Current situation
Costs	Direct healthcare related costs	
	No transfers	Transfers
Health outcomes	Included	Not included **
Time horizon	As long as incremental costs or outcomes are generated	Up to steady state
Discount rate	Costs: 3%, effects: 1.5%	No discounting
Modelling	Decision tree, Markov model…	
Handling uncertainty	Probabilistic and one- or multi-way probabilistic sensitivity analyses, scenario and subgroup analyses	
		Deterministic analysis, including best- and worst-case scenarios, for crucial variables without supporting evidence (e.g. market share)
Presenting results	Incremental cost, incremental effect, ICER, cost-effectiveness plane, CEAC, results of the sensitivity analyses	Yearly budget impact, disaggregated impact, results of the sensitivity analyses

CEAC: cost-effectiveness acceptability curve; ICER: incremental cost-effectiveness ratio.
** In most cases, the population in economic evaluations is closed. However, there are examples where this is not the case. For example, were there are contagion effects.*
*** Health outcomes as such are not included in the BIA. Nevertheless, the cost consequences of health outcomes (e.g. treatment cost of adverse events) are included in both the economic evaluations and BIA.*

The similarities in Table 6 show that BIA can partly rely on the economic evaluation. Where an economic evaluation has been performed, a lot of information is often already available: the cost of the initial treatment, the costs of avoided re-interventions, adverse event costs, exclusion of protocol-driven costs, adjustments to conduct the analysis for the real-world target population, etc. Differences should however not be neglected and several adaptations may be required to make the data from the economic evaluation useful for the BIA, such as accounting for the open population and time-dependencies required for a BIA.[7, 73] While the BIA can be performed separately, integration of the two analyses may avoid duplication of effort.[74]

6.2 Guideline 17: Perspective

As for economic evaluations, BIA should be carried out from the healthcare payers' perspective (see 5.3). Other alternatives are also possible, such as the hospital, patient or societal perspective. Nevertheless, in the context of reimbursement, the BIA calculates the impact of a policy decision on the healthcare budget. As a result, the main target of such analysis remains the healthcare payers, being government and patients. Complementary analysis from other perspectives should be separated from the reference case and justified.

6.3 Guideline 18: Target population

As for economic evaluations, the target population should be consistent with the population defined in the reimbursement request (see 5.4). Subgroup analysis can be performed if there is an appropriate justification. As for the economic evaluation guidelines this can be due to differences in safety, treatment effect, baseline risks, or costs, which will result in different ICERs.

Furthermore, BIA entails some specific considerations:

- In BIA, information about the anticipated size of the target population is needed.[6] This *potential population size* should be specified and the estimation method described and justified.[75] It is recommended to use Belgian epidemiological data. "*Some of the epidemiological data may be reported as part of clinical trials. However, these data will often be informed by local data on disease incidence and prevalence, service utilisation figures, and expert opinion. As these data are not typically derived from systematic review, care must be taken to adequately address potential bias in the data. … It is also critical to adequately account for the uncertainty or lack of precision in the estimates, and to consider data quality.*"[6] If it is not possible to accurately estimate the population size, then it is advised to perform the BIA for a number of patients that is easy to extrapolate (e.g. 100 patients). Applying this option should be justified.
- Attention should be paid to the evolution of the size of the target population over time with and without the new technology.[7, 73] In this context, it is important to consider *shifts in incidence and prevalence*. For example, if the extension of survival is expected, it is necessary to consider the increase in prevalence of a given illness.[76]
- *Shifts in disease severity* should be considered. For example, a screening program may detect more patients with a specific disease and may create a shift in identifying the disease at an earlier stage compared to the situation without screening.

- The *degree of implementation* needs to be considered (e.g. detection rate, the population percentage expected to use the technology,[75] compliance, the market share…). Justification for the estimates should be provided with a preference for evidence-based estimates.[cccc] The *market share* refers to two concepts. Firstly, there is the market share that indicates the extent to which a new intervention may replace an existing alternative. For example, the introduction of a new device may replace existing treatments. This type of market share should be included in the BIA. One of the main factors that should be considered in this case is the substitution of other interventions with the new alternative.[76] Secondly, the market share can also indicate which part of the market different competitors of a specific intervention will take. For example, if a certain intervention is reimbursed, how much of the market will be taken by company A, B, C and others that bring such a product to the market? The BIA should in the first place calculate the impact of reimbursing the intervention, and not just the companies' own product. Such additional information may be provided in a separate analysis, especially if the competitors' price is different.
- If several relevant *subpopulations* are distinguished, both subpopulation-specific BIA and aggregated BIA for the general target population should be performed and reported.[76] This is especially relevant if the economic evaluation points at differences in cost-effectiveness of applying the intervention in specific subpopulations.
- The budget impact should be calculated for *both the indication under discussion in the reimbursement request*, as well as *all indications of the intervention*. This should avoid *'salami slicing'* to minimize the potential budget impact of a specific intervention. For example, a pharmaceutical product may be evaluated for the treatment of an orphan disease but also be used for a more common disease(s). This should be explicitly stated and the budget impact should be presented separately for the indication(s) under consideration and those for which there is already reimbursement.[dddd]
- *Off-label use* is a complex issue. Several types of off-label use should be distinguished. Firstly, off-label use may be observed without any hard underlying evidence. This aspect of the BIA may especially be of importance in a reimbursement revision or to demonstrate the importance of introducing preventive measures.[76] Secondly, there is off-label use because certain interventions are included in clinical practice guidelines while being off-label (e.g. use in paediatrics because the pharmaceutical product is only licensed for adults). Lastly, it may be the case that the company does not apply for marketing authorisations for a specific indication,[77] or similarly, does not apply for an alternative treatment schedule if more profitable alternatives are at their disposal. If there is evidence that these alternatives are effective and possibly more cost-effective, then the BIA should take these alternatives into account. This might support conditions for reimbursement or justify the initiation of further research.

As for all input variables, sources should be clearly described and uncertainty should be reflected in sensitivity analyses.

[cccc] Evidence-based estimates of, for example, market penetration or market share can be based on the use of the intervention in similar indications and/or on international experience. Unfortunately, such information is often not easily transferable to the Belgian target population, in which case expert opinion is often used. In such cases, the methods used to collect this information should be reported and the uncertainty surrounding this information should be appropriately addressed through sensitivity analyses (avoiding the use of too narrow confidence intervals) (see part 6.9).

[dddd] The more detailed budget impact guidelines apply to the indication under consideration. For the other indication(s), the realised budget impact from previous years can be presented.

6.4 Guideline 19: Comparators

The BIA calculates the predicted financial impact of introducing an intervention compared to the current situation. The intervention in the BIA is the same as in the economic evaluation, but the comparator may be different since cost-effectiveness is calculated on the efficiency frontier (see 5.6 and Appendix 6.2).

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

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

Several BIAs should be performed for all relevant treatment alternatives (i.e. for those on the efficiency frontier). As such, it is not only relevant to calculate the budget impact for the intervention under consideration given the current standard of care, but also compared to (a) more cost-effective alternative(s) (i.e. based on the results of the economic evaluation performed).

6.5 Guideline 20: Costs and outcomes

It is obvious that the cost of the intervention under consideration should be included in the BIA. It should be specified if the new intervention seems to replace or if it is used in addition to currently used alternatives. This should be justified and the budget impact of abandoning these alternatives should also be included.[75, 76]

The inclusion of particular cost items is directly related to the chosen perspective. Similar to the guidelines for economic evaluations, direct healthcare related costs are included in the reference case. The impact on productivity and other items outside the healthcare system costs should not routinely be included in a BIA as these are not generally relevant to the budget holder.[7, 73] Nevertheless, significant direct non-healthcare related costs (e.g. transport) or indirect non-healthcare related costs (e.g. productivity costs or costs for unpaid caregivers) could be included in BIA, provided that the relevance of these costs is considered.[76] This should be performed as a complementary analysis, clearly separated from the reference case analysis. In line with the guidelines for economic evaluations, the friction cost method should be applied in the case of long-term absence from work (see part 5.9.3.9).

The cost consequences of the treatment effect, side effects and other short and long term consequences (e.g. follow-up treatment) should be included in the BIA since they will have an impact on the healthcare budget. The data source for estimating the treatment effect should be based on studies with the appropriate design (i.e. preferably RCTs). If information from the underlying studies is insufficient for determining the impact of e.g. side effects on the healthcare budget, this should be noted in the analysis.[76]

Protocol-driven costs should be excluded from the analysis.[76]

The input variables for the BIA should be presented transparently. The level of detail should be such that the reader could duplicate all the calculations in the model.[73] An overview of these input variables should be provided in a table (containing at least the name of variables, mean cost, uncertainty, source). Assumptions should be explicitly noted. It is recommended to present the measurement of resource use or volumes and the valuation or unit costs separately.

The valuation of cost items is related to the perspective of the BIA (see part 6.2). Researchers should strive to use Belgian real-world expenditures. Further details on cost calculations and an overview of databases are given in part 5.9 and Appendix 2. Similar to economic evaluations, the focus in BIA is also on the mean value. Cost distributions are often skewed, typically with outliers with higher costs resulting in a higher average than the median. Multiplying the average costs by a volume estimate will

lead to a better estimate of the total budget impact, while applying the median of a right-skewed distribution (i.e. with a long tail on the right side of the distribution) will underestimate total costs.

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

The BIA should also include (or at least discuss) the costs related to possible requirements to introduce the intervention under consideration. This may involve the need to train the personnel or the use of existing specific diagnostics, care facilities or infrastructure.[75, 76, 78] Discussion of preconditions or the effective introduction of the intervention should focus on those conditions that are necessary for the effective, cost-effective, and socially accepted use of the new healthcare intervention. Financial needs for establishing these preconditions should be summarised.[78]

It is recommended to calculate both the global budget impact and consequences for the different health care payers. Transfers of budgets between different governments and/or patients are not considered in economic evaluations since they are not an incremental cost to the healthcare payer. In general, in an economic evaluation, it is not clear who bears the cost. In the BIA, the total budget impact is calculated in the first place. Nevertheless, introducing an intervention may have a different impact on the funds at different levels: federal, communities, regions, municipalities or other parties. Savings for one party may result in expenditures for another. For example, savings for the federal government from accelerated rehabilitation and possible shorter hospital stays may increase expenditures for communities due to increasing use of home care for patients that are sent home.[79] Another example is the shift in expenditures when starting preventive campaigns, at the expense of communities, while this possibly creates savings at the federal level.

Finally, the issue related to the presence of managed entry agreements and potential price discounts should also be taken into account in the BIA. Similarly for economic evaluations, the presence of a managed entry agreements should be checked first for comparators and follow-up treatments (see part 5.9.3.3). If there is certainty regarding a managed entry agreement, then the uncertain price discount should be reflected in scenario analyses performed under the reference case.

6.6 Guideline 21: Time horizon

The time horizon of the BIA depends on the time needed to reach a steady state. This is the case, for example, when an intervention is gradually introduced to the market where it takes several years before the entire target population is reached. In this case, we recommend to put the focus on the BIA that takes into account the expected stabilised number of patients. Another example occurs when an implant device needs a replacement after a certain time period. In this case, after a couple of years, there is the budget impact of new patients in the target population receiving the implant but also of patients treated in the past who receive a device replacement. Also re-interventions or adverse events may have an additional impact on budgets several years later. In such cases, only considering the earlier years might result in an underestimation of the actual budget impact. Therefore, the analyst should calculate the yearly country-specific budget impact up to this steady state. The ISPOR guidelines state that "*BIAs should be presented for the time horizons of relevance to the budget holder, in accordance with their budgeting process and periods (e.g., monthly, quarterly, and annual). A time horizon of 1 to 5 years is common, with the results presented for each budget period after the new intervention is covered. The framework should also allow for other time horizons. Although time horizons that go beyond a few years require considerable assumptions, they may be needed to illustrate the offsetting disease cost savings from the intervention that may occur in future years.*"[7]

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

It is clear that the budget impact in the long term may be a multiple amount of the budget impact in the short term. The population examined in the BIA is open, which means that particular patients enter or leave the population when they meet or fail to meet the defined inclusion criteria at a given moment.[75] This contrasts to the clinical efficacy/effectiveness and the economic analysis, where the examined population usually is closed (a cohort of patients is defined at the start and all the included patients remain in the examined population within a given time horizon).[75]

In general, for policy makers, it is not only important to know if we can afford to fund an intervention given the current budgets, but also to know what the long term budget impact may be. Therefore, an assessment of the budget impact of a given intervention should be performed over a time period that is sufficient to reach a steady state impact on the general annual health care budget. Many factors, such as the diffusion rate, type of treatment and disease survival, long-term events, evolution of target population, etc. may thus have an impact on the appropriate time horizon for the BIA.

6.7 Guideline 22: Discount rate

The BIA provides an estimate of financial means over time. Discounting is performed to reflect time preferences. However, the BIA calculates the (yearly) budget impact of introducing an intervention, without presenting the current value of these financial streams. Therefore, in agreement with other guidelines,[6, 7, 75] the Belgian guidelines recommend not to discount costs in the BIA.

6.8 Guideline 23: Modelling

Similar to economic evaluations, modelling may be needed to calculate the budget impact for several reasons: conducting the analysis for the real-world target population, account for the appropriate comparator, include real-world costs (e.g. excluding protocol-driven costs), extend the analysis to the appropriate time horizon, etc. In other words, modelling may be needed to synthesise the best available data from different sources. The applied methods and an overview of all input variables should be transparently reported. The (Excel) file with the input values and the formulas of the calculations should be made available.[eeee] For further details, we refer to part 5.14.

If an economic evaluation was performed, the BIA model should be consistent with the clinical and economic assumptions in this economic evaluation.[73] For example, assumptions on compliance should be the same in both cases. In contrast, the justified comparator in an economic evaluation (working on the efficiency frontier) may be different from the comparator in the BIA (actual financial streams compared with the current situation).

6.9 Guideline 24: Handling uncertainty

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

As in the economic evaluation guidelines, the probability of particular values for a range of input variables is accounted for through probabilistic sensitivity analysis (PSA). One- or multi-way sensitivity analysis can be performed on the most important variables such as the price of the intervention or the uptake/diffusion rate. The variability between subgroups is handled in subgroup analysis and structural or methodological uncertainty is dealt with in scenario analysis. The subgroup and scenario analyses should also be performed probabilistically. For further details, we refer to part 5.15.

[eeee] RIZIV-INAMI guidelines from the CRIDMI request attaching an Excel file with the calculations, making clear which input values were used and allows the formulas of the calculations to be checked. (https://www.riziv.fgov.be/SiteCollectionDocuments/irreq_handleiding_lijst_20231201.pdf)

In BIAs, there are a number of crucial variables for which there is often no evidence, such as the future number of patients that will be treated or the market share that a particular intervention will take.[ffff] There may be evidence based on experience with the intervention abroad or in other indications. Nevertheless, these are often assumptions. In this case, no probability distribution based on evidence can be derived. To address this in a practical manner, we recommend explicitly stating that the input for these variables are (expert-based) assumptions for which a deterministic analysis can be performed. In addition, for these variables, we recommend carrying out comprehensive deterministic sensitivity analyses (i.e. including best- and worst-case scenarios).

6.10 Guideline 25: Reporting

6.10.1 Reporting data

As in economic evaluations, all input parameters must be reported transparently in the BIA. Analogously to part 5.16.1, it is recommended that, in addition to a general description of all input variables, a summary table is included (see Table 4) presenting each variable's value (with a focus on the mean), the uncertainty (e.g. the 95% CI), the probability distribution applied (and its parameters) for variables included in a PSA, and the underlying source. If there is no evidence (i.e. no supporting data) for a specific input variable, it should be clearly noted that an assumption is made. If an economic evaluation was also carried out, we recommend consistency with the BIA. This applies both to the values of the input variables, as well as to, for example, the choice regarding the target population and subgroups (if relevant).

6.10.2 Reporting results

Presented results should be transparent, complete and understandable. In order to do so, the budget impact should be presented for each year within the relevant time horizon. This will show the evolution of expenses over time (inclusive of the steady state).

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

Results should also be disaggregated. The contribution of different components to the budget impact should be reported separately from the general budget impact: e.g. the impact of the initial intervention, replacement costs, re-hospitalisations or re-interventions, adverse events, follow-up costs, etc.

We recommend presenting the budget impact at different levels:

- The first level shows the budget impact of the intervention itself, e.g. the pharmaceutical product or surgical procedure to place an implant or invasive medical device.
- The second level displays the impact on other existing expenditures. This takes into account the other pharmaceutical products or interventions that might be replaced by the new intervention.
- The third level also takes into account the impact of other elements within the healthcare payer's perspective such as, e.g. re-hospitalisations or re-interventions, adverse events, follow-up costs, etc.

[ffff] If there is a reimbursement request for an indication for which multiple health technology developers offer a similar intervention (e.g. a specific medical device), then initially the total budget impact of all providers that might also receive reimbursement for the same indication should be calculated.

- Lastly, at the fourth level it is possible to deviate from the reference case and also reflect the budget impact of elements outside the healthcare payer's perspective, such as the impact on productivity. These costs should be taken into account in the same way as in an economic evaluation (see friction cost method in part 5.9.3.9).

For interventions that do not fall into the category of pharmaceutical products or implants and invasive medical devices, a similar multi-level approach can be used.

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

- Outcomes can be presented separately for the different healthcare payers. A distinction is not only possible between government and patients,[gggg] but also between e.g. the federal government and the communities.
- Outcomes can be presented in natural (e.g. number of unpaid working days) and monetary units.[73, 76]
- Impact on the pharmaceutical budget, the budget of implants and invasive medical devices or other budgets must be presented separately.

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

[gggg] This also includes transfer payments in case of e.g. unemployment benefits, sickness or disability allowances. While these transfers are excluded from an economic evaluation (see part 5.9.3.11) they might be relevant in a BIA.

7 DISCUSSION

This guideline creates a common framework with general guidelines for conducting economic evaluations and BIA for a wide range of interventions. This scope implies that not all specific aspects that might be relevant for particular interventions are elaborated in this guideline.[hhhh] This guideline can thus be complemented with information from other guidelines, some of which we refer to in Appendix 10.

A wide range of stakeholders were given the opportunity to submit comments and suggestions on the previous guidelines, as well as a first draft version of the new guidelines. This involved open discussions at several stakeholder meetings around a number of key elements, including the inclusion of evidence-based off-label use as a relevant comparator, the consideration of confidential price discounts on comparators and/or follow-up treatments, etc. In the guidelines, we aimed to clearly formulate and justify the choices made to support policy-relevant evaluations.

Stakeholders also requested additional recommendations related to e.g. what to do when no RCT data is available, information on important outcomes is missing, data is immature, etc. These important questions primarily relate to the estimation of relative and absolute treatment effects, which is essential for any economic evaluation. For these aspects, we refer to the guidance documents developed and approved under the HTA Regulation. The documents describe a scientifically neutral way of representing the (reliability of the) evidence about the relative treatment effect and the uncertainty surrounding it. However, no value judgement is made, which is part of an appraisal at national level. This is also the case for these guidelines for economic evaluations and BIA. For example, the potential problems in using RWD to estimate the relative treatment effect are pointed out, but the potential use of RWD is also highlighted. It is not possible to describe in this guideline all situations where certain (suboptimal) approaches are or should not be allowed. The final appraisal is ultimately something that has to be done case-by-case in every reimbursement request.

We recognize that guidelines need to be updated from time to time. Wherever possible, we have used publicly available sources where users can access the most up-to-date information. We will also keep an eye on other future developments, such as the possible integration of environmental considerations into HTA. Where elements are not addressed in this guideline, which will be the case given the scope and number of possible situations, we generally recommend transparent justification of the choices made and reference to reliable sources. With these guidelines, we try to support those who set up study protocols, perform economic evaluations and BIAs, and those who evaluate these analyses as much as possible.

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hhhh Elements beyond the scope of this guideline are e.g. about which statistical tests should be performed when evaluating the impact on primary and secondary endpoints in a clinical trial, evaluating the validity of clinical study results, recommendations on how to perform a cost analysis or activity-based costing, more specific guidelines on static or dynamic modelling, collecting information from experts, etc.

APPENDICES

APPENDIX 1. SEARCH STRATEGY

Guidelines for economic evaluations and Budget Impact Analysis of healthcare interventions used in European countries, US, Canada, Australia and New Zealand, were searched in July 2024.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has a webpage presenting pharmacoeconomic guidelines around the world: https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines. Our search strategy started with identifying relevant reports on this webpage. The websites of the HTA institutes publishing these guidelines were checked to see whether there were any updates available. Only reports published since 2012, i.e. the year of the previous version of the Belgian guidelines, were retained. A language restriction only including reports available in English, Dutch and French was applied.

The following guidelines were identified:

- Academy of Managed Care Pharmacy (AMCP – US). Guidance on Submission of Pre-approval and Post-approval Clinical and Economic Information and Evidence. AMCP Format for Formulary Submissions 5.0. Journal of Managed Care + Specialty Pharmacy (JMCP). Volume 30 Number 4-b. April 2024. 64 pages.[19]
- Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH. March 2017. 76 pages.[18]
- Haute Autorité de santé (HAS – France). Choices in Methods for Economic Evaluation – a methodological guide. October 2012. 55 pages.[25]
- Haute Autorité de santé (HAS – France). Choix méthodologiques pour l'analyse de l'impact budgétaire à la HAS – guide méthodologique. November 2016. 102 pages.[80]
- Pharmaceuticals Pricing Board (HILA – Finland). Application instructions health economic evaluation. 19 June 2024. 15 pages.[37]
- Health Information and Quality Authority (HIQA – Ireland). Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. 2018. 50 pages.[6]
- Health Information and Quality Authority (HIQA – Ireland). Draft National Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. 21 October 2024. 61 pages.[81]
    - Remark: the final HIQA guidelines have been published after the Belgian guidelines were validated and finalised: Health Information and Quality Authority (HIQA – Ireland). National Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. 26 March 2025. 62 pages.[82]
- Health Information and Quality Authority (HIQA – Ireland). Guidelines for the Economic Evaluation of Health Technologies in Ireland. 2020. 109 pages.[83]
- Health Information and Quality Authority (HIQA – Ireland). Draft National Guidelines for the Economic Evaluation of Health Technologies in Ireland. 21 October 2024. 98 pages.[20]
    - Remark: the final HIQA guidelines have been published after the Belgian guidelines were validated and finalised: Health Information and Quality Authority (HIQA – Ireland). National Guidelines for the Economic Evaluation of Health Technologies in Ireland. 26 March 2025. 103 pages.[84]
- Health Improvement Scotland (HIS). Guidance to submitting companies for completion of New Product Assessment Form (NPAF). April 2022. 72 pages.[27]

- Institute for Quality and Efficiency in Health Care (IQWiG – Germany). General Methods – Version 6.1 of 24 January 2022. 282 pages.[85]
- National Centre for Pharmacoeconomics (NCPE – Ireland). Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluations. Version 3.2. 17 May 2023. 16 pages.[38]
- Nationale Institute for Health and Care Excellence (NICE – UK). NICE health technology evaluations: the manual. NICE process and methods [PMG36]. 31 October 2023. 200 pages.[17]
- Norwegian Medicines Agency (NoMA). Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. 20 May 2020. 64 pages.[86]
- Pharmaceutical Benefits Advisory Committee (PBAC – Australia). Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (Version 5.0). September 2016. 216 pages.[87]
- Pharmaceutical Management Agency (PHARMAC – New Zealand). Prescription for pharmacoeconomic analysis – methods for cost-utility analysis. Version 2.2. 2015. 72 pages.[88]
- Zorginstituut Nederland (ZIN – the Netherlands). Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Herziene versie 2024. 42 pages.[16]
- Zorginstituut Nederland (ZIN – the Netherlands). Kostenhandleiding voor economische evaluaties in de gezondheidszorg: methodologie en referentieprijzen. Herziene versie 2024. 81 pages.[36]
- Zorginstituut Nederland (ZIN – the Netherlands). QALY en kwaliteit-van-leven-metingen. Verdiepingsmodule. Herziene versie 2024. 19 pages.[14]

In addition, the following guidelines set up within the EUnetHTA collaboration were also retained:

- European Network for Health Technology Assessment (EUnetHTA). Methods for health economic evaluations – a guideline based on current practices in Europe. May 2015. 100 pages.[89]
- European Network for Health Technology Assessment (EUnetHTA). Endpoints used for Relative Effectiveness Assessment: Health-Related Quality of Life and Utility Measures – guideline. Adapted version 2015. 53 pages.[33]
- European Network for Health Technology Assessment (EUnetHTA) JA3WP6B2-5 Authoring Team (Neyt M, Eriksson M, Garcia-Perez L, Johansson P, Midy F, Teljeur C). Practical considerations when critically assessing economic evaluations – Guidance document. March 2020. 154 pages.[15]

For BIA, the ISPOR report on good research practices for BIA was also selected:

- Sullivan SD, Mauskopf JA, Augustovski F, et al. Principles of good practice for budget impact analysis II: report of the ISPOR Task Force on Good Research Practices – Budget Impact Analysis. Value Health. 2014;17(1):5-14.[7]

APPENDIX 2. LIST OF BELGIAN DATABASES FOR THE MEASUREMENT AND VALUATION OF RESOURCE USE

Table 7 gives an overview of the national databases that can be used to measure and value resource use and the extent to which KCE, RIZIV–INAMI and distributors have access to those data.

We also refer to the Belgian Health Data Agency (HDA, https://www.hda.belgium.be/en), which "*in collaboration with regional and federal data holders and users, will facilitate access to quality health (care) data and data related to health (care) in a simplified and more uniform, reliable, transparent and secure manner, through the development of a framework in which the re-use (secondary use) of quality health (care) data and data related to health (care) is optimally facilitated. Within the framework of the tasks described in the law, the HDA supports the re-use of health and health-related data for population management, health prevention and healthcare policy, through research and innovation based on health needs and the active role of citizens, thereby contributing to better health and quality of life.*"(https://www.hda.belgium.be/en/about_us)

Table 7 – Belgian national databases for the measurement and valuation of resource use and access to these databases

Database	Description (owner)	Input parameters that can be obtained from the database	Access by KCE	Access by RIZIV–INAMI	Access by distributors	Access by universities
Doc. N	Health care interventions and lump sums reimbursement (RIZIV–INAMI)	Volume and amounts reimbursed for health care interventions (by age, sex and district)	Yes, regular RIZIV–INAMI transmission (aggregated by code[iiii])	Yes	Yes, upon request	Yes, upon request
Doc. P	Health care interventions and lump sums reimbursement by providers (RIZIV–INAMI)	Volume and amounts reimbursed for health care interventions, patient ambulatory follow-up possible for RIZIV–INAMI	Yes, aggregated (not at patient level)	Yes (at patient level)	Yes, upon request, with limitations	Yes, upon request
Doc. PH	Pharmaceutical products reimbursement delivered in hospital pharmacies (RIZIV–INAMI)	Volume and amounts reimbursed of pharmaceutical products delivered in hospitals	Yes, upon request	Yes	Yes, upon request, with limitations	Yes, upon request
Farmanet – Pharmanet	Pharmaceutical products reimbursement delivered in public pharmacies (RIZIV–INAMI)	Volume and amounts of pharmaceutical products reimbursed delivered in the community	Yes, upon request	Yes	Yes, upon request, with limitations	Yes, upon request
AZV–SHA/ ADH–HJA	Hospital billing data (RIZIV–INAMI)	Volume and amounts reimbursed of health care provisions in hospitals	See TCT	Yes	No	Yes, upon request
MZG–RHM	Hospital discharge data (FPS Public Health)	When specific ICD code(s) available: volume, co-morbidities, risk of adverse events (readmissions), patient characteristics, length of stay	Yes, upon request	Yes, upon request	Yes, upon request	Yes, upon request
TCT Data	Linked and validated individual data of the Hospital clinical data MZG–RHM) of the FPS Public	When specific ICD or billing code(s) available: volume, cost of hospitalisation and follow-up (readmissions), and risk and cost of adverse events (readmissions)	Yes, under conditions	Yes, under conditions	Yes, upon request	Yes, upon request

[iiii] Detailed by age and sex upon request.

	Health and on the billing data of the RIZIV–INAMI. (MZG–RHM + AZV–SHA / ADH–HJA)					
Financial Feedback per pathology	Feedback of hospital reimbursements and length of stay, aggregated by MDC, APR-DRG and SOI, based on the TCT data (TCT).	When specific APR-DRG(s) available: volume and cost of hospitalisation (broken down by pharmaceutical products, medical fees, etc.)	Yes	Yes	Yes	Yes
IMA–AIM Database	Individual data on health care reimbursements and patients' share for all insured patients, ambulatory and hospital settings (IMA–AIM)	When specific billing code(s) available: volume, cost of hospitalisation and follow-up (hospital or ambulatory), and risk and cost of adverse events	Yes, Through a cooperation model	Yes, under conditions	No	Yes, upon request
EPS	Stratified sample of the IMA–AIM Database (IMA–AIM)	When specific billing code(s) available: volume, cost of hospitalisation and follow-up (hospital or ambulatory), and risk and cost of adverse events	Yes, under conditions	Yes, under conditions	No	Yes, upon request
MZG–RHM / EPS	Linkage MZG–RHM/ EPS: legal implementation ongoing	When specific ICD or billing code(s) available: volume, cost of hospitalisation and follow-up (hospital or ambulatory), and risk and cost of adverse events	Yes, under conditions?(*)	Yes, under conditions?(*)	No	Yes, under conditions?(*)

ADH–HJA: Hospital Day-care Anonymous Hospital Stays (Anonieme Dag Hospitalisaties – Hospitalisations de Jour Anonymes); APR-DRG: All Patient Refined-Diagnosis Related Group; AZV–SHA: Hospital Inpatient Anonymous Hospital Stays (Anonieme ZiekenhuisVerblijven – Séjours Hospitaliers Anonymes); EPS: Permanent Sample (Echantillon Permanent – Permanente Steekproef); FPS: Federal Public Service; ICD: International Classification of Diseases; IMA–AIM: Intermutualistisch Agentschap – Agence Intermutualiste; MDC: Major diagnostic category; MZG–RHM: Minimale Ziekenhuis Gegevens – Résumé Hospitalier Minimum; SOI: Severity of illness; TCT: Technical Cell (Technische Cell – Cellule Technique);
(*) Not published in April 2023. Source: Camberlin et al., 2023.[90]

APPENDIX 3. CHECKLISTS FOR ASSESSING ECONOMIC EVALUATIONS

There are many different economic evaluation checklists available,[91] such as, the 36-item Drummond and Jefferson checklist,[92] the Drummond Ten Point checklist,[93] the Consensus on Health Economic Criteria (CHEC)-list,[94] the Philips checklist,[95] the Quality of Health Economic Studies (QHES) checklist,[96] and the CHEERS checklist.[67] The latter guideline, which is a reporting checklist for economic evaluations rather than a quality assessment tool, was published simultaneously by many journals (https://www.equator-network.org/reporting-guidelines/cheers/) and its use has increased significantly since publication.[91]

Also NICE has an appraisal checklist to determine whether an economic evaluation provides evidence that is useful to inform the decision maker. It is available under the following link: https://www.nice.org.uk/process/pmg20/resources/appendix-h-appraisal-checklists-evidence-tables-grade-and-economic-profiles-pdf-8779777885. The items from the NICE checklist for economic evaluations are presented in Table 8 and try to determine the applicability and limitations of the study. More information related to these questions is provided in the supporting NICE document (see previous link).

It should be noted that for some questions in the available checklists, the assessor will have to make value judgements. Applying a checklist is more than just indicating whether or not specific information is reported and therefore will not preclude critical appraisal of the study quality by the researcher.

Table 8 – The NICE checklist for economic evaluations (part 1/2)

Study identification Include author, title, reference, year of publication		
Guidance topic:		**Question no:**
Checklist completed by:		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?		
1.2 Are the interventions appropriate for the review question?		
1.3 Is the system in which the study was conducted sufficiently like the current UK context?		
1.4 Is the perspective for costs appropriate for the review question?		
1.5 Is the perspective for outcomes appropriate for the review question?		
1.6 Are all future costs and outcomes discounted appropriately?		
1.7 Are quality-adjusted life years (QALYs), derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).		
1.8 **Overall judgement:** Directly applicable/partially applicable/not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		
Other comments:		



Table 8 – The NICE checklist for economic evaluations (part 2/2)

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?		
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?		
2.3 Are all important and relevant outcomes included?		
2.4 Are the estimates of baseline outcomes from the best available source?		
2.5 Are the estimates of relative intervention effects from the best available source?		
2.6 Are all important and relevant costs included?		
2.7 Are the estimates of resource use from the best available source?		
2.8 Are the unit costs of resources from the best available source?		
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?		
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?		
2.11 Has no potential financial conflict of interest been declared?		
2.12 **Overall assessment:** Minor limitations/potentially serious limitations/very serious limitations		
Other comments:		

Source: 'Appendix H: Appraisal checklists, evidence tables, GRADE and economic profiles' from the NICE manual 'Developing NICE guidelines, available from https://www.nice.org.uk/process/pmg20 (available under 'Tools and resources'). GRADE: Grading of Recommendations, Assessment, Development and Evaluation.

APPENDIX 4. DATA EXTRACTION SHEET FOR ECONOMIC EVALUATIONS

A data extraction sheet is a working document that can be used when extracting relevant information from published economic evaluations. This working document can be used to prepare overview tables for e.g. the input used in these economic evaluations. This can support the critical assessment of existing literature. An example of a data extraction sheet is given in Table 9.

Table 9 – Data extraction sheet for economic evaluations: template

Reference	
Sponsor(s) of the study (~CoI)	
Country	
Research question	
Perspective	
Population	
Intervention	
Comparator(s)	
Analytic technique	
Study Design	
Time horizon	
Discounting (Yes/No + rate)	
Cost items included (incl. currency & price year) & data sources for costs	
Outcomes parameter & data sources for outcomes	
Assumptions	
Uncertainty	
Results:	
Costs	
Outcomes	
Cost-effectiveness	
Sensitivity analyses	
Conclusions	
Remarks	E.g. limitations of the study.

CoI: conflict of interest.

APPENDIX 5. ASSESSMENT OF EXTERNAL VALIDITY

This list of issues for external validity has been derived from a paper published by Rothwell.[24]

Setting of the trial

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

Selection of patients

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

Characteristics of randomised patients

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

Differences between the trial protocol and routine practice

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

Outcome measures and follow-up

- Clinical relevance of surrogate outcomes
- Clinical relevance, validity and reproducibility of complex scales

- Effect of intervention on most relevant components of composite outcomes
- Who measured the outcome
- Use of patient-centred outcomes
- Frequency of follow-up
- Adequacy of the length of follow-up

Adverse effects of treatment

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

For more information and discussion about the definition and assessment of external validity of RCTs we refer to the article of Jung et al.[97]

APPENDIX 6. THE COST-EFFECTIVENESS PLANE, COST-EFFECTIVENESS ACCEPTABILITY CURVE, AND EFFICIENCY FRONTIER

Appendix 6.1. Cost-effectiveness plane and cost-effectiveness acceptability curve

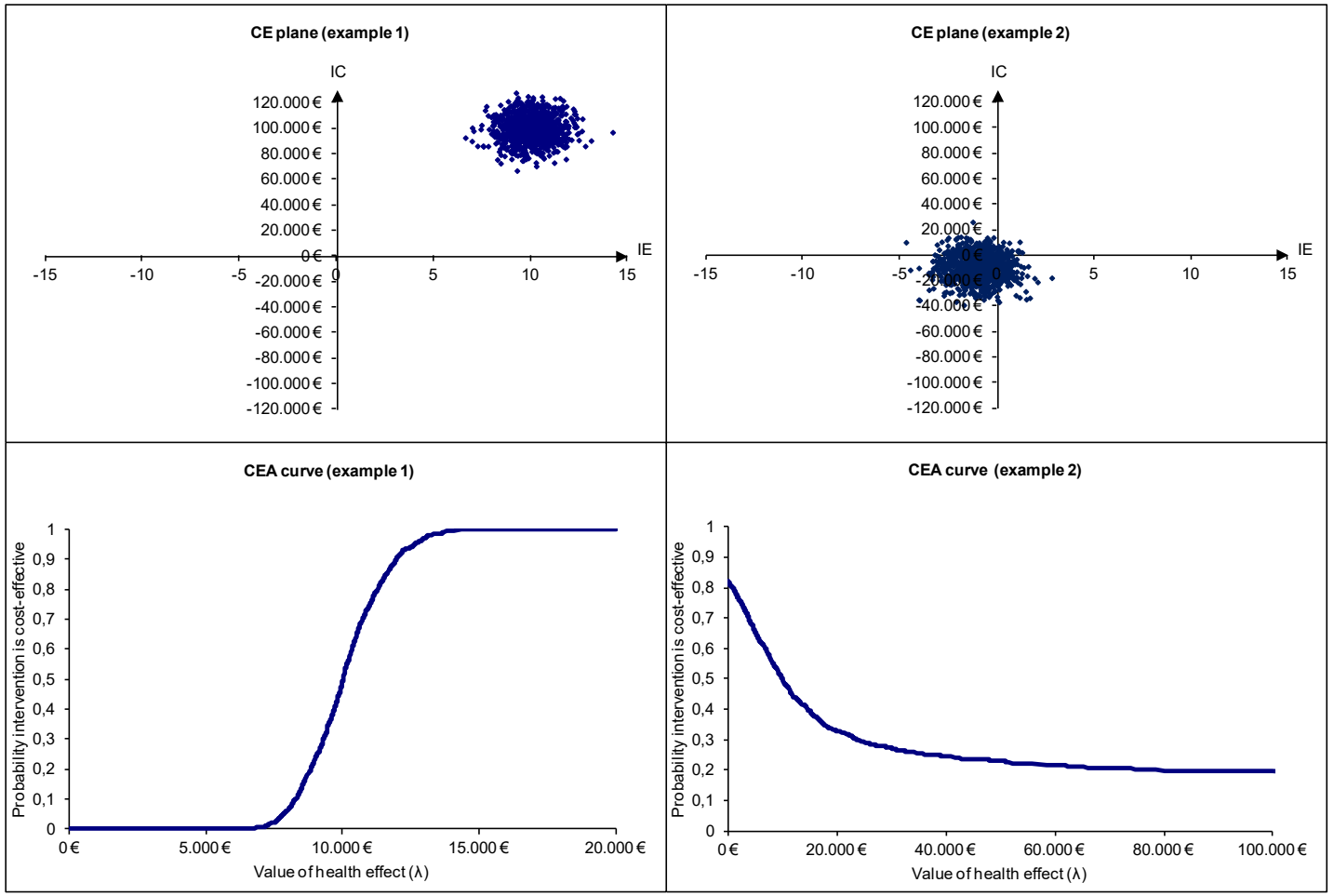
The *cost-effectiveness plane* is used to present the results of a CEA or CUA. Incremental effects (life years or quality-adjusted life years (QALYs)) are presented on the x-axis. The y-axis shows the incremental costs. The centre of the figure shows the comparator. As such, there are four quadrants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

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

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

The *cost-effectiveness acceptability curve (CEAC)* presents the probability that a given intervention is considered cost-effective on the basis of the value assigned to an additional life year or QALY. The shape of this curve depends on the location and proportion of incremental costs and effects over the four quadrants of the cost-effectiveness plane. In Figure 2, two examples are shown. For more information we refer to Fenwick et al.[98]

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



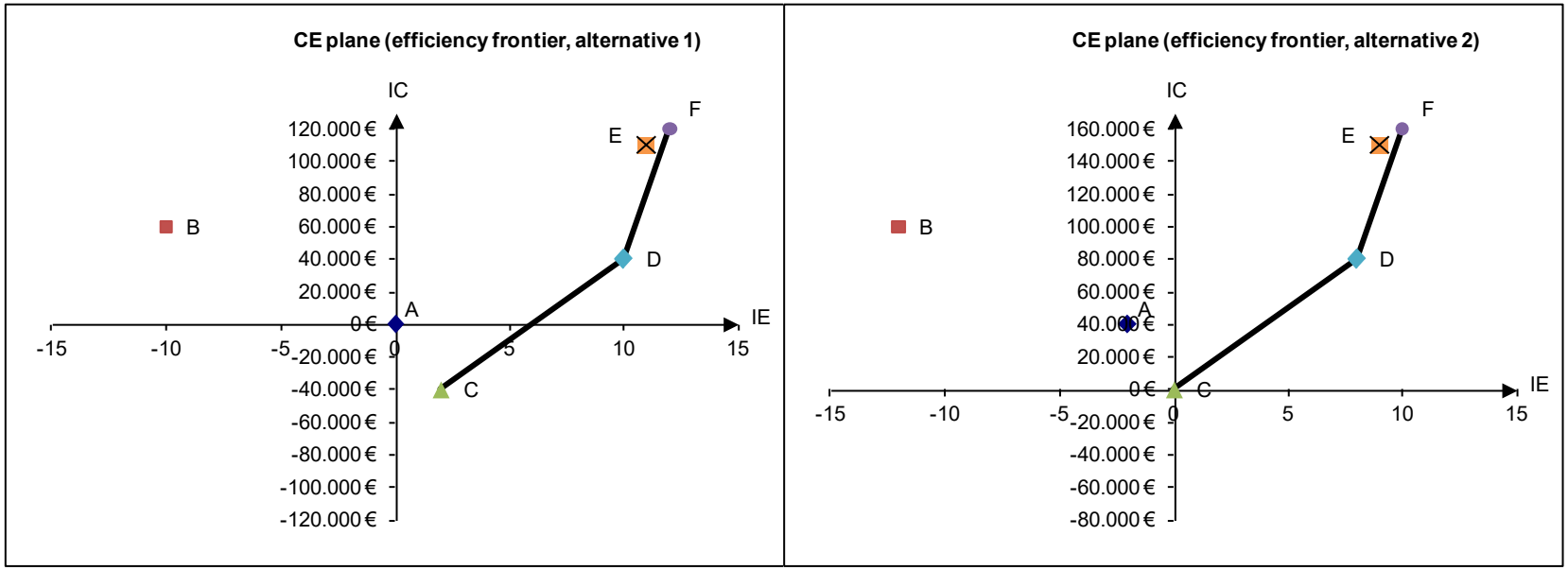
CE: cost-effectiveness; IC: incremental cost; IE: incremental effect

Appendix 6.2. Efficiency frontier

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

Figure 3 provides an example. In this example, interventions A, B, C, D, E and F are all alternative interventions for a specific population with a certain disease. Intervention B (quadrant IV) is dominated by intervention A. Intervention A is dominated by C (quadrant II). Therefore, C becomes a justified comparator for intervention D. E is excluded due to extended dominance, i.e. there is a linear combination of other strategies (D and F) that can produce the same (or greater) benefit at lower (or the same) cost. As such, the comparator of intervention F becomes alternative D. Working on the efficiency frontier can have a large impact on results, conclusions and policy recommendations.[28] In this deterministic example, F would have an ICER of €10 000 per QALY if compared with (the non-efficient) alternative A. However, taking into account alternative D, this becomes €40 000 per QALY.

Figure 3 – The efficiency frontier



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

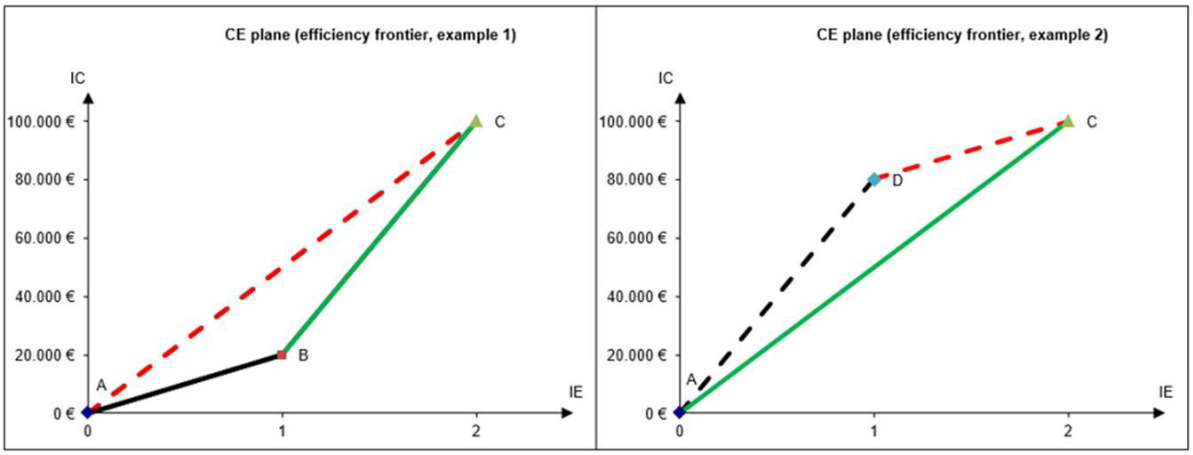
Appendix 6.3. Incorrect inclusion or exclusion of comparators

Cost effectiveness is a relative concept in which incremental costs of an intervention versus an alternative are compared with the incremental effects. One of the most important variables in such analyses is the choice of the comparator.[28] The inappropriate inclusion or exclusion of a comparator can have a major impact on the results of an economic evaluation. This is shown by the theoretical examples in Figure 4:

- Example 1 on the left side: intervention B is more cost-effective than intervention C. If intervention B is (inappropriately) excluded, then the cost-effectiveness of C is represented by the red dotted line. The correct comparator for C should be intervention B (i.e. the green line).
- Example 2 on the right side: intervention D is less cost-effective than intervention C and this intervention should be excluded because of extended dominance. If C was (inappropriately) compared with D, then the cost-effectiveness of C is represented by the red dotted line. The correct comparator for C should be intervention A (i.e. the green line).

This theoretical example shows that both the incorrect exclusion of an intervention that is more cost-effective (intervention B), as well as the incorrect inclusion of an intervention that is not cost-effective (intervention D) results in overly optimistic ICER calculations.

Figure 4 – The impact of an incorrect exclusion or inclusion of a comparator

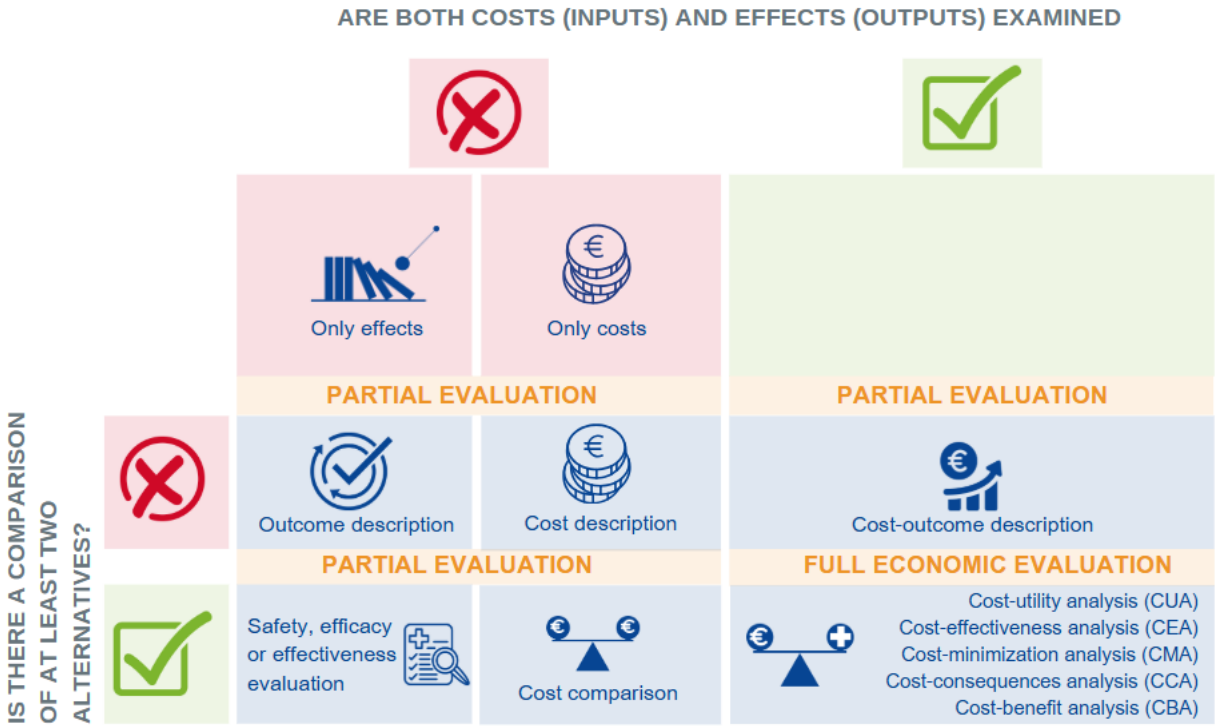


CE plane: cost-effectiveness plane; IC: incremental costs; IE: incremental effects (expressed in e.g. QALYs gained).

APPENDIX 7. CLASSIFICATION OF ECONOMIC STUDIES

A full economic evaluation is described as an analysis comparing both costs and effects of an intervention with the comparator. There are five common types of economic evaluations (see Figure 5). A description of the different types of economic evaluations is provided in part 5.7.

Figure 5 – Classification of economic studies



Adapted from Drummond et al., 2015.[99]

APPENDIX 8. TECHNICAL NOTES

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

Appendix 8.1. Use of expert panels

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

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

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

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

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

For more information about the use of expert panels we also refer to the Dutch guidelines (paragraph 3.4, 5.1.4 and tables B1-B3 in appendix of the Dutch report).[16]

Appendix 8.2. Transferring foreign costs through HICP and PPP

As mentioned in part 5.9.3.1, when transferring costs from another country, inflation should be calculated using the Harmonised Index of Consumer Prices (HICP) for the local currency of that foreign country, before converting to the Belgian equivalent in euros using purchasing power parity (PPP) indices. A theoretical example is shown in Table 10.

Table 10 – Transferring foreign costs through HICP and PPP

Year	HICP France	Transfer France €50 (in year 2017) to Belgium € (in year 2024)
2017	101.47	***1) Inflate using the HICP from the origin country***
2018	103.60	France € (year 2024) = €50 x (123.29 / 101.47) = €60.75
2019	104.95	So, France €50 in 2017 is equivalent to France €60.75 in 2024.
2020	105.50	***2) Convert to Belgium using the PPP***
2021	107.68	PPP Belgium (national currency per US$, 2022*) = 0.69464
2022	114.04	PPP France (national currency per US$, 2022*) = 0.674139
2023	120.50	Belgium € = €60.75 x (0.69464 / 0.674139) = €62.60
2024	123.29	**So, France €50 in 2017 is equivalent to Belgium €62.60 in 2024.**
Year	**HICP UK**	**Transfer UK £75 (in year 2016) to Belgium € (in year 2024)**
2016	100.70	***1) Inflate using the HICP from the origin country***
2017	103.40	UK £ (year 2024) = £75 x (133.86 / 100.70) = £99.70
2018	105.90	So, UK £75 in 2016 is equivalent to UK £99.70 in 2024.
2019	107.80	***2) Convert to Belgium using the PPP***
2020	108.75	PPP Belgium (national currency per US$, 2022*) = 0.69464
2021	111.56	PPP UK (national currency per US$, 2022*) = 0.651254
2022	121.66	Belgium € = £99.70 x (0.69464 / 0.651254) = €106.34
2023	130.54	**So, UK £75 in 2016 is equivalent to Belgium €106.34 in 2024.**
2024	133.86	

*GDP: gross domestic product; HICP: Harmonised Index of Consumer Prices; PPP: purchasing power parity; UK: United Kingdom; US: United States; Sources: HICP: https://www.oecd.org/en/data/indicators/inflation-cpi.html; PPP: https://www.oecd.org/en/data/indicators/purchasing-power-parities-ppp.html. * Remark: PPPs for more recent years are not (yet) available. We recommend using the most recent PPP.*

Appendix 8.3. Hospital per diem prices

The financing of non-medical hospital activities (i.e. capital expenditures for buildings and medico-technical facilities, hotel function, nursing care, etc.) is based on the reforms introduced in 2002. Since 2002, Belgian hospitals receive an annual budget (so called "budget of financial means (BFM–BMF") which covers their activities for the period July to June the 30th of the next year. The budget can be adapted in January, it is computed by the Federal Public Service (FPS) Public Health and its amount is different for each hospital. The budget is composed of three major parts (A-Capital costs, B-Operational costs and C-Corrective measures), which are further divided into subparts. The share of each (sub-)part in the total budget is given in parentheses in Table 11.[jjjj]

Table 11 – Components of the hospital budget of financial means

Categories		Description
A (~5%*)	A1	Investment costs
	A2	Short-term credit costs
	A3	Investment costs for medico-technical services which are exclusively financed via the hospital budget (not via fees)
B (~90%)	B1	Common operational costs (administration, maintenance, laundry) (17%)
	B2	Clinical costs (personnel and medical equipment) (33%)
	B3	Operating costs for medico-technical departments (radiotherapy, MRI and PET scans) (1.2%)
	B4	Some specific (mostly) lump sum costs (as a result of legal obligations), e.g. hospital hygiene, quality assessment, palliative care and recording of hospital data (16%)
	B5	Pharmacy costs (1.5%)
	B6	Costs for carrying out the social agreements for personnel not included in the budget of financial means (1.2%)
	B7	Extra costs for teaching hospitals or university function of the hospital (applied scientific research, the development of new technologies and the training of specialists) (2%)
	B8	Specific costs for patients with a weaker socioeconomic profile or social function of the hospital (0.3%)
	B9	Extra-legal financial benefits (17%)
C (~5%)		Corrective measures

** These are the percentages for the year 2024 for acute hospitals.*

How is this budget paid to the hospitals? The payment of the budget of financial means to a hospital contains two parts: a fixed part and a variable part. The *fixed part* is paid by the health insurance funds on the basis of monthly advances (the so-called provisional twelfths). This part includes (theoretically) 80% of subparts B1 and B2, and 100% of all other parts. The *variable part*, including 20% of subparts B1 and B2, is paid, via an invoice, according to the number of admissions (10% of the budget) and the number of nursing days (10% of the budget) for the acute hospitals, and exclusively according to

jjjj This share may vary from year to year. Information is available under the following link: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/2.3._evolutie_van_het_bfm_op_1_juli_2024_per_onderdeel_en_per_budgettair_type_nl.pdf.

the number of days (20% of the budget) for the other hospitals. The invoice is submitted by the hospitals to the health insurance fund for all patients enrolled in a health insurance fund. Specific RIZIV–INAMI tariff codes (from the nomenclatuur – nomenclature) have been created for this purpose). The amounts per admission and per nursing day are hospital-specific and also depend on the type of hospital stay (e.g. acute (A), burns (BRA), geriatrics (G), psychiatric (P), palliative (PAL) and specialized stays for chronic conditions (Sp)). They are adapted twice a year.

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

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

The above description only holds for patients enrolled in a health insurance fund. For patients not enrolled in a health insurance fund, the invoice (with the full per diem price covering categories A, B and C) is sent to the paying authorities (i.e. OCMW/CPAS (Public Welfare Centre; Openbaar Centrum voor Maatschappelijk Welzijn; Centre Public d'Action Sociale), a private health insurance or a work accident insurance). The 100% per diem price is the same for all patients, regardless of whether they are enrolled in a health insurance fund.

kkkk https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/wat-het-ziekenfonds-terugbetaalt/verzorging-in-ziekenhuizen/verpleegdagprijzen-ziekenhuizen.

Appendix 8.4. Valuation of lump sums for pharmaceutical products, medical imaging and clinical biology in hospitalized patients

As mentioned in part 5.9.3.7, lump sum payments exist in the Belgian hospital payment system for laboratory tests, medical imaging and a subset of inpatient pharmaceutical specialities. The general approach recommends not to perform conversions from the lump sum to the real consumption cost if the intervention being evaluated is not covered by a prospective lump sum. If the intervention being evaluated is covered by a prospective lump sum, adjustments should be made to obtain 100% of the cost of that intervention. The following paragraphs describe the appropriate methods for adjustment.

Hospital lump sum for pharmaceutical products

Since 1 July 2006, a prospective budget for pharmaceutical products administered to hospitalized patients in a general acute hospital was introduced by means of lump sum allocations, regardless of actual consumption.[100]

This prospective system covers all reimbursed pharmaceutical products (classes A, B, C, Cs, Cx, Fa, Fb), with the exclusion of the pharmaceutical products listed on a so-called “exclusion list”.

Pharmaceutical products excluded from the prospective system are:

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

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

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

Until 30 June 2024, payments to the hospital for pharmaceutical products included in the *prospective budget* came from two different mechanisms:

- Fee-for-service: the hospital retrospectively charged the health insurance fund for 25% of the reimbursement basis for each delivered pharmaceutical product.
- Lump sum: the hospital received prospective lump sum payments per inpatient admission that covered 75% of the reimbursement basis for the pharmaceutical products included in the prospective budget, regardless of the quantity (or lack) of pharmaceutical products administered.

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llll https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/wat-het-ziekenfonds-terugbetaalt/geneesmiddelen/geneesmiddel-terugbetalen/vergoedbare-farmaceutische-specialiteiten/vergoedbare-farmaceutische-specialiteiten-referentielijsten-en-referentiebestanden.

mmmm https://www.inami.fgov.be/fr/programmes-web/medicaments-et-produits-radio-pharmaceutiques-remboursables-par-l-assurance-soins-de-sante.

From 1 July 2024, the lump-sum covers 100% of the reimbursement basis of the pharmaceutical products included in the prospective budget, so there will no longer be any reimbursement on a fee-for-service basis.[nnnn]

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

Lump sums per admission are hospital-specific and depend on the case mix (APR-DRG) of each hospital, taking into account the severity of illness. In 2024, lump sums varied from €72.63 to €178.25 per admission. Lump sums per admission are published on the RIZIV–INAMI website.[pppp]

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

Pharmaceutical products administered in the hospital are thus financed as presented in Table 12. The extrapolation factors from fee-for-service expenses to total expenses are shown in Table 15.

Table 12 – Sources of financing – Hospital pharmaceutical products for patients in general acute hospitals

	Health insurance fund	Ordinary patient*
Pharmaceutical products included in the lump sum	Until 30 June 2024: 75% lump sum per admission (varies per hospital) 25% of the reimbursement basis as fee-for-service From 1 July 2024: 100% lump sum per admission (varies per hospital)	€0.62 per inpatient day
Pharmaceutical products outside the lump sum (exclusion list)	Reimbursement as a fee-for-service (according to the reimbursement categories A, B, C, Cs, Cx, Fa, Fb).	
Pharmaceutical products in reimbursement class D	-	100% out of pocket

** Patient not entitled to preferential reimbursement.*

nnnn https://www.ejustice.just.fgov.be/eli/besluit/2018/02/01/2018010896/justel#Art.127. There is still a registration of individual use (at 0%) allowing identification of actual use.

oooo https://cbip.be/fr/ or https://bcfi.be/nl/.

pppp https://www.inami.fgov.be/fr/professionnels/etablissements-et-services-de-soins/hopitaux/forfaitarisation-des-specialites-pharmaceutiques.

qqqq Pseudocode 750002 (https://webappsa.riziv-inami.fgov.be/Nomen/fr/750002).

Hospital lump sum for laboratory testing

Laboratory testing for patients hospitalized in a general hospital is financed through a mixed system of fee-for-service and (for the greater part) lump sum payments.[100]

- Fee-for-service: the hospital retrospectively charges the health insurance fund for 25% of the honorarium fees for each test performed.
- Lump sum 1: the hospital receives prospective lump sum payments per inpatient day, including the first day.
- Lump sum 2: the hospital receives lump sum payments per inpatient admission.

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

The *lump sums per inpatient day* are hospital-specific and depend on the case mix of each hospital (APR-DRG). In November 2024 they varied from €0.25 to €20.49. Lump sums per day for each hospital can be found on the RIZIV–INAMI website.[rrrr] Lump sum payments per inpatient day are paid regardless of the actual number of tests performed (and are also paid for days without any tests).

Basic *lump sums per admission* are fixed at €36.65 (01/01/2025 values). If the laboratory works 24 hours a day and is staffed by 2 full-time biologists, the lump sum reaches €64.13, €87.03 with 3 full-time biologists and €94.05 with 4 full-time biologists. In each of these cases, patients pay €7.44 of this lump sum, regardless of the actual number of tests performed.[ssss]

Laboratory tests performed on patients admitted to a general hospital are thus financed as presented in Table 13. The extrapolation factors from fee-for-service expenses to total expenses are shown in Table 15.

Table 13 – Sources of financing – Hospital laboratory testing for patients in general hospitals (2025 values)

	Health insurance fund	Ordinary patient*
Laboratory tests	Fee-for-service: 25% of the honorarium fee Prospective lump sum per inpatient day (varies per hospital)	-
"Remuneration for the biologists"	€29.21: basis lump sum per admission €56.69: lump sum per admission 24h service + 2 biologists €79.59: lump sum per admission 24h service + 3 biologists €86.61: lump sum per admission 24h service + 4 biologists	€7.44 per admission

** Patient not entitled to preferential reimbursement.*

rrrr https://www.inami.fgov.be/fr/professionnels/etablissements-et-services-de-soins/hopitaux/honoraires-forfaitaires-dans-les-hopitaux#biologie-clinique https://www.inami.fgov.be/SiteCollectionDocuments/hopitaux_pseudonomenclature_592001_20241101.pdf.

ssss https://www.inami.fgov.be/SiteCollectionDocuments/tarif_medecins_partie05_20250101.pdf. See Section IV of the document with the pseudocodes 591102, 591146, 591124, 591080.

Hospital lump sum for medical imaging

Medical imaging for patients hospitalized in a general hospital is financed through a mixed system of fee-for service (about 70% of the hospital budget) and lump sum payments (about 30% of the hospital budget):[100]

- Fee-for-service: the hospital retrospectively charges the health insurance fund for the honorarium fee for each medical imaging service provided.
- Lump sum 1: the hospital receives prospective lump sum payments per inpatient admission.
- Lump sum 2: the hospital charges a "consultancy" lump sum per inpatient stay from the first day on. This "consultancy" fee is a remuneration for the intellectual act of the radiologist providing the service.

Fee-for-service charges per medical imaging service provided and consultancy lump sums can be found on the RIZIV–INAMI website.

The *lump sum per admission* is determined by the case mix of each hospital (APR-DRG and severity level). In December 2024, it varied from €8.91 to €105.91 per admission. This lump sum is charged whether or not a medical imaging act is performed. Lump sums per admission for each hospital can be found on the RIZIV–INAMI website.[tttt]

Consultancy lump sums are fixed (on 01/01/25 €19.12 and €20.92 for non-accredited and accredited radiologists, respectively).[uuuu] Hospitalized patients pay €6.20 of this lump sum per admission, regardless of their actual consumption of services.

Medical imaging services provided to hospitalised patients are thus financed as presented in Table 14. The extrapolation factors from fee-for-service expenses to total expenses are shown in Table 15.

Table 14 – Sources of financing – Hospital medical imaging for patients in general hospitals (2025 values)

	Health insurance fund	Ordinary patient*
Medical imaging services	Fee-for-service per service provided Lump sum per admission (varies per hospital)	-
Remuneration for the radiologist "Consultancy lump sum"	€12.92: lump sum per admission for non accredited radiologist €14.72: lump sum per admission for accredited radiologist	€6.20 per admission

** Patient not entitled to preferential reimbursement.*

tttt "Honoraires forfaitaires par admission pour les prestations d'imagerie médicale"–"Forfaitair honorarium per opneming inzake medische beeldvorming" https://www.inami.fgov.be/fr/professionnels/etablissements-et-services-de-soins/hopitaux/honoraires-forfaitaires-dans-les-hopitaux#imagerie-medicale https://www.inami.fgov.be/SiteCollectionDocuments/hopitaux_pseudonomenclature_460784_20241201.pdf.

uuuu https://www.inami.fgov.be/SiteCollectionDocuments/tarif_medecins_partie04_20250101.pdf. See page 6 of the document with the pseudocodes 460703 and 460821.

Table 15 presents the extrapolation factors from fee-for-service expenses to total expenses. This is calculated by adding the lump sum expenses and the fee-for-service expenses and dividing these total expenses over the fee-for-service expenses. As shown in Table 15, this extrapolation factor is approximately 1.7, 5 and 3.5, respectively, for the last two years for medical imaging, clinical biology and pharmaceutical products included in the lump sum.

Table 15 – Extrapolation factors from fee-for-service expenses to total expenses for hospitalised patients (2008-2021)

Years	Medical imaging	Clinical biology	pharmaceutical products (forfaitized)
2008	1.62	5.09	4.32
2009	1.65	5.09	4.19
2010	1.57	4.89	4.20
2011	1.74	5.53	4.10
2012	1.63	5.38	3.96
2013	1.63	5.38	3.78
2014	1.66	5.32	3.81
2015	1.66	5.26	3.90
2016	1.66	5.52	3.84
2017	1.66	5.47	3.86
2018	1.65	5.29	3.97
2019	1.77	5.34	4.03
2020	1.69	5.01	3.55
2021	1.69	4.88	3.49

Extrapolation factors from fee-for-service expenses to total expenses (= Total expenses / Fee-for-service expenses).

Appendix 8.5. Inclusion of productivity in economic evaluations

Table 16 provides a theoretical example of how productivity losses during paid work can be calculated with the human capital approach (short absence from work) and with the friction cost method (long absence from work), see part 5.9.3.9.

Table 16 – Calculation of productivity losses

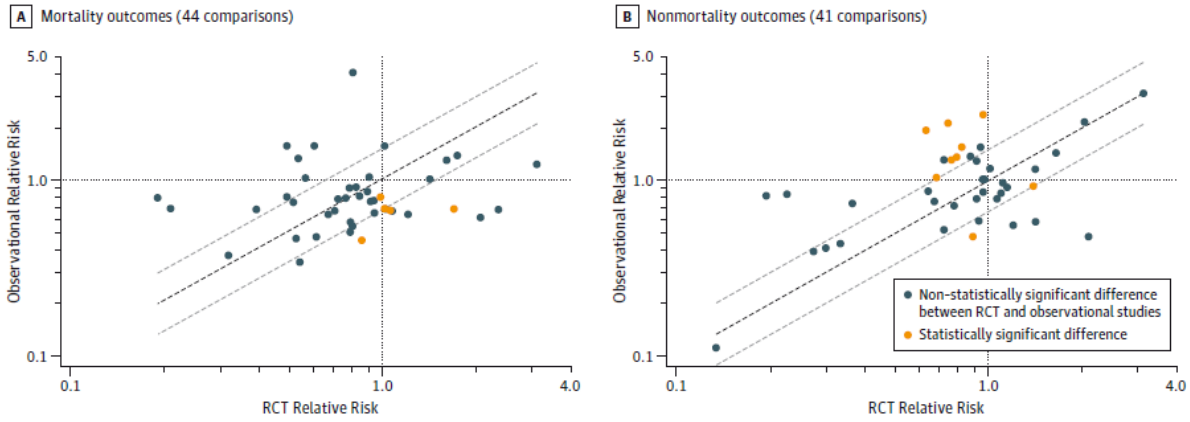
Short absence
A person works 40 hours per week, spread over 5 days a week. He/she has been absent for 2 working days in the last 4 weeks. The productivity loss is calculated as follows: 2 days x 8 hours per working day x €47.1 = €753.6.
Long absence – absence duration shorter than the friction period
A person works 40 hours per week, spread over 5 days per week. Based on the start date of the absence, the total duration of the absence is 63 (calendar) days. The productivity loss is calculated as follows: 63 calendar days = 63 x (5 working days / 7 days per week) = 45 working days. 45 working days x 8 hours per working day x €47.1 = €16 956.
Long absence – absence duration longer than the friction period
A person works 40 hours per week, spread over 5 days per week. Based on the start date of the absence, the total duration of the absence is 150 (calendar) days. The productivity cost is limited to the friction period (135 calendar days, see part 5.9.3.9). The productivity loss is calculated as follows: 135 calendar days of absence = 135 x (5 working days / 7 days per week) = 96.43 working days. 96.43 working days x 8 hours per working day x €47.1 = €36 334.3.

Adapted from ZIN 2024.[36]

Appendix 8.6. Estimates of the relative treatment effect and non-randomised studies

As mentioned in the EUnetHTA guidance document on practical considerations when critically assessing economic evaluations,[15] it might be tempting to try to use observational data to estimate a treatment effect. Observational data may include larger numbers and reflect reality. However, for estimating a treatment effect, a comparator group is needed. Inferences from observational data can lead to poor health care decisions by misrepresenting association for causation.[101] The combined results of three studies[102-104] contrasting the results of propensity score analyses and RCTs, comparing the effect of the same interventions in similar patient populations show no clear pattern of agreement (Figure 6). The authors indicate there is no way of knowing when observational study results are reliable.[101]

Figure 6 – Comparison of propensity score analyses and RCT results from 3 empirical assessments

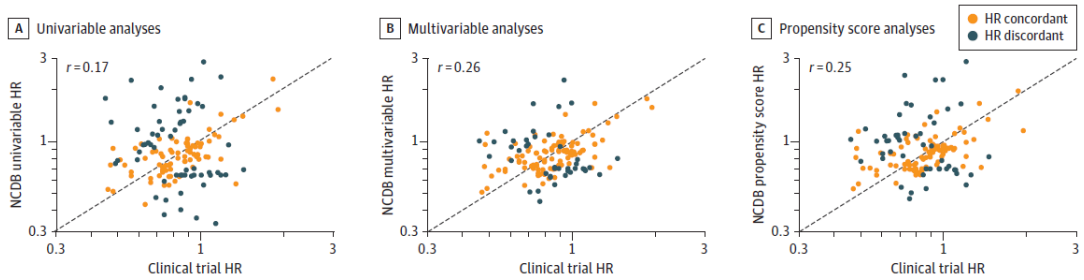


Scatter plots of results from empirical comparisons of propensity score analyses (y-axis) and corresponding randomized clinical trial (RCT) results (x-axis). Markers denote comparisons between observational and randomized study estimates for the same research question (similar populations, interventions, and outcomes); statistically significant differences ($P < .05$) are shown in orange. The dotted lines indicate lack of effect in RCTs (vertical lines) and observational studies (horizontal lines). Values lower than 1 indicate that the new treatment evaluated in the trial was more effective than the more established treatment; observational study results are expressed in the same way as the corresponding trial results. Markers in the top-right and bottom-left quadrants in each panel indicate agreement between randomized and observational results with respect to the direction of effects. Markers in the top-left and bottom-right quadrants indicate discordant direction of effects between designs. Black dashed diagonal lines indicate the line of identity (perfect agreement) between RCT and observational study results; gray dashed lines demarcate observational study relative risks that are between 0.67 and 1.5 times those produced by the corresponding RCT results. The term "relative risk" is used to denote risk, odds, or hazard ratio estimates, as reported in the 3 empirical analyses contributing data to this figure.

Source: Dahabreh and Kent, JAMA, 2014.[101]

The problems with study validity of non-randomised observational studies have also been analysed by Kumar et al.[105] In their study, results on the relative treatment effect of 141 RCTs (including 85 118 patients) were compared with results based on analyses from participants within the National Cancer Database (NCDB) (including 1 344 536 patients). Univariable, multivariable and propensity score analyses were applied. The latter two methods controlled for potential confounders, including demographic, comorbidity, clinical, treatment, and tumour-related variables.[105] Figure 7 shows the hazard ratios from the RCTs in comparison with the results from the univariable (A), multivariable (B), and propensity score analyses (C). As mentioned in the editorial, "*observational studies led to a different inference regarding therapeutic efficacy 55% of the time (i.e., point estimates that were either in a different direction, nonsignificant in non-randomized comparative effectiveness research vs significant in RCT or significant in non-randomized comparative effectiveness research but nonsignificant in RCT).*"[106]

Figure 7 – Comparison of hazard ratios from RCTs versus registry data



Hazard ratios shown for univariable analyses (A), multivariable analyses (B), and propensity score analyses (C). Each point on the scatter plot represents the HR for overall survival from 1 of the 141 randomized clinical trials in this study and the corresponding analysis within the NCDB. Yellow dots represent NCDB analyses in which the NCDB HR falls within the 95% CI of the HR in the clinical trial (concordant), and blue dots represent HRs from the NCDB analyses that fall outside the 95% CI of the HR in the clinical trial (discordant). The gray dashed line shows where clinical trial HRs equal NCDB HRs. The intersection of the axes represents an HR equal to 1.

Source: Kumar et al., JAMA Netw Open, 2020.[105]

The authors conclude the findings suggest that comparative effectiveness research using the National Cancer Database often produces results discordant with randomised clinical trials. Their findings help provide context for clinicians and policy makers interpreting observational comparative effectiveness research in oncology.[105] Methods to analyse the treatment effect based on observational data might improve in the near future. However, at this moment, evidence shows it often provides misinformation without a possibility to determine beforehand in which cases it would be possible to provide reliable estimates of the direction and size of the relative treatment effect.

Nevertheless, there is a role for observational studies, however, for the right research question: "*observational studies may clarify issues of prognosis, patterns of real-world usage, rare adverse events, and glaring disparities in cancer care delivery. However, when it comes to establishing the fundamental efficacy of therapeutic interventions, caution is warranted, and propensity score matching is not a panacea.*"[106]

For more information about direct and indirect treatment comparisons and the validity of clinical studies we refer to the guidance documents set up to support the implementation of the HTA Regulation (see part 5.10.1.1).[12, 13, 31]

Appendix 8.7. 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 HRQoL, but not all are useful for economic evaluations. There are disease specific and generic health-related quality-of-life measures, profile measures or single index measures, HRQoL can be assessed by patients themselves or by health care providers or family and valuation of a health state can be done by means of a Time-Trade-Off, Standard Gamble or Rating Scale.

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

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

The values for HRQoL 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 HRQoL directly on a visual analogue scale and these raw data are directly used for analysis, there will be a problem of comparability and aggregation. The values of one patient are not necessarily comparable to the values of another patient, which makes aggregation and calculation of means, medians and spread of little relevance. For a wide application of the utility data and for reasons of comparability across patient groups, it is important to use public preferences values for health states described by patients (indirect method) (see part 5.10.2 and Appendix 8.8).

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

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

For more information, we refer to the EUnetHTA document on HRQoL.[33] Available from: https://tools.eunethta.be/guidelines.html.

Appendix 8.8. Flemish EQ-5D-3L index values

Table 17 provides the Belgian value set, based on data from Flanders, for the EQ-5D-3L. An Excel file is available on the KCE website to convert the health states of the EQ-5D questionnaires to utilities: https://kce.fgov.be/sites/default/files/2025-05/20250508-EQ-5D-value-sets-Belgium.xlsm.

Table 17 – Flemish EQ-5D-3L index values

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

Source: Cleemput et al. 2010.[45]

APPENDIX 9. REPORTING GUIDELINES

The recommended structure of an economic evaluation report is presented below. This structure is based on the reporting guidelines developed by the Pharmacoeconomic Committee of the Belgian Society for Pharmacoepidemiology (BESPE).[107] Some specific reporting guidelines for economic evaluations and BIA are presented in part 5.16 and 6.10, respectively.

For reporting, we also refer to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement, available through the following links:

- https://www.equator-network.org/reporting-guidelines/cheers/
- https://www.ispor.org/heor-resources/good-practices/article/consolidated-health-economic-evaluation-reporting-standards-2022-cheers-2022-statement-updated-reporting-guidance-for-health-economic-evaluations

Executive Summary

Includes:

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

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.

Objectives

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

Literature review

Clinical literature review

Methods

- Review questions.
- Search strategy, including search terms and databases used.

- Selection procedures and criteria.
- Quality assessment tools and procedures.
- Data extraction strategy.
- Data analysis/data synthesis plan.

Results

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

Data need to be accompanied by relevant measures of variability.

Discussion and Conclusions of the clinical literature review

Economic literature review

Methods

- Review questions.
- Search strategy, including search terms and databases use.
- Selection procedures and criteria.
- Data extraction strategy.
- Data analysis/data synthesis plan

Results

- Flow diagram.
- Overview tables.
- Synthesis of the extracted information.

Data need to be accompanied by relevant measures of variability.

Discussion and Conclusions of the economic literature review

Data extraction sheets are provided in Appendix 4.

Basic elements of the economic evaluation

Perspective of the evaluation

Analytic technique

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

Study design

- Study design used (trial-based economic evaluation or model) + justification for this design.
- If modelling is used, describe the model's structure, including the assumptions used. Information related to model calibration and validation.

Methods used for cost assessment

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

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.

Method of analysis of the data

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

Time horizon and discount rate

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

Research Methods

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.

Identification, measurement and valuation of health-related outcomes

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

Sensitivity and scenario analyses

- Parameters on which a (probabilistic) sensitivity analysis and/or scenario analysis is performed.
- Distributions used for uncertain parameters in probabilistic sensitivity analyses (including information about e.g. the mean, upper and lower bounds, applied probability distribution and parameters of this distribution) + values used for scenario analyses.
- Sources for distributions for sensitivity analysis / values in scenario analyses.

Results

Basic results

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

Uncertainty analysis

- Present 95% confidence interval around the incremental costs, the incremental effects and the incremental cost-effectiveness ratio.
- Present cost-effectiveness or cost-utility plane.
- Cost-effectiveness acceptability curve (see Appendix 6.1).
- Present most influential input variables (e.g. tornado graph)

Discussion

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

Conclusion

Transparency of financial support

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

References

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.

APPENDIX 10. METHODOLOGICAL REFERENCES

Appendix 10.1. Country-specific guidelines

See Appendix 1.

Appendix 10.2. Methods for economic evaluations

Handbooks in health economics:

- Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth edition. Oxford: Oxford University Press, 2015. 445 pages.
- Gray A, Clarke P, Wolstenholme J, Wordsworth S. Applied Methods of Cost effectiveness Analysis in Healthcare. Handbooks in Health Economic Evaluation. Oxford: Oxford University Press; 2010. 328 pages.
- Briggs A, Claxton K, Sculpher M. Decision Modelling For Health Economic Evaluation. Handbooks in Health Economic Evaluation. Oxford: Oxford University Press; 2006. 237 pages.

Appendix 10.3. European/international guidelines and guidance documents

- HTACG (Member State Coordination Group on HTA): several guidance documents are available to support the Joint Scientific Consultation and Joint Clinical Assessment under the EU Health Technology Assessment Regulation:

  https://health.ec.europa.eu/health-technology-assessment/key-documents_en

- EUnetHTA (European Network for Health Technology Assessment): an overview of methodological guidelines created under EUnetHTA activities. Remark: several guidelines have been adapted for the joint work under the HTA Regulation (see above).

  https://tools.eunethta.be/guidelines.html

- ISPOR (International Society for Pharmacoeconomics and Outcomes Research): an overview of Good Practice Reports.

  https://www.ispor.org/heor-resources/good-practices

  https://www.ispor.org/heor-resources/good-practices/report-other-report-types/-in-category/index-types/ispor-good-practices-for-outcomes-research

- NICE (National Institute for Health and Care Excellence): a series of Technical Support Documents (TSDs) produced by the NICE Decision Support Unit.

  https://www.sheffield.ac.uk/nice-dsu/tsds

  https://www.sheffield.ac.uk/nice-dsu/tsds/full-list

APPENDIX 11. GLOSSARY

The description of the terms included in this glossary are mainly based on the glossary presented by HIQA,[20] NICE (https://www.nice.org.uk/process/pmg20/chapter/glossary), the York Health Economics Consortium (YHEC, https://yhec.co.uk/resources/glossary/), and the HTA Glossary (http://www.htaglossary.net).

Absenteeism: Productivity losses in paid work that occur due to absence from work. (See also presenteeism) (Source Brouwer et al.[108])

Absolute risk: The observed or calculated risk of an event in a defined population over a specified time period. (Source HIQA)

Absolute risk difference or reduction: A type of measure of treatment effect that shows the decrease in risk in the treatment group relative to the control group, that is to say, Pc - Pt. For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, then the absolute risk reduction would be 25% - 10% = 15%. It is the inverse of the number needed to treat. (See also number needed to treat and odds ratio and relative risk reduction) (Source HIQA)

Adherence: The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence has been used as a replacement for compliance in an effort to place the clinician-patient relationship in its proper perspective. Adherence refers to a process, in which the appropriate treatment is decided after a proper discussion with the patient. (See also compliance) (Source Chakrabarti[109])

Adverse event: An undesirable effect of a health technology. (Source HIQA)

Alternative definition: Any noxious, pathological or unintended change in a physical or metabolic function, revealed by signs or symptoms or a change in the results of laboratory tests, in any phase of a clinical study, whether or not the change is considered treatment-related. (Source HTA Glossary)

Acceptability: Economic evaluations assess the acceptability of an intervention, i.e. does it offer value for money. (see economic evaluations) (Source Neyt[110])

Affordability: Budget impact analyses help to determine if we can afford a specific intervention, i.e. which budgets do we need to implement and/or reimburse the intervention. (see budget impact analysis) (Source Neyt[110])

Base case: A base case analysis usually refers to the results obtained from running an economic model with the most likely or preferred set of assumptions and input values. Sensitivity analyses may then be used to explore how the results deviate from those of the base case analysis when input values and/or modelling assumptions are altered. (see also reference case) (Source YHEC)

Baseline: A term used to describe the initial set of measurements taken at the beginning of a study (after a run-in period, when applicable). (Source HIQA)

Baseline risk: At the time when a participant is enrolled in a study or when a patient is treated with a technology, baseline risk is the risk of future events of interest in the absence of that technology. (Source HIQA)

Bias: Systematic (as opposed to random) deviation of the results of a study from the 'true' results, caused by the way the study is designed or conducted. (Source NICE)

Alternative definition: A systematic error that may distort the results of a study because of weaknesses in its design, analysis, or reporting. (Source HTA Glossary)

Different types of bias: (Source HTA Glossary)



- Attrition bias: A bias associated with the dropping out or the differential exclusion of subjects from a study.
- Context bias: A measurement bias due to the influence of the study's context on the interpretation of the study's results.
- Crossover bias: A confusion bias that occurs when the subjects assigned to the experimental group do not receive the intervention or receive another intervention, or when some subjects in the control group receive the intervention.
- Detection bias: A measurement bias due to systematic differences between the compared groups in how the outcomes are ascertained.
- Interviewer bias: A bias that results from the action of an interviewer when eliciting, recording or interpreting information from an interview.
- Language bias: A form of bias linked to a restrictive literature search that excludes certain studies, because of the language in which they are published, from a systematic review or any other form of literature synthesis.
- Measurement bias: A bias introduced by incorrect measurement of the exposure or outcome status of participants in a study.
- Performance bias: A confusion bias due to systematic differences in care received outside the intervention being evaluated.
- Publication bias: A bias due to studies being published based on the nature and direction of their results.
- Selection bias: A type of bias due to an error in the estimation of the effect of an intervention because of the way in which the subjects were selected in the population of interest.
- Time lag bias: A form of bias due to the temporal limits of a literature search method likely to affect the inclusion of studies in a systematic review or any other form of literature synthesis. Note: Such bias may occur when the direction (positive or negative) or the strength (statistical significance) of a study's results delays its publication.

Blinding: When study participants, caregivers, researchers and outcome assessors are kept unaware about the technologies that the people have been allocated to in a study. (Source HIQA)

Budget impact analysis: A procedure for comparing only the financial costs and cost offsets of competing options, rather than comparing their clinical and economic costs and benefits. (Source HIQA)

Alternative definition: Budget impact analyses are used to estimate the likely change in expenditure to a specific budget holder resulting from a decision to reimburse a new healthcare intervention or some other change in policy at an aggregate population level. (Source YHEC)

Case-control study: A retrospective observational study designed to determine the relationship between a particular outcome of interest (for example, disease or condition) and a potential cause (for example, a technology, risk factor, or exposure). For example, a group of people with lung cancer might be matched with a group of people the same age without lung cancer. The researcher could compare how often both groups had been exposed to tobacco smoke in their lives. (Source HIQA)

Cohort study: An observational study in which two or more sub-sets of defined populations are identified by the presence of a common factor or factors (for example, non-randomly assigned to the proposed technology or to its main comparator(s)) and then followed in time to investigate the influence of the factors on the probability of occurrence of an outcome or outcomes. (Source HIQA)

Comorbidity: The coexistence of a disease, or more than one disease, in a person in addition to the disease being studied or treated. (Source HIQA)

Comparator: The alternative against which the intervention is compared. (Source HIQA)

Comparative effectiveness research (CER): The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels. (Source Institute of Medicine[111])

Compliance: The extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider. It refers to a process where the clinician decides on a suitable treatment, which the patient is expected to comply with unquestioningly. (see also adherence) (Source: Chakrabarti[109])

Confidence interval: The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied). (Source NICE)

Alternative definition: The computed interval with a specified probability (by convention, 95%) that the true value of a variable such as mean, proportion, or rate is contained within the interval. (Source HIQA)

Conflict of interest: The potential for conflict of interest and bias exists when professional judgement concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest. (Source ICMJE[112])

Confounder: A factor that distorts the apparent effect of an intervention on the outcome of interest, or that distorts the apparent association between the exposure and the outcome. (see also confounding) (Source HTA Glossary)

Confounding: The distortion of a measure of the effect of an exposure (for example, to therapy involving the proposed pharmaceutical product) on the risk of an outcome under investigation brought about by the association of the exposure with other factor(s) that can influence the outcome. (see also confounder) (Source HIQA)

Consumer Price Index (CPI): Consumer price indices (CPI) measure the change in the prices of a basket of goods and services that are typically purchased by specific groups of households. (Source OECD[113])

Alternative definition: The consumer price index is an economic indicator whose main task is to objectively reflect the price evolution over time for a basket of goods and services purchased by households and considered representative of their consumer habits. (https://statbel.fgov.be/en/themes/consumer-prices)

Control group: A group of participants who are observed but who do not receive treatment involving the proposed pharmaceutical product or technology. They may receive alternative treatment, no treatment or placebo. They provide data on the streams of outcomes (clinical and economic) for comparison with the streams of outcomes observed for participants who take therapy involving the proposed pharmaceutical product or technology. (Source HIQA)

Correlation coefficient: A number between -1 and +1 that expresses the strength of the linear association between two numerical variables. (Source HTA Glossary)

Cost analysis: A partial economic evaluation that only compares the costs in monetary units of the proposed technology with its main comparator(s). (Source HIQA)

Cost-benefit analysis (CBA): A type of economic evaluation in which the costs and benefits are measured using the same monetary units (for example, euro) to see whether the benefits exceed the costs. (Source NICE)

Cost-consequences analysis (CCA): A type of economic evaluation in which the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment are compared with those for a suitable alternative. Unlike CUA or CEA, it does not attempt to summarise outcomes in a single measure (such as the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out. (Source NICE)

Cost effective (value for money): A proposed technology is considered cost effective for a specified main indication if the incremental benefits of the proposed technology versus its main comparator(s) justify its incremental costs and harms. (Source HIQA)

Cost-effectiveness acceptability curve (CEAC): A graph plotting a range of possible cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost effective on the vertical access. CEAC provide a visual representation of the uncertainty surrounding cost-effectiveness estimates. (Source HIQA)

Cost-effectiveness analysis (CEA): A type of economic evaluation in which the benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which the intervention extends life). CEA assesses the cost of achieving the same benefit by different means. CEA is also used as an umbrella term to cover all types of economic evaluation. (Source NICE)

Cost-effectiveness (efficiency) frontier: Linking the non-dominated strategies on the cost-effectiveness plane produces a cost-effectiveness efficiency frontier. (Source HIQA)

Alternative definition: The cost-effectiveness frontier is the line connecting successive points on a cost-effectiveness plane which each represent the effect and cost associated with different treatment alternatives. The gradient of a line segment represents the ICER of the treatment comparison between the two alternatives represented by that segment. The cost-effectiveness frontier consists of the set of points corresponding to treatment alternatives that are considered to be cost-effective at different values of the cost-effectiveness threshold. The steeper the gradient between successive points on the frontier, the higher is the ICER between these treatment alternatives and the more expensive alternative would be considered cost-effective only when a high value of the cost-effectiveness threshold is assumed. Points not lying on the cost-effectiveness frontier (usually above and to the left of the frontier) represent treatment alternatives that are not considered cost-effective (compared with a relevant alternative lying on the frontier) at any value of the cost-effectiveness threshold. (Source YHEC)

Cost-effectiveness plane: A graph plotting difference in effect (between the technology of interest and the comparator) on the horizontal axis against the difference in costs on the vertical access, providing a visual representation of cost effectiveness. (source HIQA)

Cost-effectiveness threshold: The maximum amount a decision-maker is willing to pay for a unit of health outcome. If the cost-effectiveness (ICER) of a new therapy (compared with a relevant alternative) is estimated to be below the threshold, then (other things being equal) it is likely that the decision-maker will recommend the new therapy. However for values near the threshold, the level of uncertainty may become important. Thresholds are often established by analysis of previous (reimbursement) decisions: they are not themselves outputs of cost-effectiveness analyses, but guides (or rules) to interpretation of these outputs for decision-making, and they are specific to each unit of health outcome used. They are closely related to the economic concept of ‘opportunity cost’, in which the value of an intervention is considered to be the value of what is foregone in order to implement the intervention. The threshold value stands for the health outcome that could have been achieved if the resource required to implement the intervention of interest had been used elsewhere.

Although some countries (e.g. NICE for England and Wales) make the thresholds that they use explicit, in other countries the thresholds may not be explicit and they may vary by health care sector or disease area. (source YHEC)

Cost-minimization analysis (CMA): In a cost-minimisation analysis, the costs of different interventions that provide the same benefits are compared. If they are equally effective, only the costs are compared because the cheapest intervention will provide the best value for money. In practice, there are relatively few cost-minimisation analyses because it is rare for two healthcare interventions to provide exactly the same benefits. (Source NICE)

Cost-utility analysis (CUA): A type of economic evaluation in which the benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). (Source NICE)

Critical appraisal: The process of systematically assessing the report of a piece of research (for example, a clinical trial, meta-analysis or CEA) in terms of the validity and correct application of its methods, correct reporting of the results and justification for the interpretation of the results. (Source YHEC)

Data extraction: The process of retrieving relevant information and data from a data source. Data for systematic reviews can come from a range of sources including both published and grey literature. A data extraction form is designed to capture the information of interest in a structured and systematic way, allowing easy manipulation and analysis at later stages of the review, as well as quality checking of the extraction process. (Source YHEC)

Decision analysis: A technique that formally identifies the options in a decision-making process, quantifies the probable outcomes (and costs) of each, determines the option that best meets the objectives of the decision-maker and assesses the robustness of this conclusion. (Source HIQA)

Decision tree: A graphical representation of the probable outcomes following the various decision options in a decision analysis. (Source HIQA)

Alternative definition: A decision tree is a form of analytical model, in which distinct branches are used to represent a potential set of outcomes for a patient or patient cohort. A decision tree consists of a series of ‘nodes’ where branches meet: each node may take the form of a ‘choice’ (a decision about which alternative intervention to use) or a ‘probability’ (an event occurring or not occurring, governed by chance). Probabilities at any specific node must always add to 1. Costs and outcomes are assigned to each segment of each branch, including the end (‘leaf’) of each branch. Outcomes and costs for each branch are combined using branch possibilities and the tree is ‘rolled back’ to a decision node, at which the expected outcome and cost for each treatment alternative can be compared. Decision trees are frequently used to model interventions that have distinct outcomes that can be measured at a specific time point, as opposed to evaluations where the timing of the outcome is important. (Source YHEC)

Delphi technique: A technique used for reaching agreement on a particular issue, without the participants meeting or interacting directly. It involves sending participants a series of questionnaires asking their views. After completing each questionnaire, participants are asked to give further views in the light of the group feedback until the group reaches a predetermined level of agreement. The judgements of the participants may be analysed statistically. (Source NICE)

Deterministic analysis: Data parameters represented by the expected values of individual data elements (i.e., point estimates). (Source CADTH[18])

Deterministic sensitivity analysis (DSA): A method of decision analysis that uses both one-way (variation of one variable at a time) and multi-way (two or more parameters varied at the same time) sensitivity analysis to capture the level of uncertainty in the results that may arise due to missing data, imprecise estimates or methodological issues. (see also probabilistic sensitivity analysis) (Source HIQA)

Direct comparison: Comparison of treatments either by means of a single comparative study or a pairwise meta-analysis or other method for synthesis of comparative studies without indirect comparisons. (Source HTA CG[31])

Direct costs: The fixed and variable costs of all resources (goods, services, and so on) consumed in the provision of a technology as well as any consequences of the intervention such as adverse effects or goods or services induced by the intervention. These include direct medical costs and direct non-medical costs such as transportation or child care. (Source HIQA)

Direct medical costs or direct health care costs: All the fixed or variable costs directly related to the delivery of health care and health services. (Source HTA Glossary) (see examples in Table 3)

Direct non-medical costs or direct non-health care costs: The non-medical costs of treating a patient, such as transportation provided to and from a medical appointment. (Source HIQA) (see examples in Table 3)

Disability-adjusted life years (DALYs): A unit of healthcare status that adjusts age-specific life expectancy by the loss of health and years of life due to disability from disease or injury. DALYs are often used to measure the global burden of disease. (Source HIQA)

Discount rate: The interest rate used to determine the present value of future costs and benefits. (Source HTA Glossary)

Discounting: Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present. (Source NICE)

Disutility: The decrement in utility (valued quality of life) due to a particular symptom or complication. Disutility values are often expressed as a negative value, to represent the impact of the symptom or disease. They may be derived by subtracting utility values for a health state which includes the component (symptom, complication) of interest from a health state that is identical except for the absence of that component. Disutilities may be combined (usually additively, although occasionally multiplicative combinations are used) to provide a combined value of their collective impact on a patient's quality of life. However, as with utilities, this needs to be done with care as there are situations where disutility (A+B) ≠ (disutility (A) + disutility (B)) when the individual and combined health states are valued independently. (Source YHEC)

Dominance: A dominant treatment option is one that is both less costly and results in better health outcomes than the comparator treatment (the former 'dominates' the latter). Whatever cost-effectiveness threshold is used it is impossible that the comparator could be considered economically preferable. Conversely, a treatment option that is both more expensive and results in poorer health outcomes is said to be 'dominated'. (Source YHEC)

Dynamic model: Mathematical model in which the force of infection is a function of the proportion of infectious people in the population at each time point. The force of infection can thus change over time in this type of model. (source WHO[57]) (see also static model)

Economic evaluation: The comparative analysis of alternative courses of action in terms of both their costs and consequences. (Source NICE)

Alternative definition: Compares the costs and outcomes of at least two alternative interventions. There are five different types of economic evaluation: cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-consequences analysis and cost-benefit analysis.

Effectiveness: The extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) in routine clinical practice. (Source HIQA)

Alternative definition: Effectiveness refers to the ability of an intervention (drug, device, treatment, test, pathway etc.) to provide the desired outcome(s) in the relevant patient population. Effectiveness is

typically assessed through a clinical trial. When considered at the same time as cost-effectiveness and side effects, the effectiveness of an intervention can be measured in QALYs, or quality-adjusted life years. (Source YHEC)

Efficacy: The extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) when studied under controlled research conditions. (Source HIQA)

Alternative definition: Efficacy is the benefit of an intervention gained under ideal conditions, such as in a randomised controlled trial. 'Ideal conditions' refers to an experimental and controlled setting, where contextual factors (treatment administration, population characteristics, healthcare system characteristics) are fixed and balanced across the two (or more) study groups through randomisation, blinding and standardisation. The design of the clinical trial is usually optimised to show the greatest benefit of the investigated intervention(s). Regulatory authorities are primarily interested in the balance of efficacy and harms (adverse effects) measured in clinical trials, whereas in health technology assessment the focus is on benefits that are achieved in usual practice, where the contextual factors are not fixed. (Source YHEC)

Efficiency: The allocation of available healthcare resources that maximize health outcomes for society. (Source HTA Glossary)

Alternative definition: In health economics efficiency refers to either obtaining the greatest health benefit from interventions using the available resources, or achieving a given health benefit in a way that minimises costs/resource use. A distinction is often made between technical efficiency and allocative efficiency. Technical efficiency concerns how best to achieve a single, given, objective: for example, how can a procedure such as a coronary artery bypass graft (CABG) be undertaken to achieve the best outcome for patients in terms of quality-adjusted survival? Alternatively, how can a CABG be successfully performed by making the best use of the resource inputs (hospital staff and theatre time, diagnostic work-up, medications, follow-up care…)? Allocative efficiency concerns competing objectives, which may not all be capable of implementation: whether to implement a particular intervention (and if so how much), given competing demands on the health care budget? What mix of interventions delivers the greatest health gain? For example, should we expand the use of CABG to a new group of patients, or should we invest in a new screening programme for patients at risk of coronary artery disease? Opportunity cost is a key concept in making judgements about allocative efficiency, often represented in health technology assessment by a willingness to pay threshold. (Source YHEC)

Endpoint: An indicator chosen for determining the effect of an intervention. (Source HTA Glossary)

Epidemiology: The study of the distribution and determinants of health-related conditions or events in defined populations. (Source HIQA)

EQ-5D: The EuroQol Five Dimension (EQ-5D) is an example of a generic measurement of quality of life, which is used in many clinical trials and other prospective studies. The EQ-5D questionnaire consists of 5 questions relating to different domains of quality of life (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) for each of which there are 3 levels of response (no problems, some problems or severe problems). More recently, questions with 5 levels of response have been introduced (called EQ-5D-5L). The instrument is quick and easy to use, extensively researched/validated and translated into many different languages. Most importantly it is not disease-specific and therefore applicable to most disease areas (but less applicable in mental health and diseases causing specific disabilities such as blindness) and comparisons of interventions across disease areas. The importance of EQ-5D is that, based on population surveys, utility scores are available for each of the possible responses. These can be combined with appropriate durations for each measurement to generate quality-adjusted life years for each study subject, which in can be used to drive cost-utility analyses of the intervention of interest. It is generally recommended that in clinical trials EQ-5D is administered alongside a disease specific quality of life instrument which is more sensitive to specific aspects of the condition and the potential impact of therapy. NICE guidelines state that the EQ-5D is the preferred measure of HRQoL in adults, and "when EQ-5D data are not available



or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D". (Source YHEC)

For more information on the EQ-5D, see www.euroqol.org.

Equity: As it relates to health, 'fairness' in allocation of resources, technologies, or outcomes among individuals or groups. (Source HIQA)

Evidence-based medicine: Evidence-based medicine is the deliberate and explicit use of the current best evidence in combination with clinical knowledge and experience when making decisions on patient care, rather than basing clinical decisions solely on tradition or theoretical reasoning. Coined by a group from McMaster University in the late 1980s, the aim of 'Evidence-based medicine' aims to make clinical practice more grounded in up-to-date science, and therefore more safe, consistent, and cost-effective. Evidence based research recognises the inability of traditional authorities (especially text books) to keep pace with rapid development of evidence, the emerging availability of information technology to provide access to evidence, and the need for strong critical appraisal skills to evaluate and interpret the results of different types in real time. A strong emphasis was placed on the importance of RCTs as sources of unbiased evidence to inform evidence based research, and metrics such as 'numbers needed to treat' to summarise and communicate evidence in clinical settings. Writing in the BMJ in 1996, Sackett et al. defined evidence-based medicine as "requir[ing] a bottom up approach that integrates the best external evidence with individual clinical expertise and patients' choice". (Source YHEC)

Exchangeability: If patients from one treatment group were substituted into another, the same treatment effect is expected; contains the components similarity, homogeneity, and, in the case of indirect comparisons, consistency. (Source HTA CG[31])

Exclusion criteria: Literature review: Explicit criteria used to decide which studies should be excluded from consideration as potential sources of evidence. Study participants: Criteria that define who is not eligible to participate in a study. (Source NICE)

Expected value of partially perfect information (EVPPI): The expected value of information for a single or a group of uncertain aspects of the disease and/or intervention under study. (source WHO[57])

Alternative definition: The expected value of partially perfect information is the price that a healthcare decision maker would (in theory) be willing to spend in order to gain perfect information for one or more factors (i.e. inputs to an economic model) which may influence which treatment alternative is preferred, based on the analysis of uncertainty in the relevant cost-effectiveness analysis. The EVPPI is calculated as the difference in the monetary value of health gain associated with a decision between therapy alternatives (and represented in an economic model) between when a choice is made on the basis of currently available information (i.e. uncertainty in the factor(s) of interest) and when the choice is made based on perfect information (no uncertainty in these factors). EVPPI is closely related to EVPI (and EVSI) and is primarily used to assess the value of collecting further information, especially when this may involve expensive trials, registries or other observational studies. (Source YHEC)

Expected value of perfect information (EVPI): The value (in monetary terms) of eliminating all uncertainty about an intervention being cost-effective or not. (source WHO[57])

Alternative definition: The expected value of perfect information is the price that a healthcare decision maker would be willing to pay to have perfect information regarding all factors that influence which treatment choice is preferred as the result of a cost-effectiveness analysis. This is the value (in money terms) of removing all uncertainty from such an analysis. EVPI is calculated as the difference in the monetary value of health gain associated with a decision between therapy alternatives between when the choice is made on the basis of with currently available information (i.e. uncertainty in the factors of interest) and when the choice is made based on perfect information (no uncertainty in all factors). (Source YHEC)

Expected Value of Sample Information (EVSI): The expected value of sample information estimates the value of a decision to collect additional sample information. Typically, additional research reduces, rather than eliminates uncertainty meaning perfect information is not available. Therefore, EVSI can be utilised to help determine the optimal research design (study population, comparison to be tested, sample size) to maximise both the reduction in uncertainty and the value to the society of conducting the study. (Source YHEC)

Extended dominance (or weak dominance): When one intervention is both less costly and more effective than a linear combination of two other interventions with which it is mutually exclusive. (source WHO[57])

External validity: The extent to which one can generalise study conclusions to populations and settings of interest outside a study. (Source HIQA)

Extrapolation: In data analysis, predicting the value of a parameter outside the range of observed values. (Source NICE)

Follow up: The observation over a period of time of study or trial participants to measure changes in outcomes under investigation. (Source HIQA)

Friction-cost method: A method of estimating the cost of the production loss resulting from the absence of an employee during the period needed by the organization to replace the employee and return to the initial level of productivity. (Source HTA Glossary)

Generalisability: The problem of whether one can apply or extrapolate results obtained in one setting or population to another; term may also be referred to as 'transferability', 'transportability', 'external validity', 'relevance', or 'applicability'. (Source HIQA)

Alternative definition: The extent to which the results of a study based on measurements in a particular population or a specific context hold true for another population or in a different context. (Source NICE)

Gross or macro costing: Costing approach that uses large components as basis for costing, such as cost per hospital day. (see also micro costing) (Source HIQA)

Half-cycle correction: In economic models that use Markov-type processes, it is generally recommended that a 'half-cycle correction' be built into the analysis, to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle. For example, if we know that 100 people are alive at month ten, and that 90 people are alive at month eleven, we do not necessarily know at what point those 10 patients died between months ten and eleven. In such cases, it is usual to assume that the event occurred at the mid-point of the cycle. However, for many health events, the implications of the event may not actually become apparent until the next cycle. For instance the increased costs associated with disease progression may not occur until progression is clinically confirmed, which may only happen at regular routine follow-up visits (i.e. at the start or end of a cycle). Likewise, if packs of medicine are prescribed on a monthly basis, then a monthly cost to the healthcare system would occur in full, no matter what point the person died within the cycle. Therefore, it is usually recommended that half cycle correction is applied carefully, and only to those aspects where the timing of the event and its consequences are not known. (Source YHEC)

Harmonised Index of Consumer Prices (HICP): The HICP is an economic indicator designed to measure over time the price evolution of goods and services purchased by households. The HICP therefore allows for a comparable measurement of inflation in the euro area, the EU, the European Economic Area and for all other countries including candidate countries for the European Union. The HICP is calculated in a harmonised manner and on the basis of common concepts. The HICP is the official measure of inflation in the euro area to enable the European Central Bank to conduct its monetary policy. (https://statbel.fgov.be/en/themes/consumer-prices)

Hazard ratio: A measure of effect produced by a time-to-event survival analysis. This represents the increased instantaneous rate with which one group is likely to experience the outcome of interest. (Source HIQA)

Health index: The health index is derived from the consumer price index and has been published since January 1994. The current value of this index is determined by removing a number of products from the consumer price index product basket, in particular alcoholic beverages (bought in a shop or consumed in a bar), tobacco products and motor fuels except for LPG. (https://statbel.fgov.be/en/themes/consumer-prices)

Health-related quality of life (HRQoL): A combination of a person's overall physical, mental and social wellbeing; not merely the absence of disease. (Source NICE) (See also Quality of life for alternative definition)

Health technology: The application of scientific or other organised knowledge — including any tool, technique, product, process, method, organisation or system — in healthcare and prevention. In healthcare, technology includes drugs, diagnostics, indicators and reagents, devices, equipment and supplies, medical and surgical procedures, support systems and organisational and managerial systems used in prevention, screening, diagnosis, treatment and rehabilitation. (Source HIQA)

Health technology assessment (HTA): A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.

Note 1: Definition of health technology: An intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system.

Note 2: The process is formal, systematic and transparent, and uses state-of-the-art methods to consider the best available evidence.

Note 3: The dimensions of value for a health technology may be assessed by examining the intended and unintended consequences of using a health technology compared to existing alternatives. These dimensions often include clinical effectiveness, safety, costs and economic implications, ethical, social, cultural and legal issues, organisational and environmental aspects, as well as wider implications for the patient, relatives, caregivers, and the population. The overall value may vary depending on the perspective taken, the stakeholders involved, and the decision context.

Note 4: HTA can be applied at different points in the lifecycle of a health technology, i.e., pre-market, during market approval, post-market, through to the disinvestment of a health technology.

(Source HTA Glossary)

Herd immunity: The reduction in exposure of susceptible people to a pathogen through vaccination of other people; herd immunity can also be induced by non-vaccine interventions, such as administration of antivirals, isolation/quarantine. (Source WHO[57])

In confidence material: Information (for example, the findings of a research project) defined as 'confidential' because its public disclosure could affect the commercial interests of a particular company ('commercial in confidence') or the academic interests of a research or professional organisation ('academic in confidence'). (Source NICE)

Incidence: The number of new cases of a disease or condition in a population at risk over a given period, usually one year. (Source HTA Glossary)

Inclusion criteria: Explicit criteria used to decide which studies should be considered as potential sources of evidence. (Source NICE)

Incremental cost-effectiveness ratio (ICER): The additional cost of the more expensive intervention compared with the less expensive intervention, divided by the difference between the effects of the interventions on the patients (the additional cost per QALY, for example). (Source HTA Glossary)

Alternative definition: The difference in the mean costs between 2 interventions, strategies or programmes in the population of interest divided by the differences in the mean outcomes between the 2 interventions, strategies or programmes in the population of interest. (Source NICE)

Incremental costs: The absolute difference between the costs of alternative management strategies of the same medical condition, disease or disorder. (Source HIQA)

Incremental effects: The absolute difference between the effects of alternative management strategies of the same medical condition, disease or disorder.

Incremental net monetary benefit (INMB): Incremental NMB measures the difference in NMB between alternative interventions, a positive incremental NMB indicating that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold. In this case the cost to derive the benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit. (Source YHEC)

Indirect comparison: A broad term to refer to any evidence synthesis in which treatment groups from different studies are compared. This includes evidence synthesis in which inference about the relative effectiveness of two treatments is made without the use of trials comparing both treatments head-to-head; indirect comparisons are also made when more general methods of network meta-analysis are applied, even when head-to-head studies for the comparison of interest are available. (Source HTA CG[31])

Indirect (non-health care) costs: The cost of time lost from work and decreased productivity due to disease, disability, or death. (In cost accounting, it refers to the overhead or fixed costs of producing goods or services.) (Source HIQA) (see Table 3)

Indirect health care costs: Unrelated medical costs in years of life gained, in other words costs of future medical interventions that are not related to the disease examined in the economic evaluation. (Source ZIN[36]) (see Table 3)

Intermediate outcome: See surrogate endpoint

Internal validity: A trial has internal validity if, apart from possible sampling error, the measured difference in outcomes can be attributed only to the different therapies assigned. (Source HIQA)

Alternative definition: A measure of how well a research study has been designed and how well it avoids bias. That is, the extent to which the cause-and-effect relationships in a study are true for the people and conditions of the study. (Source NICE)

Joint Clinical Assessment (JCA): The scientific compilation and the description of a comparative analysis of the available clinical evidence on a health technology in comparison with one or more other health technologies or existing procedures, in accordance with an assessment scope …, and based on the scientific aspects of the clinical domains of HTA of the description of the health problem addressed by the health technology and the current use of other health technologies addressing that health problem, the description and technical characterisation of the health technology, the relative clinical effectiveness, and the relative safety of the health technology.(Art. 2 HTA Regulation[8])

Joint Scientific Consultation (JSC): Offers recommendations to Health Technology Developers (HTDs) on their development plans for a medicinal product or medical device, ensuring that evidence meets requirements for a subsequent JCA. This guidance can streamline preparation for JCA and enhance the quality of clinical studies. (https://health.ec.europa.eu/document/download/3385c0cd-e468-4384-a591-0123c3e6a521_en?filename=hta_htar_factsheet-jsc_en.pdf)

Kaplan-Meier (KM) survival curve: The Kaplan-Meier survival curve is defined as the probability of surviving in a given length of time while considering time in many small intervals. (Source Altman[114])

Literature review: A summary of the evidence from several studies, with conclusions about the findings. It may or may not be systematically researched and developed. (Source NICE)

Markov modelling: A decision-analytic technique that predicts future events occurring in a group over a period of time by assigning group members to a fixed number of health states and then modelling transitions among the health states. (Source NICE)

Alternative definition: The Markov model is an analytical framework that is frequently used in decision analysis, and is probably the most common type of model used in economic evaluation of healthcare interventions. Markov models use disease states to represent all possible consequences of an intervention of interest. These are mutually exclusive and exhaustive and so each individual represented in the model can be in one and only one of these disease states at any given time. Examples of health states that might be included in a simple Markov model for a cancer intervention are: progression-free, post-progression and dead. Individuals move ('transition') between disease states as their condition changes over time. Time itself is considered as discrete time periods called 'cycles' (typically a certain number of weeks or months), and movements from one disease state to another (in the subsequent time period) are represented as 'transition probabilities'. Time spent in each disease state for a single model cycle (and transitions between states) is associated with a cost and a health outcome. Costs and health outcomes are aggregated for a modelled cohort of patients over successive cycles to provide a summary of the cohort experience, which can be compared with the aggregate experience of a similar cohort, for example one receiving a different (comparator) intervention for the same condition. Markov models are limited in their limited ability to 'remember' what occurred in previous model cycles. For example the probability of what occurs after disease progression may be related to the time to progression. Although to some extent health states can be defined ingeniously to address this complexity, other modelling approaches may be required for more complex diseases. (Source YHEC)

Mean: A measure of central tendency calculated by dividing the sum of all the observed values by the number of observations. (Source HTA Glossary)

Median: A measure of central tendency corresponding to the value below which 50% of the observations are found. (Source HTA Glossary)

Meta-analysis: The synthesis of two or more comparative studies with a common intervention and comparator, to produce a pooled estimate of the relative treatment effect. Sometimes referred to as pairwise meta-analysis to distinguish from network meta-analysis. (Source HTA CG[31])

Alternative definition: A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment. (Source NICE)

Micro-costing: Costing approach based on detailed resources used by patient on item by item basis. (see also macro costing) (Source HIQA)

Model inputs: Information needed for economic modelling. This may include information about effectiveness, adverse events, diagnostic accuracy, prognosis, quality of life, resource use and costs. (Source NICE)

Monte Carlo simulation: Monte-Carlo simulation is a form of modelling used in many areas of science where model inputs are drawn from distributions and are not treated as fixed values. Key elements of a Monte-Carlo simulation are to (a) define a domain of possible inputs (parameter); (b) generate input values randomly from probability distributions across the domain; (c) perform a deterministic computation of the model output based on the selected inputs; (d) repeat for a sufficient number of 'draws' of input values; (e) aggregate the results. (Source YHEC)

Moving target: A subject of evaluation (a technology, for example) that is difficult to define because it is changing rapidly. (Source HTA Glossary)

Multi-way sensitivity analysis: Multi-way sensitivity analysis is a technique that accounts for the fact that more than one parameter in a model is uncertain and the output of the model is sensitive to the choice of value for each of these parameters (commonly the key parameters in the model). During multi-way sensitivity analysis the value of each parameter is changed simultaneously, and the impact that this has on the model output is investigated. This technique is limited to investigating the impact of changing relatively few (2 to 5) parameters simultaneously, given that the number of possible combinations of parameter values has the potential to get very large. (Source YHEC)

Net monetary benefit (NMB): A summary statistic that represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit (for example a measure of health outcome or QALY) is known. The use of NMB scales both health outcomes and use of resources to costs, with the result that comparisons without the use of ratios (such as in ICERs) can be made. NMB is calculated as (incremental benefit x threshold) – incremental cost. (Source YHEC)

Network meta-analysis (NMA): Generalisation of meta-analysis to evidence networks consisting of more than two treatments, which can include both direct evidence and indirect evidence. NMA incorporates other terms used in the literature to describe the synthesis of both direct and indirect evidence, such as mixed treatment comparisons and indirect treatment comparisons. (Source HTA CG[31])

Number needed to treat (NNT): A measure of treatment effect that provides the number of patients who need to be treated to prevent one outcome event. It is the inverse of absolute risk reduction (1 / absolute risk reduction); i.e., 1.0 / (Pc - Pt). For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the number needed to treat would be 1.0 / (0.25 - 0.10) = 6.7 patients. (See also absolute risk reduction, relative risk reduction, and odds ratio) (Source HIQA)

Non-randomised controlled trial: These are trials in which participants (or groups) are allocated to receive either the intervention or a control (or comparison intervention) but the allocation is not randomised. This type of study is often called a controlled before-and-after (CBA) study. (Source NICE)

Non-reference case: Alternative methods to those recommended in the reference case for the purposes of assessing methodological uncertainty. Can accompany the reference case and be provided to decision-makers, but the impact of departing from the reference case should be explicitly stated. (Source CADTH[18])

Number needed to harm (NNH): The number of subjects treated per subject experiencing an adverse effect. (Source HTA Glossary)

Number needed to treat (NNT): A measure of treatment effect that provides the number of patients who need to be treated to prevent one outcome event. It is the inverse of absolute risk reduction (1 / absolute risk reduction); i.e., 1.0 / (Pc - Pt). For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the number needed to treat would be 1.0 / (0.25 - 0.10) = 6.7 patients. (See also absolute risk reduction, relative risk reduction, and odds ratio) (Source HIQA)

Observational study: Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups (for example, cohort studies and case–control studies). (Source NICE)

Alternative definition: A study in which the investigators do not manipulate the use of, or deliver, a technology (for example do not assign patients to treatment and control groups), but only observe patients who are (and sometimes patients who are not as a basis of comparison) exposed to the intervention, and interpret the outcomes. These studies are more subject to selection bias than experimental studies such as randomised controlled trials. (Source HIQA)

Odds: The ratio (quotient) of the probability that an event will occur to the probability that this event will not occur. (Source HTA Glossary)

Odds Ratio: An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. (Source HIQA)

One-way sensitivity analysis (or univariate sensitivity analysis): Univariate/one way sensitivity analysis allows a reviewer to assess the impact that changes in a certain input (parameter) will have on the output results of an economic evaluation (most frequently those based on a model) – this may

be referred to as assessing the robustness of the result to that parameter. The parameter of interest should be varied between plausible extremes, preferable justified by review of available evidence. This is the simplest form of sensitivity analysis since only one parameter is changed at one time, and correlations between parameters is not taken into account. Tornado diagrams are often used to summarise univariate sensitivity analyses testing a set of input variables in turn. (Source YHEC)

Opportunity cost: The value of the forgone benefits because the resource is not available for its best alternative use. (Source HIQA)

Alternative definition: The opportunity cost of an intervention is what is foregone as a consequence of adopting a new intervention. In a fixed budget health care system where increased costs will displace other health care services already provided, the opportunity cost is measured as the health lost as a result of the displacement of activities to fund the selected intervention. In terms of choosing to fund intervention A over intervention B, the opportunity cost of choosing A would be the potential value or the difference (incremental benefits) of A compared to B and the difference in cost (incremental cost) of A compared to B. Often, when a new costly intervention is adopted within a health system, the opportunity cost (i.e. the health benefits displaced) will be unknown and unrelated to the intervention being adopted. (Source YHEC)

Parameter uncertainty: The acknowledgment that a precise value of a parameter is not always known. This is also referred to as 'second order' uncertainty. It is represented in an analysis by specifying variables as distributions/ranges. (Source WHO[57])

Patient-Reported Experience Measures (PREMs): Patient-reported experience measures (PREMs) are psychometrically validated tools (e.g. questionnaires) used to capture patients' interactions with healthcare systems and the degree to which their needs are being met. PREMs are designed to determine whether patients have experienced certain care processes rather than their satisfaction with the care received (which may be subject to bias). A PREM may, for instance, be used to collect information on the patient experience of hospital admission. Data derived from this could be used to inform service development and configuration. (Source YHEC)

Patient-Reported Outcome Measures (PROMs): Patient-reported outcome measures (PROMS) or patient-reported outcome instruments (more commonly used in the US) are psychometrically validated tools, such as questionnaires used to collect PROs. In clinical trials, for example, PROMs may be used to collect PRO data to enable a pharmaceutical company ("sponsor") to support a claim in the product labelling (USA) or summary of product characteristics (SmPC, Europe). (Source YHEC)

Patient-reported outcome (PROs): Patient-reported outcomes (PROs) are any reports directly from patients on their health, condition, etc. that is made solely by such patients without any input, suggestions or interpretation from their doctors, family, friends or other individuals. PRO is a blanket term relating to single or multidimensional aspects of patients' symptoms, health, quality of life, treatment satisfaction, medication adherence, etc. PROs are often recorded in clinical trials, using validated instruments to measure the impact of the intervention as perceived by the patient. (Source YHEC)

Persistence: The duration of time from initiation to discontinuation of therapy. (Source Cramer et al.[115])

Perspective: Perspective of the bearers of the costs and benefits of an intervention (e.g. health care payers, society, government, health-care providers, patients). (Source WHO[57])

PICO: A structured approach for developing review questions about interventions. The PICO framework divides each question into 4 components: the population (the population being studied), the interventions (what is being done), the comparators (other main treatment options) and the outcomes (measures of how effective the interventions are). (Source NICE)

Population-adjusted method for indirect comparisons: Method for indirect comparisons in which a mix of individual patient data (IPD) from one or more trials, and aggregate data from other trials, are

used to adjust for relevant population characteristics that differ between studies in order to estimate a treatment effect. (Source HTA CG[31])

Pragmatic Trials: Many clinical trials of new healthcare interventions, especially those required to meet the requirements of regulatory authorities, are 'explanatory' in nature. This means that they are executed to strict protocols including tight inclusion and exclusion criteria, tightly controlled delivery of the intervention and comparator as well as any concomitant therapy, measures in place to ensure string adherence to the intervention, intensive follow-up data and a pre-specified analysis plan. The underlying purpose is that the trial should have the best chance of identifying differences in efficacy or safety. However there is increasing concern that effectiveness in 'real world' situations (routine practice) differs from that predicted from efficacy reported such trials. This has led to increased interest in more 'pragmatic' trials, where many of the strict protocol elements are relaxed, and results may be more immediately generalisable to routine practice. (Source YHEC)

Preference-based measures (or generic utility instruments): Preference-based measures (PBM) or generic preference-based measures are increasingly used in health economic evaluations to calculate quality-adjusted life years (QALYs). Such measures usually comprise a number of domains (or descriptive set) that patients can use to describe various aspects of their health (e.g. limitations in daily activities and mobility, pain and discomfort). These patient-reported values (profile scores) are then converted to an index score using a selected algorithm (sometimes country-specific). These algorithms area based on surveying the general public's preferences for different combinations of health states, which is why these measures are referred to as "preference-based". The index scores (sometimes called 'utilities') usually range between 0 and 1, where 1 is usually taken to reflect a valuation of "perfect health" and 0 refers to valuation of "death". In some of these measures values below zero may be possible, representing health states perceived to be worse than death. Examples of PBMs include the EQ-5D, SF-6D and the Health Utilities Index. The EQ-5D is NICE's preferred instrument for cost-utility evaluations in healthcare technology assessments. (Source YHEC)

Presenteeism: The problem of workers being on the job, but, because of illness or other medical conditions, not fully functioning. (see also absenteeism) (Source Hemp[116])

Alternative definition: Productivity losses in paid work can occur due to both absence from work ('absenteeism') and reduced productivity while being at work (often called 'presenteeism'). (Source Brouwer et al.[108])

Prevalence: The number of people in a population with a specific disease or condition at a given time, usually expressed as a proportion of the number of affected people to the total population. (Source HTA Glossary)

Probability distribution: A mathematical function describing the probabilities associated with each value. (Source HTA Glossary)

Probabilistic analysis: Data parameters represented by statistical distributions rather than point estimates. (Source CADTH[18])

Probabilistic sensitivity analysis (PSA): A type of sensitivity analysis where probability distributions are applied to a plausible range of values for key parameters to capture uncertainty in the results. A Monte Carlo simulation is performed and a probability distribution of expected outcomes and costs is generated. (see also deterministic sensitivity analysis) (Source HIQA)

Productivity costs: The costs associated with lost or impaired ability to work because of morbidity or death. (Source HIQA)

Prospective study: A study to evaluate the effects of exposure to a given intervention or factor, in which the subjects are divided into groups that are exposed or not exposed to the intervention or factor of interest before the outcomes have occurred. (Contrast with retrospective study) (Source HTA Glossary)

Purchasing power parity (PPP): PPPs are currency converters that equalise price levels between countries. PPPs have been calculated by comparing the prices in OECD countries of a common basket of about 2500 goods and services. Countries are not required to price all the items in the common basket because some of the items may be hard to find in certain countries. However, the common basket has been drawn up in such a way that each country can collect prices for a wide range of the goods and services that are representative of their markets. (Source OECD[113])

Alternative definition: PPPs are the rates of currency conversion that try to equalise the purchasing power of different currencies, by eliminating the differences in price levels between countries. (https://www.oecd.org/en/data/indicators/purchasing-power-parities-ppp.html)

Quality of life: Quality of life is a broad, multidimensional concept of an individual's subjective evaluation of aspects of his/her life as diverse as physical, social, spiritual and emotional well-being, as well as possibly touching on others areas such as his/her environment, employment, education and leisure time. Within this wide-ranging definition HRQoL is used to refer to the impact a medical condition and/or treatment has on a patient's functioning and well-being. HRQOL is increasingly being measured in clinical trials alongside other outcome measures to evaluate the full range of effects of an intervention (e.g. a new medicine) from the patients' perspective. For instance, in oncology trials symptom burden may be measured in addition to survival and progression-free survival. (Source YHEC)

Quality-adjusted life year (QALY): A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. (Source NICE)

Alternative definition: The quality-adjusted life year is a summary outcome measure used to quantify the effectiveness of a particular intervention. Since the benefits of different interventions are multi-dimensional, QALYs have been designed to combine the impact of gains in quality of life and in quantity of life (i.e. life expectancy) associated with an intervention. In this case it is the incremental (i.e. differences between two or more alternatives) QALYs, compared with the incremental costs, that provides the measure of economic value. If a wide range of aspects (domains) of quality of life is included in the quality component, the resulting QALYs should be comparable across disease areas, which is valuable when considering broad-based resource allocation decision-making. More specifically, QALYs are based on utilities, which are valuations of HRQoL measured on a scale where full health is valued as 1 and death as 0. These valuations are the multiplied by the duration of time (in years) that a subject spends in a health state with that particular utility score, and aggregate QALYs are then summed over the subject's projected lifetime (or other time period corresponding to the time horizon of the analysis). For example, if someone experiences a health state with a utility of 0.8 for 10 years and then a health state with a utility of 0.5 for 5 years (and then dies), his/her aggregate QALYs will be (0.8×10) + (0.5×5) = 10.5 QALYs. QALYs are recommended by NICE as its preferred measure of health outcome for use in technology appraisals. (Source YHEC)

Randomisation: The random allocation of subjects of a clinical trial to the intervention and control groups using mechanisms such as a random number table or a computer-generated random number list. (Source HTA Glossary)

Randomised controlled trial (RCT): Trials in which participants (or clusters) are randomly allocated to receive either intervention or control. If well implemented, randomisation should ensure that intervention and control groups differ only in their exposure to treatment. (Source NICE)

Real-world data (RWD): Data collected during the routine delivery of health care. (Source HTA Glossary)

Alternative definition: Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD. Examples of RWD include data derived from electronic health records (EHRs);

medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, administrative and medical claims databases) can be used for data collection and, in certain cases, to develop analysis infrastructure to support many types of study designs to develop RWE, including, but not limited to, randomized trials (e.g., large simple trials, pragmatic clinical trials) and observational studies (prospective or retrospective). (Source FDA[117])

Reference case: Specifies the methods considered by KCE to be the most appropriate for performing and assessing economic evaluations and budget impact analyses when conducting HTA in Belgium.

General definition: A 'reference case' is used by some health technology assessment bodies to summarise their guidance to those making and assessing submissions for reimbursement. The reference case gives a formal statement of accepted methods and assumptions underpinning analyses to which submissions should conform. The purpose is to ensure a level of consistency between submissions and assessments of evidence. (see also base case) (Source YHEC)

Relative risk: Relative risk (RR), or risk ratio, is an estimate the magnitude of an association between an exposure and a disease, giving the likelihood of developing the disease on the exposed group compared with the unexposed. This is calculated as the ratio of the cumulative incidence of the disease in each group. In clinical trials this corresponds to the probability of developing the outcome of interest in the treatment group compared with (divided by) the equivalent probability in the comparison group. A relative risk of 1 means that there is no difference in risk between the groups compared, <1 (>1) means that the risk is lower (higher) in the treatment group. For relatively rare events relative risks are similar in magnitude to odds ratios, which have statistical properties that favour their use in meta-analyses. However risk models (that may form the basis of more complex economic models) often built on sets of relative risks associated with different risk factors for outcomes of interest. (Source YHEC)

Relative risk difference or reduction: A type of measure of treatment effect that compares the probability of a type of outcome in the treatment group with that of a control group, i.e.: (Pc - Pt) / Pc. For instance, if the results of a trial show that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the relative risk reduction would be: (0.25 - 0.10) / 0.25 = 0.6. (See also absolute risk reduction, number needed to treat, and odds ratio) (Source HIQA)

Retrospective study: A study in which the investigators do ex-post analysis of the outcomes in a group of subjects selected on the basis of their exposure to a given intervention or factor. Note: This type of study is more subject to bias than are prospective studies. Case-control studies are always retrospective, cohort studies sometimes are, and randomised controlled trials never are. (Source HTA Glossary)

Sample size: The number of patients studied in a trial, including the treatment and control groups, where applicable. In general, a larger sample size decreases the probability of making a false-positive error (α) and increases the power of a trial, that is, decreases the probability of making a false-negative error (β). Large sample sizes decrease the effect of random variation on the estimate of a treatment effect. (Source HIQA)

Sensitivity analysis: A means to determine the robustness of a mathematical model or analysis by examining the extent to which results are affected by changes in methods, parameters or assumptions. (Source HIQA)

Standard gamble (SG): A method of preference assessment used to measure utilities, that is, to ascertain an individual's preference for different health states that differ in quantity or quality of life. Preference is ascertained by choosing between a given health state, or gambling between perfect health and immediate death. The probability of perfect health or immediate death is changed until the



individual is indifferent between the health state and the gamble. (Compare with time trade-off) (Source HIQA)

Static model: Mathematical model in which the force of infection is assumed to be independent of the proportion of infectious people at each time point. Essentially this type of model assumes that vaccination does not infer herd immunity. (source WHO[57]) (see also dynamic model)

Statistical significance: A conclusion that a technology has a true effect, based upon observed differences in outcomes between the treatment and control groups that are sufficiently large so that these differences are unlikely to have occurred due to chance, as determined by a statistical test. Statistical significance indicates the probability that the observed difference was due to chance if the null hypothesis is true; it does not provide information about the magnitude of a treatment effect. (Statistical significance is necessary but not sufficient for clinical significance.) (Source HIQA)

Subgroup: A defined set of individuals in a population group or of participants in a study such as subgroups defined by sex or age categories. (Source HIQA)

Subgroup analysis: An analysis in which the intervention effect is evaluated in a subgroup of a trial, including the analysis of its complementary subgroup. Subgroup analyses can be pre-specified, in which case they are easier to interpret. If not pre-specified, they are difficult to interpret because they tend to uncover false positive results. (Source HIQA)

Surrogate outcome or surrogate endpoint: A surrogate outcome is an outcome that is intended to replace an outcome of interest that cannot be observed in a specific clinical study.[49] It is a variable that provides an indirect measurement of effect in situations in which direct measurement of a patient-centred effect is not feasible or practical.[50] A surrogate outcome may be a biomarker that is intended to substitute for a patient-centred outcome, or it may be an intermediate outcome. A surrogate outcome is expected to only predict the treatment effect of an outcome that is not observed in a clinical study. A biomarker is a surrogate which can be defined as a characteristic that is an objective measure of an indicator of normal biological processes, pathogenic processes or pharmacological responses to an intervention.[51] Examples of biomarkers used as surrogacy for mortality and/or morbidity and/or disease remission include levels of cholesterol, haemoglobin A1C (HbA1C), and antibody titre after vaccination. An intermediate outcome is a surrogate outcome such as a measure of a function or of a symptom (disease-free survival, angina frequency, exercise tolerance) but is not the long-term or final outcome of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction).[52] (Source HTA guidance[44])

Survival analysis: Survival analysis is an analytical method focusing on time-to-event data. Frequently the event is death (overall survival), but many other events can be considered in this way, such as disease progression/relapse, or event occurrence (for prevention). Survival analysis is typically used in oncology, where patient survival (death from any cause) and time-to-progression are often key endpoints of a clinical trial: the analysis frequently forms the basis of associated economic evaluations using (partitioned) survival models. The attraction of survival analysis for economic evaluation is that economic endpoints such as (gains in) life-years and quality-adjusted life years are represented as areas under the (quality-adjusted) survival curve. Health outcomes are considered longitudinally over time, and not cross-sectionally at a specific point in time. The Kaplan-Meier method provides a non-parametric representation of survival over the time period that data was collected, allowing for incomplete patient records where patients are lost to follow up (censoring). Parametric representations of survival, defined using a number of different statistical distributions, such as Weibull, Gompertz or exponential, allow for survival to be extrapolated beyond measured patient experience, important for economic modelling. (Source YHEC)

Systematic (literature) review: A review that summarises the evidence on a clearly formulated review question according to a predefined protocol, using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, analyse, collate and report their findings. It may or may not use statistical meta-analysis. (Source NICE)

Alternative definition: A form of structured literature review that addresses a question that is formulated to be answered by analysis of evidence, and involves objective means of searching the literature, applying predetermined inclusion and exclusion criteria to this literature, critically appraising the relevant literature, and extraction and synthesis of data from the evidence base to formulate findings. (Source HIQA)

Threshold analysis: The value of a parameter is varied to find the level at which the results changed, e.g. the level at which the cost per QALY gained reaches a pre-specified WTP threshold. (Source based on WHO[57])

Time horizon: The time period over which the main differences between interventions in effects and the use of resources in health and social care are expected to be experienced, taking into account the limitations of the supporting evidence. (Source NICE)

Time trade-off (TTO): A method of preference assessment used to measure utility. The utility value is measured by finding the point at which an individual is indifferent between two scenarios. That is, choices are provided to determine the length of time in an ideal health state that an individual would consider equivalent to a longer length of time with a specific condition. (Compare with standard gamble) (Source HIQA)

Tornado diagram: In economic evaluations tornado diagrams are used to present the result of multiple univariate sensitivity analyses on a single graph. Each analysis is summarised using a horizontal bar which represents the variation in the model output (usually an ICER) around a central value (corresponding to the base case analysis) as the relevant parameter is varied between two plausible but extreme values. Typically the horizontal bars are ordered so that with those with the greatest spread (i.e. parameters to which the model output is most sensitive) come at the top of the diagram, and those with the lowest spread at the bottom. The resulting diagram of stacked horizontal bars has a distinctive tornado shape. Tornado diagrams are used to help the reviewer assess which of the model's parameters have the greatest influence on its results. (Source YHEC)

Alternative definition: Diagrammatic display of the results of one-way sensitivity analysis; each bar represents the range of change in model results when the parameter is varied from its minimum to maximum values. (Source HIQA)

Transfer payment: Payment made to individual (usually by government body) that does not perform any service in return; examples are social security payments and employment insurance benefits. (Source HIQA)

Transferability: A trial, study or model has transferability if it can produce unbiased inferences to another specified healthcare system (for example, from another country to Belgium). (Source HIQA)

Uptake: In budget impact analysis, it is usual to compare a hypothetical future scenario (i.e. the approval of a new technology) against the counterfactual (i.e. no approval of the technology). Because it is rare for a new technology to be provided universally to all eligible patients, budget impact models usually make an assumption about the 'uptake' of the technology. This is usually characterised as the proportion of patients that would receive the technology in each consecutive year after its introduction. Often, the uptake may start slowly (with a low % of patients) and gradually increase over time. Careful consideration should be given to whether the new technology will only to new (incident) patients, to existing (prevalent) patients or to both. (Source YHEC)

Usual care: This is the most common or most widely used alternative in clinical practice for a specific condition. This is also referred to as 'routine care' or 'current practice' or 'typical care'. (Source HIQA)

Utility: A measure of the relative desirability or preference (usually from the perspective of a patient) for a specific health outcome or level of health status compared to alternative health states. A numerical value is assigned on a cardinal scale of 0 (death) to 1 (optimal or 'perfect' health). Health states considered to be worse than death may be assigned a negative value. (Source HIQA)

Alternative definition: In economic evaluation of healthcare interventions utilities (also called health state preference values) are used to represent the strength of individuals' preferences for different health states. When utility values are averaged over a population of responders they can be considered to be valuations of health states. Conventionally the valuations fall between 0 and 1, with 1 representing the valuation of a state of perfect health and 0 representing the valuation of death (non-existence). In some scoring systems a negative utility value is also possible, which indicates that a (very poor) health state is valued as less preferable than death. Sequences of utility values reported over periods of time for individual patients or cohorts of patients may be aggregated to derive quality-adjusted life years, commonly used as outcomes in economic evaluation. Several methods are used to obtain health state preference values (utilities). Direct methods involve individuals being asked to describe and assess health states and place weights on them, using techniques such as Standard Gamble or Time Trade-off. Indirect methods involve the use of generic multi-attribute scoring systems to classify health states according to a number of distinct domains. Utility tariffs for health states described in this way are derived from population surveys. Study subjects are asked to describe their health status at different time points using these systems, and their responses are converted to utilities by using the appropriate tariff. Generic multi-attribute scoring systems are preferred to disease-specific ones as they cover general aspects of health and can facilitate comparisons across different disease areas. The most commonly used multi-attribute utility instrument is EQ-5D (preferred by UK NICE), which has domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. (Source YHEC)

Validity: The extent to which a technique measures what it is intended to measure. (Source HIQA)

Value for money: See cost effective

Value of information (VOI) analysis: When used in health technology assessment, value of information (VOI) analysis is an umbrella term referring to the estimation of the value, in terms of cost and health outcomes, of collecting more data/information on key parameters influencing a decision, for example reimbursement of a new technology. Typically this is most useful where the output of an economic evaluation (e.g. incremental cost-effectiveness ratio (ICER)) is uncertain, yet close to a decision threshold (willingness to pay), and a key parameter on which the output is based is itself uncertain. As such, new information reducing uncertainty in that parameter will increase the chance of the correct decision being made, and the 'value' of this information is a function of how likely it would enable a decision to be made or changed. The usefulness of collecting information on parameters that have high certainty, or those which have a small bearing on the output of the economic evaluation, is likely to be low. VOI analysis may be particularly useful in assessing whether a further, expensive, study is likely to yield helpful results (e.g. of effectiveness). VOI analysis may be performed using conventional economic models as long as probabilistic sensitivity analysis is included. Common outputs of VOI analysis are the Expected Value of Perfect Information (EVPI), Expected Value of Partially Perfect Information (EVPPI) and Expected Value of Sample Information (EVSI). (Source YHEC)

Visual analogue scale (VAS): The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement. (Source Euroqol.org)

Alternative definition: A tool used to help a person rate the intensity of certain sensations and feelings, such as pain. The visual analogue scale for pain is a straight line with one end meaning no pain and the other end meaning the worst pain imaginable. A patient marks a point on the line that matches the amount of pain he or she feels. It may be used to help choose the right dose of pain medicine. (Source https://www.cancer.gov/publications/dictionaries/cancer-terms)

Willingness-to-pay: Willingness-to-pay (WTP) is the valuation of health benefit in monetary terms, often so that this can be used in a cost-benefit analysis. The term WTP may also refer to survey techniques used to derive WTP valuations. However in many health care system patients do not make

direct purchasing choices for much of their care, and so WTP are not frequently used except in certain situations (e.g. waiting times, access arrangements to care, types of care usually obtained through direct payment) where monetary valuations may be more straightforward to make. One commonly used WTP valuation method is contingent valuation, where individuals are asked to compare different hypothetical situations about the intervention under investigation. For example, they could be asked to state their WTP for IVF treatment when presented with different probabilities of success. (Source YHEC)

Willingness-to-pay threshold: See cost-effectiveness threshold

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