eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

GUIDELINE

Methods for health economic evaluations

- *A guideline based on current practices in Europe*

May 2015

The primary objective of EUnetHTA JA2 WP 7 methodology guidelines is to focus on methodological challenges that are encountered by HTA assessors while performing relative effectiveness assessments of pharmaceuticals or other health technologies.

As such the guideline represents a consolidated view of non-binding recommendations of EUnetHTA network members and in no case an official opinion of the participating institutions or individuals.

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Acronyms - Abbreviations

BIA	budget-impact analysis
CBA	cost-benefit analysis
CCA	cost-consequences analysis
CE	cost-effectiveness
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CE plane	cost-effectiveness plane
CI	confidence interval
CMA	cost-minimization analysis
CUA	cost-utility analysis
DSA	deterministic sensitivity analysis
EQ-5D	EuroQol 5 dimensions
EVPI	expected value of perfect information
HRQoL	health-related quality of life
HTA	health technology assessment
HUI	health utilities index
HYE	healthy-years equivalent
ICER	incremental cost-effectiveness ratio
LYG	life-years gained
MAUI	multi-attribute utility instrument
NMB	net-monetary benefit
PPP	purchasing power parity
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life years
QoL	quality of life
REA	relative effectiveness assessment

SF-6D	short-form 6 dimensions
SG	standard gamble
TTO	time trade-off
VAS	visual analogue scale

Summary and table with main recommendations

The work with the present guideline was initiated to set a general framework for EUnetHTA on how to conduct economic evaluations as well as to increase the transferability of economic evaluations among EUnetHTA partners. This is especially important in order to enhance the usefulness of economic evaluations conducted within EUnetHTA. A common guidance document may also be useful for countries that do not have a methodological guideline for health economic evaluations. The target group of the guideline is represented by health economists and health technology assessors in Europe, who either review economic evaluations that have been performed by others, or who perform de novo economic evaluations themselves, within projects of EUnetHTA.

In order to make health economic evaluations as useful and transferable as possible to the collaborating and associated partners of EUnetHTA (henceforth called partners), there is a need to explore the similarities and differences between the methods used by these partners. Hence, this guideline is based on a review of methodological guidelines developed by the partnerss of EUnetHTA. The response rate among the 33 countries that the EUnetHTA partners represent was 100 percent. Thus, this review gives a complete picture of the current methodological guidelines used by the countries involved in EUnetHTA. However, only 25 countries reported having some kind of methodological guideline for health economic evaluations. Guidelines for health economic evaluations regarding pharmaceuticals were most common, but some countries also have guidelines for other types of health interventions (e.g. diagnostics and medical devices), and some countries have general guidelines that apply to any type of health interventions.

By comparing the different viewpoints of the EUnetHTA partners, it was possible to identify several methodological issues for which the partners have a common view. Based on these commonalities, recommendations for economic evaluations within EUnetHTA could be formed. This was deemed possible for topics such as the time horizon of the analysis, presentation of results, and use of decision models. On issues where not all partners were in agreement, it was in some cases still possible to form recommendations on how to facilitate the exchange of results of economic evaluations between European countries. These recommendations include for instance the choice of outcome measure, perspective of the analysis, presentation of data on resource use, and how to analyse the uncertainty related to the results.

The review also identified various aspects for which no common view could be found. For example, the EUnetHTA partners have different views on the acceptability of some outcome measures, costs to be included, the rates for discounting costs and effects, as well as on the methods for deriving health-related quality of life (HRQoL) weights for calculation of quality-adjusted life years (QALYs). A more thorough examination of these issues would therefore be of value to EUnetHTA. In such examinations, current methodological guidelines issued by organisations such as ISPOR could be helpful.

In conclusion, the content of this guideline will hopefully improve the usefulness of economic evaluations performed within EUnetHTA and also constitute an important step towards a common European view on conducting health economic evaluations. Nevertheless, there are still methodological issues that need to be investigated further.

The main recommendations presented in Table 1 represent methodological issues where the guidelines of the EUnetHTA partners either are in agreement or where the usability of

the evaluations may be increased by presenting the results in a specific way, even if no agreement can be reached.

Table 1. Main recommendations

	Recommendation	References
1	**Type of analysis** Health economic evaluations may be conducted for all types of health care interventions. To enhance the usability of the economic evaluations, it is recommended that results be presented in terms of both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). A cost-minimization analysis (CMA) is sufficient when it is demonstrated that there is no difference in effect between an intervention and its relevant comparators. If appropriate and adequately justified, a cost-consequence analysis (CCA) may be a useful alternative in cases where CEA and CUA cannot be undertaken.	Section 2.3.3, page 29-31
2	**Sources for clinical effectiveness** It is recommended that the clinical evidence is collected by a systematic review of the literature. The clinical evidence should be based on the most appropriate sources, which in most cases is considered to be RCT studies. If no RCT studies have been carried out or cannot answer the research question on the intervention under consideration, other sources may be acceptable depending on the type of technology under consideration. The quality of all sources needs to be assessed and reported.	Section 2.3.7.1, page 36-37
3	**Time horizon** The primary time horizon for the reference case analysis should be sufficiently long to reflect all important relevant differences in costs or outcomes between the technologies being compared. The choice concerning any alternative time horizon for the reference case analysis should be clearly justified and described.	Section 2.3.2, page 28-29
4	**Use of models** The use of decision models is recommended. However, modelling should always be justified and be presented as transparently as possible so that it can be reproduced. The choice of appropriate modelling technique should depend on the research question. When data are extrapolated beyond the duration of the clinical trials informing the economic model, all assumptions need to be clearly presented and analyzed using different scenarios. Providing an electronic version of the model to users could further enhance its transparency and usefulness.	Section 2.3.4, page 31-33

5	**Perspective of the analysis** Economic evaluations should at minimum be conducted from a health care perspective. However, several countries require a societal perspective. Presenting the use of resources as related to other sectors of society may increase the usefulness of the analysis to more EUnetHTA partners. Regardless of perspective taken, it is recommended that the use of resources is presented in as detailed a manner as possible. For example, if a societal perspective is used, indirect costs should be presented separately.	Section 2.3.5, page 33-34
6	**Costs** To facilitate adjustments of costs to local settings, it is recommended that the use of resources is clearly presented in natural units, e.g. hospital days or physician visits.	Section 2.3.6.2, page 36
7	**Outcome measures** The primary outcome measure(s) should where appropriate be presented as natural units (including life-years) and as QALYs.	Section 2.3.7.3, page 39-40
8	**Discounting** Most countries use a discount rate between 3 to 5 percent for both costs and effects. It is recommended that both costs and effects are discounted in the base case analysis with the same rate. Furthermore, sensitivity analyses that explore the effect of varying the discount rate and differential discount rates (that is a lower discount rate for benefits than costs) should be performed; setting both discount rates to zero is also recommended.	Section 2.3.9, page 46-47
9	**Presentation of results** In a CEA or CUA, results should be presented in terms of absolute and incremental values, separately for both costs and health outcomes, and in terms of incremental cost-effectiveness ratios (ICERs).	Section 2.3.11, page 49-50
10	**Uncertainty** Uncertainty should be explored in sensitivity analyses. To meet the preferences of the majority of the countries, deterministic as well as probabilistic sensitivity analysis should be conducted.	Section 2.3.12, page 50-51

1. Introduction

1.1. Definitions of central terms and concepts

This section describes the central terms and main concepts used within this report to describe the features of economic evaluations. The terms are presented in the order they normally appear when conducting an economic evaluation. Parts of the text are based on, or loaned from, the Costs and economic evaluation (ECO) domain of the HTA Core Model® (1) and have been reproduced here with the authors' permission. Some of the original text has been edited to better suit the purpose of this document.

1.1.1. Intervention

The term intervention refers to the index intervention that is being compared to one or more comparators in the economic evaluation. The intervention can be diagnostic, surgical, medical, behavioural or complex, and include pharmaceuticals and medical devices.

1.1.2. Comparator

The term comparator(s) refers to all interventions, or scenarios, that the index intervention is being compared with. To do nothing may also be a comparator in some cases.

1.1.3. Indirect comparisons

When searching for data on health effects, several studies may be identified. These studies do not always contain head-to-head comparisons of all interventions of interest. In these cases, indirect treatment comparisons can be used to infer the relative efficacy or effectiveness of two or more treatments through the combination of direct and indirect evidence (2). The comparisons based on the combined studies form a network of evidence, enabling comparisons that otherwise would not have been feasible. For example, an indirect comparison may be relevant if there are no studies that directly compare treatment A with treatment B but there are studies that compare each of the two treatments with placebo. Since both treatments are compared to placebo, an indirect comparison of treatment A to treatment B can be made via the individual comparisons to placebo.

1.1.4. Perspective of the analysis

The chosen perspective of an economic evaluation is a key element in defining which costs and consequences are included in the analysis (3). For instance, the choice of perspective affects the way direct and indirect costs are handled (e.g. productivity losses). The most comprehensive perspective is the societal perspective, where all relevant costs and outcomes of the technologies have to be identified, measured and valued, no matter on whom these costs and consequences fall. Other possible perspectives include those of a specific institution, individual patients, or the target group for a specific technology. A health care perspective means that all costs and outcomes related to the health care sector are included in the analysis.

1.1.5. Time horizon

An important consideration is the choice of the time horizon, i.e. the time span for which costs and effects should be measured or estimated. The length of the time horizon may depend on the perspective of the economic evaluation, which may extend to the expected remaining lifetime of the patients or population under investigation, or even into future generations.

1.1.6. Types of economic evaluation

Five main types of economic evaluation can contribute to HTA: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-minimisation analysis (CMA) and cost-consequences analysis (CCA). However, it is known that these terms are used in various ways by different authors and do not always accurately describe the nature of published studies (3). The difference between them is based on how health outcomes are measured and valued and whether they are commensurable or not. It should also be noted that a combination of more than one type of analysis can be useful (3).

1.1.6.1. Cost-effectiveness analysis (CEA)

Cost-effectiveness analysis (CEA) is traditionally associated with the economic concept of technical efficiency. CEA compares the costs and effects of at least two alternative technologies. The effects of the different technologies are usually measured using unidimensional final (e.g., life-years gained) or surrogate outcomes (e.g., progression-free survival), providing information on the ‘greatest effect for a given cost’, or alternatively, one that achieves a ‘given effect at minimum cost’ (4). Since it may imply that different disease areas use different natural units (or metrics) to measure outcomes, it is a potential disadvantage of CEA that the results are not comparable between disease areas in the same way as they are in cost-utility analysis (CUA).

1.1.6.2. Cost-utility analysis (CUA)

Cost-utility analysis (CUA) is a form of CEA which uses health-related outcomes that share many of the characteristics of ‘utility’ (4). The most common form of CUA can also be referred to as cost-per-QALY analysis. CUA uses health-state-value scores as a measure of outcome which, conceptually, allows the measurement and comparison of different outcomes with the same metric (e.g., QALY (Quality-Adjusted Life Year) or DALY (Disability-Adjusted Life Year)). The term ‘cost-utility analysis’ is widely used, but should be used in the knowledge that, here, ‘utility’ refers to a valuation of health-related outcome.

1.1.6.3. Cost-benefit analysis (CBA)

Cost-benefit analysis (CBA), in the form of comparative analysis of costs and money-valued benefits, is currently not widely used as a type of health-economic evaluation (4). One main reason for its limited use is the problems associated with unbiased and precise estimates of benefits required for its successful application. The methodology of economic valuation of such benefits is advancing, but numerous methodological uncertainties and problems remain (5).

1.1.6.4. Cost-minimisation analysis (CMA)

Cost-minimisation analysis (CMA) can be conducted if the technologies under comparison can be assumed to have the same desired effects (benefits) and undesired effects (risks/harms) (4). The appropriateness of conducting CMA has been questioned, in part due to its assumption(s) that the effects of the technologies being compared are equivalent (6). If measured or hypothesised differences between the technologies in outcomes cannot

be adequately distinguished, then CCA, CEA or CUA with sensitivity analysis could be more useful (7).

1.1.6.5. Cost-consequences analysis (CCA)

Cost-consequences analysis (CCA) examines costs and consequences, without the necessity of focusing on a single consequence and without combining disparate consequences into a single, commensurable measure (see, e.g., (4), (8) and (9)). It has been classed both as a variant of CEA (3) and as a balance sheet approach to CBA (10). It can be used to enhance reporting transparency (11) and it can be especially useful when the outcomes are not adequately measured. This approach may be preferable to CEA or CUA by policy makers when multiple consequences are to be weighed together simultaneously.

1.1.7. Budget impact analysis

The purpose of economic evaluation is different from the objective of a budget impact analysis (BIA). Economic evaluations attempt to provide information about the most economically efficient ways to utilise or allocate available health-care resources. BIA, on the other hand, estimates the financial and organisational consequences of adopting a new health care technology without directly taking health consequences into account.

1.1.8. Costs

Cost items may be classified in numerous ways, such as the costs of health-care technologies that are borne by the health-care sector, other sectors and patients and families. Time, productivity or wider-economic costs can also be classified separately. The inclusion or exclusion of cost items may depend upon chosen perspective or analytical approach.

1.1.8.1. Direct costs

Direct costs can include all costs directly related to a disease or technology. They may include costs borne inside the health-care sector (e.g., materials, equipment, personnel and services – often referred to as direct health-care costs) as well as outside the health-care sector (e.g., patients’ travel time – often referred to as direct non-health-care costs). A broad agreement exists, on a theoretical level, that all costs related to the disease or technology in question should be included in the analysis.

1.1.8.2. Indirect costs

Indirect costs can include temporary absence from work due to illness, reduced working capacity due to illness and disability, or lost productivity due to early death. The most common methods for estimating these costs are the human capital method and the friction cost method (3).

1.1.9. Outcome measures

There is a wide range of outcome measures that can be used in economic evaluations. However, the choice of outcome measure is closely related to the chosen type of analysis. The selection depends, to a large extent, on the purpose of the information being produced, with different recommendations existing in different jurisdictions or health-care systems (1). The suitability of using one or more health-outcome measures also depends on the type of technology that is being analysed, as well as on the plausibility that it appropriately describes relevant aspects of health. Health outcomes may be measured,

estimated or valued as changes in clinical indicators, number of health-related events (e.g., cases of diseases or deaths), QALYs or any other effects which could be deemed important to decision makers.

1.1.9.1. Quality-adjusted life years (QALYs)

One of the most widely-used forms of health outcomes is the composite measures referred to as quality-adjusted life years (QALYs). QALYs refer to a type of outcome measure that takes into account both aspects of the quantity (longevity/mortality) and the health-related quality of life (HRQoL, e.g. morbidity, psychological, functional, social, and other factors) (12). QALY approaches can be considered as an important set of health outcomes when technologies affecting a wide range of medical conditions are being compared.

The HRQoL aspects of the QALY are captured in a HRQoL weight. The derivation of HRQoL weights for calculation of QALYs can be made indirectly by the use of specific pre-scored questionnaires and/or through direct elicitation using methods such as a visual analogue scale (VAS), standard gamble (SG) or time trade-off (TTO).

The indirect methods are based on generic multi-attribute health state questionnaires that are usually completed by patients. The index scores, or HRQoL weights, are derived by using pre-scored value sets that have been elicited using one or several of the direct methods. The generic multi-attribute instruments include the EQ-5D (EuroQol), HUI (Health Utilities Index Mark II/Mark III), SF-6D (based on a selection of questions from the SF-36), 15D, QWB (Quality-of-Well Being Scale) and AQoL (Assessment of Quality of Life) (1). A direct method is one which values health states without using the intermediary of a questionnaire. The most common methods include SG, TTO and VAS, but related methods include person trade-off (PTO) and discrete choice experiments (DCE). In most of the direct methods, the utility of a health state or intervention is derived by asking respondents to make choices between alternative situations, or to indicate a relative value.

1.1.9.2. Intermediate/surrogate outcome measures

A surrogate or intermediate outcome measure is an outcome measure that does not represent the final goal of using an intervention but has an association with the final outcome measure and may be used as a proxy for the final outcome measure in clinical trials (13). For example, a surrogate for an intervention’s effect on myocardial infarction could be the effect on a patient’s blood cholesterol level. In health economic evaluations, surrogate outcome measures may be used as the main outcome measure in a CEA, or as a point of departure in a decision model where an intervention’s effect on the surrogate (intermediate) outcome measure is extrapolated to the effect on final endpoints, such as life years or QALYs.

1.1.9.3. Willingness-to-pay (WTP) and contingent valuation

To express the benefits in monetary units, such as in a CBA, there are three general approaches; human capital, revealed preferences and stated preferences of willingness-to-pay (WTP) (3). In the latter, which is also known as contingent valuation, respondents are asked to reveal the maximum they would be willing to pay for an intervention or a benefit.

1.1.10. Cost-effectiveness

Whether a technology can be referred to as ‘cost effective’ depends on its relation to the ‘decision-makers’ willingness-to-pay’ or the ‘societal willingness-to-pay’ for an additional unit of health outcome, or a so-called ‘ICER threshold’ or ‘cost-effectiveness threshold’. If one main aim of a health system is to maximize health-related outcomes given the

resources available, a technology can be considered as being ‘cost effective’, i.e., improving economic efficiency in health care, if its ICER is lower than a threshold value (or threshold range). If the estimated ICER is higher than the threshold, the technology is not considered to be cost effective and hence allocation of resources to this technology would be unlikely to increase economic efficiency in health care (14). It is recognized that a single ICER threshold value that fits all decisions for any decision-maker, does not exist. For some decision-making authorities, the ICER threshold may vary between technologies or diseases, depending on characteristics of the technology or disease that are not necessarily directly reflected in ICER estimates (15). The perspective of the analysis is another important factor influencing the threshold value. However, it is rare that the decision-making authorities have explicit thresholds.

1.1.11. Results of the economic evaluations

How to present the results of an economic evaluation is associated with the type of economic evaluation used, i.e., CCA, CEA, CUA, CMA, CBA or a combination of these. One or more of the approaches below are used when reporting the results of health economic evaluations.

1.1.11.1. Incremental cost-effectiveness ratio (ICER)

An ICER represents the estimated difference in costs between the intervention and the comparator divided by the estimated difference in effect between the intervention and the comparator. In an example where the effect is measured in life years, the estimated ICER could be reported as the cost per life-year gained (16). If the effect is measured in QALYs (using CUA), the estimated ICER would be reported as the cost per QALY gained.

1.1.11.2. Cost-effectiveness plane (CE plane)

The cost-effectiveness (CE) plane is a four quadrant diagram in which, by convention, the vertical axis represents the difference in cost between two interventions and the horizontal axis represents the difference in effect (16).

1.1.11.3. Cost-effectiveness acceptability curve (CEAC)

Given the observed data or evidence, a cost-effectiveness acceptability curve (CEAC) shows the probability that an intervention is cost-effective compared to its comparator or comparators (3), at different cost-effectiveness thresholds. The vertical axis of the diagram represents the probability that the intervention is cost-effective and the horizontal axis represents different CE thresholds. The curve shows the percentage of the simulated ICERs in the CE plane that are lower than any specific threshold.

1.1.12. Model-based economic evaluation

As all relevant evidence needed for an economic evaluation is rarely available from a single source, decision-analytic modelling provides a framework for synthesizing data from various sources, considering all relevant comparators, adopting sufficiently long time horizons and taking uncertainty into account (17). In the context of economic evaluation, a decision-analytical model has been defined as a model that “uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated” (17).

Decision-analytic modelling can be conducted using, e.g., decision trees, Markov models (cohort state-transition models), microsimulation or first-order Monte Carlo-models

(individual-based state-transition models), discrete-event simulation, dynamic transmission models, or combinations of these (see, e.g., (18) or (19)). For technical details on the use of models for economic evaluation a number of general textbooks have been published (for example, (17, 20),(21),(22),(23)). In addition, ISPOR has published a series of articles that relate to the application of modelling techniques to the area of health-care decision making. These articles cover the following topics: conceptualising a model (24), state-transition models (25), discrete event simulations (26), dynamic transmission models (27), parameter estimation and uncertainty (19), transparency and validation (28).

1.1.13. Discounting

Economic theory suggests that costs and outcomes that occur in the future should be discounted (see, e.g., (3), (29), (30) and (31)). Discounting, i.e. calculating the present values of future costs and consequences, may help in the comparison of health technologies whose costs and outcomes do not occur at the same time. The decisions to be made are: whether to discount both costs and effect or not; which discount rate to use; and should both costs and effects be discounted using the same discount rate? The impact of discounting in economic evaluation is often substantial and this means that the questions related to discounting need to be carefully examined.

1.1.14. Characterizing uncertainty

In economic evaluation, there are numerous sources of uncertainty and these can be characterised in different ways. In decision-analytic models, uncertainty is commonly classified into stochastic uncertainty, parameter uncertainty, heterogeneity and structural uncertainty (19). However, these terms are used in a variety of ways by different authors. In an attempt to avoid such confusion, it has been recommended that authors carefully define the terminology that they use when reporting their results (19).

Methodological uncertainty is a specific type of uncertainty that relates to methodological choices that are part of economic evaluation (32). These include the study perspective, discount rate(s), time horizon, the way health effects are valued, and so on

Stochastic uncertainty refers to random variability in outcomes between identical patients (19). It has also been called first-order uncertainty or variability.

Structural uncertainty refers to uncertainty about the extent to which a model adequately captures the relevant characteristics of the health condition and technology under evaluation (33). Structural uncertainty has also been called model uncertainty

Parameter uncertainty usually refers to uncertainty in the estimation of the parameter(s) of interest (19). Parameter uncertainty has also been called second-order uncertainty.

Heterogeneity relates to variability between patients that can be attributed to the observed characteristics of those patients (19). Heterogeneity has also been called variability.

1.1.15. Sensitivity analysis

Many forms of uncertainty can be usefully investigated either using deterministic (DSA) or probabilistic sensitivity analysis (PSA). There are various types of DSA; one-way

sensitivity analysis, multi-way analysis, scenario analysis and threshold analysis, which can complement PSA approaches.

1.1.15.1. One-way sensitivity analysis

In this type of sensitivity analysis, the impact of each parameter on the results is analysed by varying the parameters one at a time (3).

1.1.15.2. Multi-way sensitivity analysis

In this type of sensitivity analysis, various parameters are varied at the same time to analyse how the combinations of variations affect the results (3).

1.1.15.3. Scenario analysis

In this type of sensitivity analysis, a series of scenarios are based on subsets of potential multi-way analyses (3). For example, the scenarios may represent the best guess scenario, the most optimistic scenario and the most pessimistic scenario.

1.1.15.4. Threshold analysis

In this type of sensitivity analysis, the critical value/s of a parameter or parameters is identified (3). The critical value is defined as the value for which the conclusion of the analysis would change, e.g. no longer be considered cost-effective.

1.1.15.5. Probabilistic sensitivity analysis (PSA)

In a probabilistic sensitivity analysis (PSA), each input parameter is assigned a specific sampling distribution. The choice of distribution depends on the type of parameter (e.g. transition probabilities, utility, costs, etc.), its nature (discrete or continuous), the statistical variability surrounding the parameter, and the available literature on the previous elements. A value from each parameter’s distribution is then randomly drawn (often using Monte Carlo simulation) and an ICER is calculated for the combinations of parameter values. This procedure is repeated a predefined number of times (e.g. 1 000, 10 000 times). The distribution of the ICERs of the repeated samples represents an empirical distribution of the results of the analysis.

1.1.16. Expected value of information (EVI)

The underlying concept of expected value of information (EVI) is the comparison of prior and posterior information given additional information. The expected value of perfect information (EVPI) represents a “notional maximum value of further research against which cost of undertaking a particular study can be compared. The overall measure of EVPI represents the expected cost of uncertainty relating to all input parameters in a decision model” (3).

1.1.17. Net-monetary health (NHB) and net-monetary benefit (NMB)

The net health and net monetary benefit (NHB and NMB) approaches provide a framework to display uncertainty in cost-effectiveness analysis (34, 35) and they can also be of help in the interpretation of the ICER. The NMB rescales QALYs to money (healthcare resources), requiring the adoption of the new technology if: $(\lambda * QALYs) - C > 0$ where λ is the ICER threshold, and C costs. Alternatively, the NHB can be used: $QALYs - (C / \lambda) > 0$.

1.2. Problem statement

The available health care resources are not sufficient to cover all possible health technologies. In order to make well-informed decisions on which technologies to use, the choices between different alternatives can be supported by health technology assessment (HTA). In addition to relative effectiveness in terms of health benefits and harms, HTA covers assessment of the technologies' legal, social, organizational, economic and ethical aspects. Economic evaluations are an important part of the European cooperation on HTA within EUnetHTA and economic aspects constitute one of the nine domains in the EUnetHTA CORE model.

There are several theoretical and methodological texts concerning health economic evaluations, see for example (3, 36, 37). Based on these, or on other considerations, many countries have developed their own methodological guidelines. Although they share a common base, these guidelines may differ between jurisdictions. Decision makers in different countries may for example have different views on the purpose of conducting economic evaluations, what resources and costs to take into account, how to estimate the value of clinical or health outcomes, what economic model structures are the most appropriate, or how country-specific resource use and costs should be estimated. Some of these differences can be explained by different political contexts, the organisation of the health care system, or specific population characteristics. Nevertheless, some differences are rather explained by the lack of consensus on strictly methodological issues, for which there is no clear reason for regional variations. There is currently no explicit methodological guideline for economic evaluations within EUnetHTA, apart from some general recommendations related to the CORE model. Therefore, it is up to the individual authors of the economic evaluation to decide what methods to use. Since the CORE model is developed to produce HTA reports that can be used in several countries, it is important that the produced information meets the need of the HTA agencies/decision makers in these different countries.

In order to make health economic evaluations as useful as possible to the collaborating partners of EUnetHTA, there is a need to explore the similarities and differences between the methods of economic evaluation used by the EUnetHTA partners. In addition, by identifying the commonalities in the context-specific guidelines, it is possible to develop a common framework for how to conduct economic evaluations in Europe in a way that makes the evaluations useful to as many countries as possible. Furthermore, this framework may constitute guidance for countries that do not yet have a guideline. Identifying discrepancies may also guide authorities in different countries in their assessment of evaluations undertaken in other contexts, and highlight issues where there is a need for further analysis before a European recommendation can be issued.

1.3. Objective(s) and scope of the guideline

The purpose of this guideline is to set a general framework for EUnetHTA on how to conduct economic evaluations and increase the transferability of economic evaluations between EUnetHTA partners. The target audience of this guideline is health economists and health technology assessors, who either perform de novo economic evaluations themselves or review others' economic evaluations. The recommendations in the guideline are primarily formulated for the work within EUnetHTA, but can also be used by individual partners to help facilitate the exchange of results between European countries. The purpose of the present guideline can be divided into the following two points:

1. To increase the knowledge about similarities and differences between guidelines for health economic evaluations, used in European countries,
2. To develop a common framework for the methodology of economic evaluations for EUnetHTA based on the identified commonalities.

The focus of this guideline is to improve the transferability of results from economic evaluations and, apart from what is previously written in already existing EUnetHTA documents, it does not take a standpoint on different theoretical perspectives. Thus, it does not take any stand on which methods are the most appropriate. Rather, it gives guidance on how economic evaluations can be conducted to make the results useful and relevant for various European countries. The underlying review of guidelines is limited to methodological guidelines for health economic evaluations.

1.4. Related EUnetHTA documents

The following EUnetHTA documents, most of them methodological guidelines, are relevant for the present guideline:

- EUnetHTA JA2 WP 8, Work Package 8. HTA Core Model® (version 2.0 PDF); 2013 (1)
- EUnetHTA JA2 WP4, Methodological Standards and Procedures (MSP) for core HTA content development, Domain specific issues: Costs, economic evaluation of the technology (ECO), 2014 (38)
- EUnetHTA JA1 WP5, Comparator and comparisons - Direct and indirect comparisons, 2013 (2)
- EUnetHTA JA1 WP5, Comparator and comparisons - Criteria for the choice of the most appropriate comparator(s). Summary of current policies and best practice recommendations, 2013 (39)
- EUnetHTA JA1 WP5, Endpoints used for relative effectiveness assessment of pharmaceuticals: Health-related quality of life and utility measures , 2013 (40)
- EUnetHTA JA1 WP5, Endpoints used in REA of pharmaceuticals: surrogate endpoints, 2013 (41)
- EUnetHTA JA1 WP5, Endpoints used in REA of pharmaceuticals: clinical endpoints, 2013 (42)
- EUnetHTA JA1 WP5, REA of Pharmaceuticals, Background review, 2011 (43)

Some of the methodological issues covered by this guideline have been discussed in previous work by EUnetHTA. For example, questions concerning choice of comparator and indirect comparisons have been covered by previous EUnetHTA guidelines developed by JA1 WP5. However, previous work has focused on how to handle these issues in relative effectiveness assessment (REA), while the present guideline deals with these issues in the context of conducting health economic evaluations. To avoid contradictions, the recommendations from previous EUnetHTA guidelines will be summarized in relation to the relevant issues.

A previous EUnetHTA JA 1 WP5 project (43) has performed an overview on methods for REA. Even though the content of this overview is related to the present review of guidelines, they differ in purpose and scope. The present review specifically covers methods for health economic evaluations of all types of technologies, while the former focuses on methods for REA of pharmaceuticals. The methods covered by these two guidelines will in some cases be the same, but the overviews are based on different documents and have different purposes, and may therefore come to different conclusions.

1.5. Other related documents

To find related guidelines from other organisations, the ISPOR Guideline Index for Outcomes Research and Use in Health Care Decision Making was reviewed. The following guidelines were considered related to the methodological issues covered by this guideline:

- European Medicines Agency (EMA). Guideline on the investigation of subgroups in confirmatory clinical trials, 2014 (44)
- Petrou et al. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting, 2011 (45)
- Ramsey et al. Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report, 2005 (46)
- Caro et al. Modeling Good Research Practices - Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1, 2012 (19)
- Roberts et al, Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-2, 2012 (24)
- Siebert et al. State-transition modelling: A report of the ISPOR-SMDM Modeling good research practices task force-3, 2012 (47)
- Karnon et al. Modeling using discrete event simulation: A report of the ISPOR-SMDM Modeling good research practices task force-4, 2012 (26)
- Pitman et al. Dynamic Transmission Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-5, 2012 (27)
- Briggs et al. Model parameter estimation and uncertainty: A report of the ISPOR-SMDM Modeling good research practices task force-6, 2012 (48)
- Eddy et al. Model transparency and validation: A report of the ISPOR-SMDM Modeling good research practices task force-7, 2012 (28)
- Marshall et al. Applying dynamic simulation modeling methods in health care delivery research – The SIMULATE checklist: An ISPOR simulation modeling emerging good practices task force report, 2015 (49).
- Petrou et al. Economic evaluation using decision analytical modeling: design, conduct, analysis, and reporting, 2011 (18)
- ISPOR, Interpreting indirect treatments comparisons and network meta-analysis for health-care decision-making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1, 2011 (50)
- ISPOR, Conducting indirect treatments comparisons and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2, 2011 (51)
- ISPOR, Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: An ISPOR-AMCP-NPC Good Practice Task Force Report, 2014 (52)
- Shi et al. Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses: An International Perspective: The ISPOR Drug Cost Task Force Report—Part VI, 2010 (53)
- Husereau et al. Consolidated health economic evaluation reporting standards (CHEERS) statement, 2013 (54)
- WHO, WHO guide for standardization of economic evaluations of immunization programmes, 2008 (55)
- More guidelines can be found on:
    - ISPOR, Guideline Index for Outcomes Research and Use in Health Care Decision Making, Available at: http://www.ispor.org/GuidelinesIndex/Default.aspx#HEEFM

- EMA, Scientific guidelines. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb

Concerning the guideline on investigation of subgroups in confirmatory clinical trials by the European Medicines Agency (44), the recommendations on subgroup analysis for clinical trials may be similar but do not necessarily have to be the same as for health economic evaluations.

1.6. Methods for developing the guideline

This guideline was developed in a stepwise approach, starting with the collection of methodological guidelines for health economic evaluations used by EUnetHTA partners. Existing guidelines were listed based on ISPOR´s collection of country-specific pharmaco-economic guidelines (56) and other published scientific sources. This list was sent to contact persons of all EUnetHTA partners, together with questions concerning the current use of the document(s). For instance, they were asked if the listed guidelines were the latest version available or if any other relevant guidelines were being used in their region, and if those documents were available in English (see Annexe 6). Personal contacts and authors of relevant published papers were also contacted when no answer was received from any of the partners in a country. Each country may be represented in EUnetHTA by several organisations. Since policies for health care decisions are often made on a national level, the guidelines were grouped according to the country they represent, and regional differences were only indicated when relevant.

Once the relevant guidelines had been collected, each partner of the draft group was asked to extract information from guidelines from a number of countries. To facilitate the process of extracting the relevant information from the guidelines, a template for extraction of data was developed (see Annexe 7). This template was developed based on items from a few examples of the partner guidelines (12, 57), the topics covered in ISPOR´s collection of country-specific pharmaco-economic guidelines (56), issues included in the CHEERS statement (54), and the checklist for economic evaluations provided by Drummond et al (58). The template was reviewed by the draft group and modified accordingly.

Before starting the extraction phase, a calibration exercise was performed. The Belgian guideline was used as an example in this exercise. Two persons from each organisation represented in the draft group independently extracted information from the Belgian guideline using the extraction template. The extracted information from all partners in the exercise were then compared and discussed during an e-meeting. Based on these discussions, a few of the questions in the template were modified.

The succeeding extractions were all made by two persons independently, who then agreed on a final common version that was sent to the primary investigators. At least one person on each guideline had to have participated in the calibration exercise. For guidelines that were not available in a language of the draft group members, the information was extracted by the primary investigators using information in checklists based on the guidelines, ISPOR’s collection of country-specific pharmaco-economic guidelines and/or using tools for translation.

When all extractions were completed, the information from all guidelines was summarized in tables with one table for each methodological issue. In a few cases, two or more issues were merged into one table. If the extracted information was unclear, the information was

clarified with the extractors. Based on the tables, a summary describing the methods used by the EUnetHTA countries was written for each issue. The content of the tables and the summary was validated by at least one contact person in each country involved in EUnetHTA. If other EUnetHTA guidelines contained information related to the relevant issue, this was summarized in a specific section after the summary of the guidelines.

On methodological issues for which it was possible to find a common view, general recommendations were formulated. To be defined as a commonality, all guidelines that contain a recommendation on the specific issue had to be in agreement. Furthermore, on issues where not all partners were in agreement, it was in some cases still possible to form recommendations on how to conduct and present economic evaluations in a way that facilitates the exchange of results between European countries. An example of such a recommendation is to present the outcome of the analysis both in natural units and in QALYs. The main recommendations concern methodological issues in which the guidelines of the EUnetHTA partners either are in agreement, or in which the usability and/or transferability of the evaluations may be increased by presenting the results in a specific way.

2. Analysis and discussion of the methodological issue

In total, the review included 51 guidelines from 25 countries (Table A1 in Annexe 3 and Figure 1). The response rate among the 33 EUnetHTA countries that were included in the survey was 100 percent, but eight countries had no methodological guideline for health economic evaluations (see Figure 1). The countries that reported having no guideline were Bulgaria, Cyprus, Greece, Lithuania, Luxembourg, Malta, Romania and Turkey.

For some countries more than one guideline was reported. Within UK, England and Scotland each have their own separate guidelines. In addition, NICE in England has three different guidelines (for all type of technologies, medical devices, and diagnostics, see table A1), and these are presented separately when considered relevant. Similar specifications are made for Denmark, Norway, Poland, Russia, Spain and Sweden. Since Estonia and Latvia use the same guideline, these will be presented together in section 2.3 about methods for economic evaluations.

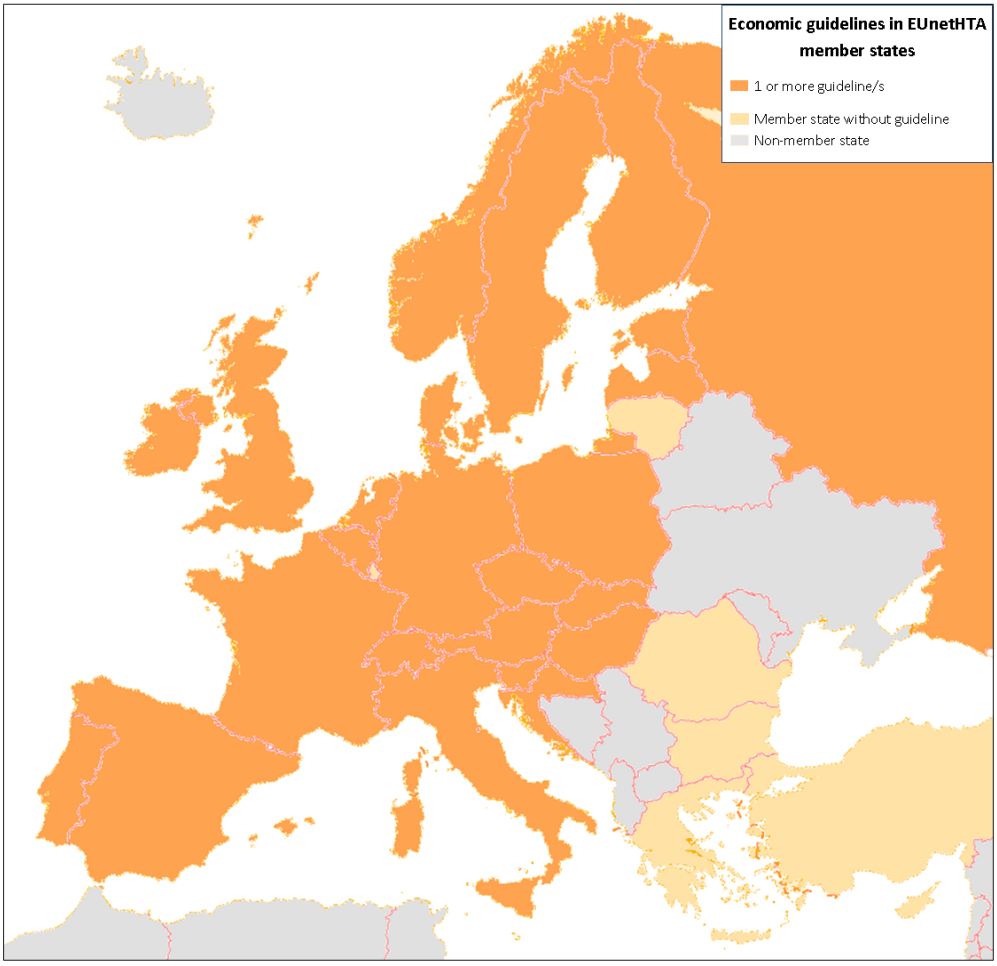

Figure 1. Map over countries involved in EUnetHTA, indicating which countries have any kind of methodological guideline for health economic evaluations.

2.1. Information about the collected guidelines

Of the 51 collected guideline documents, 28 were developed primarily for evaluations of pharmaceuticals, 19 for all type of technologies, one for pharmaceuticals and medical devices, one for medical devices, one for diagnostics, and one for disposables (Table A1 in Annexe 3). This means that of 25 countries with guidelines, more than 70 percent (n=18) have at least one guideline that is primarily focused on pharmaceuticals.

Most of the countries have at least one methodological guideline used for reimbursement (n=19) and/or that is mandatory (n=19) for governmental agencies performing the evaluations or the companies applying for reimbursement (see Table A2 and A3 in Annexe 4).

2.2. Requirements on populations and comparators

2.2.1. Choice of comparators for health economic evaluations

Results from the review of guidelines

Almost all countries with guidelines recommend that the main comparators in the economic evaluation should be those used in [routine] clinical practice (Table A4 in Annexe 5). For example, guidelines from Germany (59) and France (60) state that all therapeutic alternatives that are relevant in a particular therapeutic area should be included. Some guidelines (from Finland, Norway, Scotland, and Slovakia) specify that at least one comparator should be the one that the new intervention will most likely replace. It is also specified in some guidelines that the use of “no treatment” as comparator is accepted if this represents the most common clinical practice (e.g. by Croatia, Italy, Norway, Russia and Sweden). In the Irish guideline (61), comparators are not limited to specific interventions, but may include alternative treatment sequences or alternative rules for starting and stopping therapy. Most guidelines also describe when other comparators than what is most often used in clinical practice can be used. For instance, guidelines from Poland (62) recommend other additional comparators, such as the cheapest and the most efficient alternatives.

An example of a more explicit recommendation for the choice of comparator is made in the guideline by Belgium (63), in which it is stated that the relevant comparator should be selected by help of an efficiency frontier. 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 each intervention compared to the next best alternative. This method is also recommended in some other guidelines, e.g. the guidelines from France Norway, and England.

In summary, the guidelines generally seem to agree that at least one of the comparators in an economic analysis should represent those being used in clinical practice. However, most guidelines describe occasions when additional comparators should be used.

Other relevant guidelines

In a published guideline by EUnetHTA (JA1 WP5) on criteria for the choice of the most appropriate comparator(s) (39), it is stated that the comparator should be the reference treatment according to up to date high-quality clinical practice guidelines at European or international level. When there is no European-wide agreed reference comparator, there is a need for evidence indicating that the chosen comparator intervention is routinely used in clinical practice, or that the comparator intervention is validated for the respective clinical indication/population. In a survey concerning methods for Relative Effectiveness Assessment (REA) from the same work package (43), similar findings as the ones in Table A4 have been presented. The survey showed that in many jurisdictions, several options can exist for the choice of comparator in REA and that the majority (almost 70%) of the

jurisdictions had reported “best standard care” and/or “other” as an option for the choice of comparator.
In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that it is important to provide a detailed description of the alternative technologies and to justify the choice of comparator, in order to help study users to assess the transferability to their own setting. What represents ‘current practice’ is stated to likely vary over time and between countries.

Conclusions for choice of comparator in health economic evaluations

Based on the results of the current review of the guidelines used by EUnetHTA partners and previous EUnetHTA guidelines, it is recommended that the comparator(s) reflect the most relevant alternative intervention(s) used in clinical practice. The choice of comparators should be clearly presented and justified.

2.2.2. Subgroup analysis in health economic evaluations

Results from the review of guidelines of EUnetHTA partners

Most countries with guidelines (n=21) have recommendations for when subgroup analyses are suitable (Table A5 in Annexe 5). Subgroup analyses are recommended when the cost-effectiveness of the assessed technologies are believed to vary between different groups of individuals, for instance due to patients’ characteristics such as age, gender, prognosis or risk levels. Some guidelines mention the importance of these subgroups being identified a priori based on plausible, clinical or care-setting arguments (e.g. Belgium (63)**,** Germany (59)**,** Ireland (61)**,** and Scotland (64)). For example, the German guidelines specify that only those patient subgroups for whom a statistically significant and relevant difference in benefit or harm has been established in the precedent RCTs should be assessed in the health economic evaluation (59).

Other relevant guidelines

The European Medicines Agency (EMA) has a guideline for the investigation of subgroups in confirmatory clinical evidence (44). This guideline states that “the more heterogeneous the study population the greater the importance of subgroup analysis to check that the overall effect is broadly applicable and supports assessment of risk-benefit across the breadth of the proposed indication”. However, the recommendations for subgroup analysis of clinical trials do not necessarily have to be the same as for health economic evaluations.

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that all subgroup analyses should be clearly defined and clinically justified. In addition, it is specified that the methods for conducting subgroup analyses should be described.

Conclusions for requirements on subgroup analysis in health economic evaluations

Based on the results of the current review of the guidelines used by EUnetHTA partners, it is recommended to perform subgroup analyses in the economic analysis when there is a clinical rationale to believe that the cost-effectiveness of the assessed technologies may vary between sub-groups. It is important that the choice of subgroups is clearly justified and described.

2.3. Methods for health economic evaluation

2.3.1. Systematic review of previous health economic evaluations

Results from the review of guidelines

Only a few of the countries with guidelines request that a systematic review over previous economic evaluations is presented (Croatia (65), England (12), France (60), Poland (66), Slovakia (67) and Spain (AETSA (68)) (Table A6 in Annexe 5). The few guidelines that explicitly state that a systematic review is not required, still specify that they consider it useful to perform such a review (Austria (69), Belgium (63), and the Netherlands (70)). Some guidelines mention the need to compare the economic findings with results from previous studies, even though they do not specifically request a systematic review.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that if a literature review has been undertaken to identify existing economic studies, the methods of the review should be reported in sufficient detail to enable the review to be reproduced. However, it is not stated that a systematic review of economic evaluations has to be performed.

Conclusions for requirements on systematic review of health economic evaluations

Based on the results of the current review of the guidelines used by EUnetHTA partners, it is regarded as useful to conduct a systematic review of previous economic evaluations of the technology.

2.3.2. Time horizon

Results from the review of guidelines

A vast majority (n=18) of the 25 countries with guidelines recommend that the time horizon of the economic evaluation should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared (Table A7 in Annexe 5). A few guidelines (e.g. from England, Finland, Ireland, Norway and Spain) explicitly state that this may mean that costs and outcomes are estimated for the estimated remaining life time of the patients. Nevertheless, there are guidelines that ask for other time horizons in sensitivity analyses. For example, the Scottish guidelines (64) further specify that results (in net cost per QALY gained) need to be reported at different time horizon intervals e.g. at end of study follow-up, at 5 years follow-up and at 5-year intervals thereafter.

The only guideline which partly depart from this view is one from Germany (71), in which it is stated that the time horizon should be at least the length of RCTs. Yet the appropriate time horizon is also stated to depend on the nature of the disease. Consequently, the German guideline can also be interpreted to be in line with the other ones.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that in order to promote comparability between analyses, the time horizon of the economic evaluations should extend far enough into the future to capture the main costs and effects of the assessed technology and its comparators. It is also stated that it is usually informative to analyze the data using different time horizons, e.g. a shorter-term

horizon that includes only primary data and a longer-term horizon that also incorporates modelled data.

Conclusions for the choice of time horizon

Based on the results of the current review of the guidelines used by EUnetHTA partners and previous EUnetHTA guidelines, it is recommended that the time horizon for the reference case analysis should be sufficiently long to reflect all relevant differences in costs or outcomes between the technologies being compared. The choice concerning any alternative time horizon for the reference case analysis should be clearly justified and described.

2.3.3. Preferred type of analysis

Results from the review of guidelines

Of the 25 countries that have guidelines, 20 recommend the use of CUA as the main type of analysis (Table A8 in Annexe 5). However, several of the guidelines state that the choice of economic analysis depends on the characteristics of the technology, the nature of the disease or the availability of data (Belgium, Croatia, Hungary, Scotland, and Spain). If the main objective of the intervention is improving life expectancy and it does not have an effect on quality of life, some countries recommend a CEA with costs per life-years gained as the outcome measure instead of a CUA (e.g. France, Ireland, and the Netherlands). Other guidelines clearly state that the CUA should always be accompanied by a CEA with the costs per life-year gained as the outcome measure (Belgium, Norway, and Sweden). In the guideline by Poland (62), the use of CUA is emphasised and it is specified that it is of particular importance when HRQoL is one of the significant outcomes of the analysed technologies, and when the compared technologies give very different clinical effects.

Of the countries that do not recommend CUA as the main analysis, four (Estonia and Latvia, Germany and Switzerland) recommend using CEA while one has not indicated a preferred type of analysis (Austria). However, the Baltic guidelines (used by Estonia and Latvia) state that the results from a CUA may be presented in an additional analysis. In addition, CUA can be interpreted as the preferred type of analysis in the Austrian guideline since QALY is said to be the preferred outcome measure (69). The guideline from Switzerland (72) does not recommend any specific outcome measure but CUA ratios are explicitly mentioned as not so important. In the German guidelines (59), outcomes from clinical studies are preferred and the primary clinical measures that are used are mortality, morbidity, HRQoL, and validated surrogates. Yet, QALYs can be used in certain instances, e.g. when no other measure capturing/describing quality of life is available.

Several guidelines mention CMA as a possible choice of analysis (Belgium, Finland, Hungary, Estonia and Latvia, The Netherlands, Norway, Poland, Portugal, Russia, Scotland, Slovenia, Spain, and Sweden). In general, CMA is recommended when there is no difference in clinical effectiveness between an intervention and its comparator, i.e. when the two alternatives that are being compared have equal health effects. For example, the Scottish guidelines (64) state that “CMA may be appropriate if the proposed medicine is demonstrated by studies to be therapeutically equivalent to the relevant comparator(s), as assessed using an adequately designed and powered non-inferiority or equivalence or superiority study”. Moreover, the Norwegian guideline (73) specifies that it is essential to have good enough documentation to show that the alternatives indeed have

approximately identical effect if a CMA is to be used. The Belgian guideline (63) comes to a similar assertion.

Some guidelines mention CBA as a possible type of analysis (Finland, Portugal, Russia Spain, and Sweden). However, there are also various guidelines that state that CBA is not a recommended method (Belgium, Hungary, Italy, Norway) or that it should only be used as an additional method (Denmark, France and Poland (62)). In Norway, Helsedirektoratet (74) has stated that CBA may be used as the type of analysis for cross-sectorial public health interventions. In the guidelines from Sweden (57), it is stated that in cases where it is difficult to use QALYs, a CBA with willingness to pay as effect measure may be used. An example of when it may be difficult to use QALYs is when an intervention is associated with severe pain over a short time period.

The Medical Technologies Evaluation Programme guideline from England (75) recommends cost-consequence analysis (CCA) as the remit of the programme is to quantify the clinical benefits and associated resource impact of introducing a novel or innovative technology to the NHS. The estimated clinical benefits and resource use associated with the technology under consideration are compared against standard practice and healthcare pathways.

In summary, all countries with guidelines seem to accept either a CEA or a CUA. Most of the countries recommend CUA as the main type of analysis, even though several also expect a CEA with life-years gained as the outcome measure to be presented alongside the CUA. A number of guidelines underline that a CMA can be used when there is no difference in effect between the interventions that are being compared. However, there are differing views on the use of CBA. By one country, CCA is recommended for evaluations of medical devices.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that the choice between the different types of economic evaluations for answering a specific question depends on a combination of at least three considerations 1) the purpose of the economic evaluation, 2) the availability of suitable data and 3) any guidelines for economic evaluations that should be followed in any specific context.

Conclusions concerning type of analysis

Based on the results of the current review of guidelines used by EUnetHTA partners, it is recommended that results of an analysis be presented in terms of both CEA and CUA. A CMA is recommended when it can be demonstrated by adequately designed and powered studies that there is no difference in effect between an intervention and its relevant comparators. If appropriate and adequately justified, CCA may be a useful alternative in cases where CEA and CUA cannot be undertaken.

2.3.4. Use of models

Results from the review of guidelines

All guidelines clearly state that the use of decision-analytic models is accepted in health economic analyses (Table A9 in Annexe 5). Several guidelines (England, Finland, France, Germany, Ireland, the Netherlands, Norway, Scotland, and Spain) explicitly write that modelling is required, necessary or the preferred approach in many common situations.

Many guidelines indicate when modelling should be used. For example, the guideline from Poland (62) itemizes seven situations when modelling is necessary:

1. when there is a need to extrapolate the results beyond the time horizon of the clinical trials included in the clinical analysis;

2. when there is a need to transpose the experimental effectiveness measured (i.e. indirect results expressed on a disease-specific scale) to final utility results (e.g. life-years gained, gained QALY);

3. when there is a need to evaluate the results in real practice when only the results of experimental tests are available and the results obtained in one country can be transposed into another one;

4. to do an indirect comparative synthesis if relevant direct trials are missing;

5. to provide estimates if direct measurements are missing;

6. for preliminary assessment and scheduling of trials;

7. in early stage of development of a new technology if comprehensive trials are missing.

Some guidelines (Belgium (63) and Slovenia (76)) express that modelling should only be used when available data are insufficient and that modelling should always be justified.

The extent to which recommendations were made regarding the type of models, the program to be used, or the requirements for methods of extrapolation or validation varied between the assessed guidelines. However, there were no explicit conflicts between the guidelines regarding any of these aspects.

No guideline explicitly disallows any certain type of model, even though many guidelines only mention decision trees and Markov models. Other types of models mentioned are discrete simulation models, dynamic and static transmission models, agent-based models and systems-dynamic models. As an example, the guideline from Germany (59) states that it has no *a priori* preference for a particular modelling technique and that the choice of appropriate modelling technique depends on the research question. The Belgian (63) guideline emphasizes that the main principle is that a model should be kept as simple as possible as the more complex the model, the less likely it is that sufficient data will be available to populate it.

Most of the guidelines have no recommendation regarding choice of modelling program. The Finnish guideline (77) mentions Microsoft Excel and guidelines from the Netherlands (70) states the importance of using a “user-friendly electronic version”. It has also come to our knowledge that the Dutch template for applicants specifies that only Microsoft Excel and TreeAge models are accepted. Likewise, it is recommended in NICE’s process guide for the technology appraisals program to use Microsoft Excel, DATA, Winbugs or R. Since not all process guides have been reviewed (due to the scope of the project), similar information may be available also for other countries.

Regarding data extrapolation, those guidelines that have specific recommendations are generally in agreement with each other. For example, the Irish guideline (61) states that

when extrapolating data beyond the duration of the clinical trials, inherent assumptions regarding future treatment effects and disease progression should be clearly outlined and tested as part of the sensitivity analysis. Polish (62) and French (60) guidelines ask for three scenarios when extrapolating data: optimistic, pessimistic and neutral. Scottish (64) and English guidelines (12) also ask for multiple scenarios regarding the extrapolation of treatment benefits: no benefit after the follow-up period; the benefit continues at the same level as during the follow-up period, and; diminishing benefit in the long run.

Some guidelines have requirements on validation as well. For example, the German guideline (59) states that the following aspects of validity should be assessed: 1) face validity of the influence diagram, the model concept, the data acquisition, the processing of functional relations and the choice of modelling technique; 2) technical validation (correct model implementation); and 3) external validity.

In summary, all guidelines clearly state that the use of decision models is accepted in health economic analyses.However, the extent to which guidelines offer specific recommendations regarding what types of models should be used, or which methods should be used for extrapolating or validating data, varies. Nevertheless, there are no explicit conflicts between them regarding any of these aspects.

Other guidelines

Several guidelines on modelling have been published by ISPOR’s Good Practices Task Forces (24, 26, 28, 47-49). While Roberts et al. (2012) provide recommendations concerning the conceptualization of the model (24), Eddy et al. (2012) provide recommendations for achieving transparency and validation (28). For more detailed recommendations on modelling techniques, see Siebert et al. (2012) for state-transition modelling (47), Karnon et al. (2012) for modelling using discrete event simulation (26), and Marshall et al. (2015) for a checklist to determine when to apply dynamic simulation modelling methods (49).

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that the use of modelling is often necessary to make relevant assessments of cost-effectiveness of medical technologies. It is furthermore stated that to be able to evaluate how the results of a model should be used, users of the model benefit from knowing how well the model predicts the outcome(s) of interest. To be able to do this, the model needs to be transparently reported and validated.

Conclusions for the use of models

Based on the results of the review of guidelines used by EUnetHTA partners, as well as the recommendation in the HTA Core Model text, the use of modelling is recommended for economic evaluations. However, modelling should always be justified and presented as transparently as possible so that it can be reconstructed. The choice of appropriate modelling technique should depend on the research question. When data are extrapolated beyond the duration of the clinical trials, all assumptions need to be clearly presented and analyzed using different scenarios. Providing an electronic version of the model to users could further enhance its transparency and usefulness.

2.3.5. Perspective on costs and outcomes

Results from the review of guidelines

The perspective used in the economic evaluation is often the same for both costs and outcomes, or only described for costs. In some guidelines, however, a distinction is made between costs and outcomes. Therefore, the results are here presented separately (Table A10 in Annexe 5).

Costs:

For costs, the guidelines can generally be divided into those recommending a healthcare perspective (Belgium, Croatia, Czech Republic, England, Estonia and Latvia, Germany, Ireland, Italy, Scotland, Slovakia, Slovenia, and Switzerland) and those recommending a societal perspective (Denmark, Finland, the Netherlands, Norway, Portugal, and Sweden). Many guidelines recommend other perspectives in alternative analyses if it is likely to significantly influence the results. For example, the Belgian (63) and Croatian (65) guidelines state that health care costs borne by anyone other than the health care payers should be reported separately. The French guideline (60) recommends a “collective perspective” that includes all direct costs (i.e. the resources used to provide the health intervention regardless of the source of funding [patients, compulsory and supplementary health insurance schemes, government, informal care etc.]). This means that indirect costs, such as productivity loss, would be excluded from the base case analysis. However, an analysis of the indirect costs, if considered relevant, can be presented in an additional analysis.

Outcomes:

Many of the guidelines do not explicitly discuss perspective on outcomes, but rather perspective of the analysis (which may indicate that the same perspective is used on both costs and outcomes). The issue of perspective on outcome generally concerns whether only effects on patients are included, or if the analyses also include third parties (such as caregivers or significant others). Some guidelines explicitly state that only outcomes on patients are considered (Belgium, Germany, Slovenia, and Switzerland), while others explicitly recommend the inclusion of health effects accruing to all individuals (England, France and Ireland) or to apply a societal perspective on outcomes (the Netherlands, Norway, Portugal, and Slovakia). Other guidelines recommend a broader perspective in sensitivity analysis. For example, the Croatian (65) and Scottish guidelines (64) suggest the inclusion of effects on informal caregivers in a separate analysis if relevant. Some guidelines also discuss whether outcomes should only consider effects on HRQoL or reflect broader effects on quality of life (i.e. utility).

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that if the purpose is to inform about societal resource allocation, it may be most appropriate to take a societal perspective. For hospital HTA, the hospital perspective may be more appropriate. If information from the costs and economic evaluation domain is intended to improve decision-making within the health-care sector, appropriate viewpoints may be: a ‘health-care payer’ (both public or private); a ‘third-party payer’; or a ‘health-care sector’ perspective (e.g. (3) and (12)).

Conclusions for choice of perspective on costs and effects

Based on the results of the current review of guidelines used by EUnetHTA partners, the economic evaluations should at minimum be conducted from a health care perspective. However, several countries recommend a societal perspective. Thus, presenting resource use related to other sectors of society in a complementary analysis may increase the usefulness of an evaluation to other countries. Within the chosen perspective(s), it is recommended to present the resource use in as detailed a manner as possible.

2.3.6. Costs

2.3.6.1 Costs to include

Results from the review of guidelines

This section contains information about which type of resource use and what kind of cost estimation the guidelines are recommending to include in the economic evaluation (Table A11 in Annexe 5). This is of course related to the recommended perspective of the analysis. As previously mentioned (section 2.3.5), countries recommending a health care perspective recommend that only direct health care costs are included, while guidelines recommending a societal perspective also recommend the inclusion of indirect costs and costs borne by others sectors of the society (e.g. informal caregivers or other governmental bodies). However, several guidelines state that the indirect costs and the costs borne by others sectors of the society should be presented in an additional analysis. For example, the Dutch guidelines ask for a separate analysis for productivity costs (an analysis including productivity costs and an analysis excluding productivity costs) (70).

The Swedish guidelines (57) were during the phase of extraction of data for this report the only ones that explicitly recommended the inclusion of unrelated future costs due to prolonged survival, stating that “the costs for increased survival – total consumption less total production during gained life years – should be included”. However, this was changed in February 2015, when the updated guidelines no longer mention these costs (indicating that they should be excluded). While the guideline by Helsedirektoratet in Norway (74) proposes to wait with an inclusion of these kinds of costs until it has been discussed more broadly, the guidelines from England (12), France (60), Hungary (78), and the Netherlands (70) explicitly state that unrelated future costs should not be included. The German (59) and Slovakian (67) guidelines state that unrelated health care costs in life years gained may be calculated in separate analyses if feasible.

Some guidelines also present recommendations on how to deal with value added taxes (VAT), where England (12), Ireland (61), Norway (73) and Sweden (79) state that VAT should be excluded while the Hungarian guideline (78) states that it should be included. The guidelines from England clarify that VAT should indeed be included in calculation of the budgetary impact when the resources in question are liable for this tax. In any case, this choice should be consistent with the perspective of the analysis.

In the two oldest guidelines, which are from Denmark and Portugal, intangible costs, such as the suffering of patients, are also recommended for inclusion in the analysis (80, 81). However, these consequences are usually captured in the effect side of the analysis (e.g. in QALYs) and including them as a costs may be considered double counting.

Other guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that valuation and inclusion of productivity costs should be made in situations where it is judged to be relevant. However, it also suggests that direct costs be reported separately from indirect costs.

Conclusions for costs to include

Based on the results of the current review of guidelines used by EUnetHTA partners, there is consensus that all direct health care costs should be included in the main analysis. It is

also recommended to present costs borne by others sectors of the society, e.g. indirect costs in an additional analysis when relevant.

2.3.6.2 Sources for data on costs

Results from the review of guidelines

Costs are estimated by identifying, quantifying and valuing resource use. The identified resource use is quantified in natural units, such as the number of days a patient stays in a ward. To value the resources, the resource use is multiplied with unit costs which depend on the price level in specific countries as well as the organization of the health care system.

Most countries present no official hierarchy of sources for data neither on resource use nor unit costs (Table A12 in Annexe 5). However, many of them still provide recommendations about preferred sources. A majority mention the importance of using national sources or listing prices for the estimation of unit costs, in order to analyze the technology in a local context. For example, the guidelines for England (12, 75, 82) request that the sources for unit costs best reflect prices relevant to the NHS and personal social services. If non-national sources are used, many guidelines stress the importance of comparing them to, or validating them for, the national situation. None of the guidelines recommend expert panels as the main source of data, but neither do any explicitly discourage their use. For example, the guideline for Scotland (64) states that expert panels should only be used as a complementary source of information rather than as the sole source of information to estimate resource use. The Italian guidelines specify that expert opinion may be used for estimating costs when it has little impact on the results, provided that this is adequately described and that the uncertainty is explicitly addressed and discussed (83).

In summary, a majority of the guidelines emphasize the importance of using national sources or listing prices in order to analyze the technology in a local context.

Other guidelines

ISPOR has several guidelines on how to measure drug costs in CEA from the perspectives of the industry, government payers, managed care, and society (53, 84-88). Among other things, these guidelines emphasize that to facilitate international comparisons, units should be standardized in terms of volume of active ingredient, regardless of package and dosing strength variations across countries (53). It is also recommended that drug costs are measured in local currency per unit of active ingredient.

Conclusion for sources for data on costs

As unit costs generally vary between countries, it is difficult to transfer cost from one country to another. In order to facilitate adaptions to local settings, it is therefore recommended that resource use is clearly presented in natural units.

2.3.7. Effects

2.3.7.1 Sources for clinical effectiveness and quality of data

Results from the review of guidelines

The health economic guidelines provided by the EUnetHTA partners vary in how extensively they cover the details concerning the quality of evidence for clinical effectiveness (Table A13 in Annexe 5). However, the majority of the countries with guidelines state that they prefer systematic reviews and meta-analyses, but do also seem to accept supplementary evidence of lower quality. Several of the guidelines recommend the use of quality checklists in assessing the quality of clinical effectiveness evidence (as

well as other data). For example, the guideline from Germany (59) states that calculations based on studies of low quality may be accepted, but as the results would then contain more uncertainty, the final result of the assessment will be degraded. On the other hand, the Russian guideline (89) states that if the evidence is of sufficient quality the pharmaceutical proceeds to the next stage of evaluation, but if the level of evidence is deemed to be too low, the pharmaceuticals are not recommended for listing (may be recommended for delisting) and will not undergo further clinical or economic assessment.

Some guidelines (e.g. the various guidelines from England (12, 75, 82)) accept different types of studies and quality of evidence depending on the type of technology being assessed (pharmaceuticals, medical devices, or diagnostics). Different quality checklists are also included in the guidelines depending on the type of technology being evaluated, for example, QUADAS-2 tool is referred to for the quality assessment of diagnostic accuracy studies in England.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is stated that a thorough assessment of the methodological quality of the included studies is crucial. Tools for critical appraisal can focus on different quality aspects of studies or publications.

Conclusion for sources for clinical effectiveness and quality of data

Based on the results of the current review of the guidelines used by EUnetHTA partners, it is recommended that the clinical evidence is collected by a systematic review of the literature. The clinical evidence should be based on the most appropriate source, which in most cases is considered to be RCT studies. If no RCT studies have been carried out or cannot answer the research question on the intervention under consideration, other sources may be acceptable. The quality of all sources needs to be assessed and reported.

2.3.7.2 Indirect comparisons

Results from the review of guidelines

Some (n=7) of the 25 countries with guidelines do not include any recommendations on indirect comparisons of effectiveness in their guidelines (Table A14 in Annexe 5). The remaining 18 countries have at least one guideline that accept indirect comparisons if no direct head-to-head comparisons are available (Austria, Belgium, Croatia, Czech Republic, England, Estonia and Latvia, Finland, France, Germany, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Scotland, Spain (AETSA and CatSalut) and Sweden).

Some guidelines are more explicit about the methodological requirements that should be fulfilled for the indirect comparison to be deemed valid. For example, guidelines from Norway (73) state that the lack of direct comparative studies must be documented using systematic reviews and that the included studies must be sufficiently similar in terms of population, intervention (e.g. treatment duration and dose) and outcomes. In line with this recommendation, the guidelines from Poland (62) recommend a thorough analysis of methodology and of differences in the studies’ application of the intervention, the study population and of examined endpoints. The Scottish guideline (64), which requires an indirect comparison if no head to head evidence is available, recommends a 4-step approach to reduce the risk of bias:

- the literature should have been searched systematically
- there should be clear and plausible criteria for including and excluding studies

- the baseline characteristics of the population in each trial should be reported alongside the effect sizes to demonstrate homogeneity
- the method for arriving at a point estimate of efficacy should be clear and transparent

In addition, the Scottish guideline recommends the elicited value to be a key part of the sensitivity analysis.

In summary, all countries that mention indirect comparisons in their guidelines accept their use if no head-to-head comparison is available.

Other relevant guidelines

Several countries have separate guidelines for indirect comparisons in other contexts (i.e. not specifically for health economic evaluations). These guidelines have not been included in this review. However, it is reassuring that the results presented here are supported by the results in a previous survey by JA1 WP5 on indirect comparisons for the use in REA (43, 90).

Within JA1 WP5, EUnetHTA has previously published a guideline with the title ”Comparator and comparisons - Direct and indirect comparisons” (2). According to this guideline, the choice between direct and indirect comparison is context-specific and dependent on the question posed as well as on the kind of evidence available. Where sufficiently good quality head-to-head studies are available, the guideline recommends direct comparisons as the level of evidence is higher. If substantial indirect evidence is available, however, it can be used to validate the direct evidence. In addition, the use of indirect methods may be helpful when there is limited head-to-head evidence or more than two treatments are being considered simultaneously. When using indirect comparisons it is important that they are made in line with recommended methodology. The application of direct or indirect comparisons relies on the assumption that only comparable studies should be combined. Therefore, the guideline recommends that studies that differ substantially in one or more key characteristics (e.g. participants, interventions, outcomes measured) should not be combined. An indirect comparison should only be carried out if underlying data from comparable studies are homogeneous and consistent, otherwise the results will not be reliable. Furthermore, the guideline states that a systematic literature search is required when conducting an indirect comparison.

The ISPOR Task Force on Comparative Effectiveness Research Methods has also published two papers on how to interpret and conduct Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making (50, 51). They have also recently published a questionnaire to assess relevance and credibility of indirect treatment comparisons/network meta-analyses (52).

Conclusions for the use of indirect comparisons

Based on the results of the current review of the guidelines used by EUnetHTA partners, the use of indirect comparisons is recommended when there is limited head-to-head evidence. The methods used should be in line with the recommendations in the EUnetHTA guideline ”Comparator and comparisons - Direct and indirect comparisons” (2).

2.3.7.3. Preferred outcome measure/s

Results from the review of guidelines

As seen in the section about type of analysis (section 2.3.3), 20 of the 25 countries with guidelines recommend using CUA for the main analysis. This means that they also recommend the use of an outcome measure that represents utility. Indeed, the guidelines from all but four countries (Estonia and Latvia, Germany, and Switzerland), specify that the preferred outcome measure is QALYs or both QALYs and life years (Table A15 in Annexe 5). The four countries with guidelines that do not recommend QALYs, represent four of the five countries that do not recommend the use of CUA. The guideline from Austria states that QALY is the preferred outcome measure, even though it does not explicitly recommend a CUA.

According to the German guideline (59), QALYs may be used even though IQWiG in general is quite reluctant to use this outcome measure. More specifically, QALYs (as well as any kind of disease-specific aggregate outcome measures) can be used for comparisons within specific disease areas but should not be used for comparisons across disease areas. The German decision-making body refrains from establishing an overall cost-effectiveness threshold and the objective of health economic evaluations is regarded as to provide information on the prices of interventions within one indication. Furthermore, it is stated in the German guidelines that there are ethical and methodological concerns arising from certain methods, such as time trade-off (TTO) and standard gamble (SG), which should be considered prior to their use.

The guidelines used in Estonia and Latvia (91) recommend that QALYs only are used in complementary analyses and that the primary outcome represents improvements in terms of survival, incidence of complications, side-effects, and/or well controlled therapy symptoms, etc. In the guidelines from Switzerland (72, 92), there are no specific recommendations concerning outcome measures, but cost-utility ratios are explicitly mentioned as not so important.

If the main objective of the intervention is to prolong life expectancy, some guidelines specify that life-years gained should be used as the main outcome measure instead of QALYs (France, Ireland, and the Netherlands). Some of the guidelines clearly state that the outcome should be presented both in terms of QALYs and in terms of life years gained (Belgium, England, Norway, and Sweden). In the Spanish guideline (93), it is stated that irrespective of the approach used, the study must provide data on changes in length and quality of life separately.

In the guidelines from Scotland (64), it is stated that alternative approaches to measuring outcome can be considered in those circumstances in which the QALY may not be the most appropriate choice. The examples given in the guideline are cases when:

- The QALY does not capture the main health benefit of the intervention
- The QALY does not capture the main benefit of the intervention where the main benefit is something other than health
- Utility values used in QALYs appear to lack sensitivity in circumstances where other measures suggest health improvements or disease reductions
- Utilities used in QALYs cannot be adequately measured for the main health states generated by the condition in question (e.g. this may be the case with some mental health states).

The French guidelines (60) specify that the use of other health outcomes than QALYs and length of life may be justified if QALY or life years data are unavailable (and cannot be produced) and if the impact of the interventions studied are equivalent in terms of length

and quality of life. If data on length of life is not available, an outcome measure that has been demonstrated to correlate with mortality is preferred. Moreover, the guidelines from England (82) and Scotland (64), specify that alternative measures may be presented as an additional analysis if the assumptions underlying QALYs (for example, constant proportional trade-off and additive independence between health states) are considered inappropriate in a particular case and evidence to this effect is present. The Medical Technologies Evaluation Programme guideline from England (75) employs a cost-consequence approach and therefore outcome measures relating to clinical benefits and associated resource use such as technology and comparator costs, infrastructure or healthcare service use are specified.

In summary, all countries except four specify that the preferred outcome measure is QALYs or both QALYs and life years. Of the four countries with guidelines that do not announce QALYs as a preferred method, at least three accept QALYs in special circumstances or in complementary analyses.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is, wherever possible, suggested that the estimates are expressed in natural units before translating them to alternative units such as QALYs. When changes in survival and HRQoL are combined in one outcome measure such as the QALY, separate reporting of changes in survival and HRQoL should be requested to allow for separate consideration of both endpoints.

Conclusions for preferred outcome measures

Based on the results of the current review of guidelines used by EUnetHTA partners and previous EUnetHTA guidelines, it is recommended to present the outcome of the analysis in terms of both natural units, including life-years gained when relevant, and in QALYs.

2.3.7.4. Intermediate/surrogate outcomes

Results from the review of guidelines

All but two of the 25 countries with guidelines have some kind of recommendation concerning the use of intermediate or surrogate outcomes in health economic evaluations (Table A16 in Annexe 5). Apart from four countries that had guidelines that were somewhat unclear on this issue (Croatia, Denmark, and the Baltic guidelines [Estonia and Latvia]), all countries support the acceptance of intermediate/surrogate outcomes. In some guidelines (Austria, Belgium, England, France, Norway, and Russia) it is specified that final outcomes are preferred but that intermediate/surrogate outcomes are accepted if final outcomes are not available. Other guidelines specify that the intermediate/surrogate outcomes should be translated into final outcomes by the use of extrapolation in decision models (Belgium, England, the Netherlands, Poland, and Sweden).

Concerning the validity of the intermediate/surrogate outcome measures, some guidelines require or recommend that the association between the intermediate/surrogate outcome and the final outcome is demonstrated and/or quantified (Austria, Belgium, England, Germany, Hungary, Ireland, the Netherlands, Poland, Scotland, Slovakia, Spain, and Sweden). For example, it is stated in the Norwegian guideline (73) that ”the causal relationship between intermediate outcomes and hard outcomes must nevertheless be well-documented” and in the Spanish guideline (93) it is stated that “where intermediate outcomes are used, the connection to final outcomes must be clear and scientifically proven”. In the German guidelines (59) it is required that the surrogate outcomes are validated, which means that they should fulfil the criteria for validated surrogates stipulated in the IQWiG’s General Methods 4.1. The current methodological literature frequently discusses correlation-based procedures for surrogate validation, with estimation of correlation measures at both study and individual level. IQWiG‘s guideline (59) on benefit assessments do therefore give preference to validations on the basis of such procedures.

In summary, all countries with explicit recommendations about intermediate or surrogate outcome measures accept their use as an input to decision models or as outcome measures in CEA if final outcomes cannot be estimated. However, the association between intermediate and final outcomes should be demonstrated and some countries require that this association is explored in decision models.

Other relevant guidelines

EUnetHTA has previously published a guideline on the use of surrogate outcomes in REA of pharmaceuticals (41). That guideline does not cover the use of surrogate outcomes in health economic evaluations. However, it specifies that final clinical endpoints are preferred both for first assessment and re-assessment of pharmaceuticals. For the initial assessment, however, surrogate endpoints can be accepted if the surrogate/final clinical endpoint relationship has been validated. For re-assessments, the guideline specifies that effectiveness should, whenever it is possible, be demonstrated in terms of final clinical morbidity and mortality outcomes such as stroke, myocardial infarction, fractures etc.

Conclusions for the use of intermediate/surrogate outcomes

Based on the results of the current review of the guidelines used by EUnetHTA partners and previous EUnetHTA guidelines, intermediate/surrogate outcomes may be used in health economic evaluations if their relationship to final outcome measures, in terms of morbidity and mortality, is demonstrated.

2.3.7.5. The use of willingness-to-pay (WTP) to assess the value of health outcomes

Results from the review of guidelines

Willingness-to-pay (WTP) may refer to the patients’ or the general public’s WTP for an outcome in a CBA, or to the threshold value that is used to determine if an intervention is cost-effective. In this section, we refer to the former, i.e. the use of WTP to assess the value of health outcomes in a CBA. Most guidelines do not explicitly mention the use of WTP for this purpose (Table A17 in Annexe 5). However, several guidelines contain some kind of recommendation concerning CBA, in which outcomes are often valued by estimating the patients’ or general public’s WTP for that specific outcome (see section 2.3.3 about type of economic evaluation). Some of those guidelines include CBA in the list of possible analyses that can be performed (Finland, Portugal, Russia, Spain, and Sweden), while others state that CBA is not a recommended type of analysis (Belgium, Hungary, Norway, and Italy) or that it should only be used as a complementary analysis (Denmark, France and Poland).

For supplementary analyses with CBA, the Danish guidelines (80) recommend contingent valuation to measure outcome in monetary terms, and that the WTP should be measured in a sample of the population. The advantages of using WTP as a preference target instead of non-monetary outcome measures such as QALYs is argued to be that this outcome measure goes beyond the state of health and also captures emotional or ethical aspects. In line with this, the Portuguese guidelines (81) recommend that WTP should be assessed using contingent valuation, as it measures the basic results and can pick up on important aspects such as external use and satisfaction (utility) with the treatment process.

In the guidelines from Sweden (57), it is stated that a CBA with WTP as outcome measure may be used in cases when it is difficult to use QALYs, such as when an intervention is associated with severe pain over a short time period.

The Scottish guidelines (64) state that if outcomes have been elicited by methods such as WTP studies or a discrete choice experiment, these must be fully described and the uncertainty surrounding the results must be fully explored.

In summary, not many guidelines contain explicit recommendations about WTP but several contain recommendations about CBA. However, the view on the use of this type of analysis is mixed. In the few guidelines that give recommendations concerning how to conduct studies to assign monetary values of health outcomes, contingent valuation is the preferred method.

Conclusions for the use of willingness-to-pay to assess the value of health outcomes

Based on the results of the current review of guidelines used by EUnetHTA partners, WTP is not recommended as one of the primary outcome measures in a health economic evaluation.

2.3.8. Methods for estimating QALYs

2.3.8.1 Preferred method to derive HRQoL weights for calculation of QALYs

Results from the review of guidelines

As seen in the section about preferred outcome measure (section 2.3.7.3), all but four countries with guidelines recommend or require QALYs as one of the main outcome measures. For the derivation of HRQoL weights used to calculate QALYs, two countries

recommend using methods such as time trade-off (TTO), standard gamble (SG), or a visual analogue scale (VAS) directly on the respondents (Denmark and Sweden) while seventeen recommend the use of indirect methods (Table A18 in Annexe 5). The indirect methods are based on a questionnaire with a pre-scored value set derived by one or several of the direct methods. For example, the EQ-5D instrument consists of a questionnaire with five questions. Each combination of the responses in these questions can be assigned a HRQoL weight using specific value sets. The British value set, which is commonly used, has been developed by using TTO and VAS in a sample of the British general public (94, 95).

Of the countries that recommend indirect methods, some (Belgium, Croatia, Czech Republic, England (12, 82), Italy, the Netherlands, Poland, Scotland, and Slovakia) specifically recommend the use of EQ-5D. Austria, the Baltic guidelines (Estonia and Latvia), and France specify that EQ-5D or HUI are the preferred instruments while Ireland, Norway and Spanish CatSalut recommend EQ-5D or SF-6D. The Norwegian guidelines (73) also mention 15D as an accepted method. The Spanish recommendations (93) specify that HRQoL weights gathered from indirect methods are recommended since these are easier to obtain, compare and interpret.

Among the countries with guidelines that specifically recommend the use of EQ-5D, some present cases where other instruments may be accepted (e.g. Belgium, Croatia, England, Italy, and Scotland). For example, guidelines from England (12) specify that alternative HRQoL measures may be used when EQ-5D is not the most appropriate instrument. This refers to situations where EQ-5D has been shown to perform poorly on construct validity and responsiveness in a particular patient population. The lack of content validity and construct validity for the specific population must, however, be demonstrated by empirical evidence derived from a review of peer-reviewed literature. The alternative measures must also “be accompanied by a carefully detailed account of the methods used to generate the data, their validity, and how these methods affect the utility values” (12). Moreover, the Scottish guidelines (64) specify that “the use of the EQ-5D is not mandatory if other valid generic utility measures are available and the reasons for their use are provided” and guidelines from Croatia (65) allow for other valuation methods if “EQ-5D data are not available or are inappropriate for the condition or effects of treatment”.

Of the two countries (Denmark and Sweden) that recommend direct methods, both recommend TTO and SG. The Swedish guidelines also recommend VAS as a second choice (57). Recommending VAS clearly conflicts with the recommendation made in the Austrian guideline, where VAS is stated to be considered problematic for theoretical reasons. Moreover, the guidelines from Sweden (57) specify that indirect methods, such as EQ-5D, can be used even though patient preferences elicited by direct methods are preferred. The guidelines from Sweden are however currently under revision, and since it now exists a Swedish tariff for EQ-5D (96) valued by patients, it is possible that the recommendation will be revised towards the use of EQ-5D in the future. In the guidelines from Finland, Portugal, Russia and Slovenia no specific method for estimation of HRQoL weights is recommended. However, the guidelines from both Finland and Portugal emphasize that the chosen method must be validated.

In summary, most guidelines recommend indirect methods for the derivation of HRQoL weights. The most commonly recommended instrument is EQ-5D, but HUI, SF-6D, and 15D are also recommended in some guidelines.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), several direct and indirect methods for derivation of HRQoL weights are mentioned. No specific method is stated to be preferred over another but it is specified that it is important that the same methodology be applied consistently if comparisons across diverse technologies are to be facilitated. It is further specified that “the choice between these preference elicitation techniques, the way they are administered, and the context in which they are used all have important implications for the validity and reliability of the estimates of ‘preference’ or ‘utility’ elicited”.

There is also a specific EUnetHTA guideline about HRQoL that was published in 2013 (40). This guideline gives general recommendations related to HRQoL for REA of pharmaceuticals. It is specified in the guideline that QALYs that will be used in economic evaluations should be measured via direct utility measurement based on TTO or SG or indirect measurement (with for example EQ-5D, HUI or SF-6D). It is, however, also mentioned in the guideline that different methods may yield different results and that one particular instrument should be applied consistently.

Conclusions for methods for derivation of HRQoL weights

Based on the review of guidelines used by EUnetHTA partners, the results show that EQ-5D is the most commonly recommended instrument for derivation of HRQoL weights. However, other generic instruments, such as HUI, SF-6D or 15D, are also recommended in some guidelines.

2.3.8.1. Whose preferences should the HRQoL weights represent?

Results from the review of guidelines

The direct methods may be used to elicit preferences from either patients who value their own health state or from samples of the general public who are asked to value hypothetical health states. Equally, the value sets used for the indirect questionnaire-based instruments may represent patient or general public preferences. Sixteen of the 21 countries with guidelines that recommend the use of QALYs have some kind of recommendation concerning whose preferences the HRQoL weights should represent (Table A19 in Annexe 5). Thirteen of these recommend preferences from the general public. Several of these guidelines clarify that the measurement of changes or differences in health should be reported directly from patients using questionnaires but that the values of these changes should come from a value set representing the preferences of the general public (e.g. Belgium, England, Ireland, Poland, and Scotland). However, it is in some guidelines unclear if preferences from the general public are recommended because most of the existing value sets are based on general public preferences or because these are preferred over patient preferences.

The German, Portuguese, and Swedish guidelines differ from the others. If QALYs are used, the German guideline (59) recommends that the weights should represent preferences of the patients. The Portuguese guideline (81) recommends that the health states are valued by people that are familiar with the evolution of the disease. In the Swedish guidelines (57), it is stated that HRQoL weights based on patient preferences are preferred. However, HRQoL weights estimated with indirect methods are accepted. Since the value sets for the indirect methods are usually based on general public preferences, this means that many of the economic evaluations in Sweden include QALY calculations based on preferences of the general public.

Most of the guidelines that recommend a value set based on preferences of the general public also recommend that the value set represents preferences of the population in that specific country (e.g. Belgium, Croatia, England, France, Ireland, Poland, and Scotland).

In summary, all but three of the countries with guidelines that mention whose preferences the HRQoL weights should represent, recommend an instrument with a value set that is based on preferences of the general public.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is mentioned that HRQoL weights can be derived either from patients or from samples of the general public, but it does not give any specific recommendation on how to handle this issue.

In the specific EUnetHTA guideline about HRQoL (40) it is specified that there is no consensus across jurisdictions about whether HRQoL weights should be derived from the general public or from patients. The choice is rather described as normative and it is recommended to carefully consider the implications of the choice in terms of its consequences on decisions. However, to improve comparability and consistency it is recommended that the choice is consistent across technologies and time.

Conclusions concerning whose preferences the HRQoL weights should represent

The results of the current review of guidelines used by EUnetHTA partners show that most guidelines recommend a value set based on hypothetical preferences representing the general public.

2.3.8.2. Mapping from disease-specific quality of life measures to preference-based HRQoL weights that can be used for calculation of QALYs

Results from the review of guidelines

Most guidelines do not mention mapping from disease-specific quality of life (QoL) measures to preference-based HRQoL weights that can be used for calculating QALYs (Table A20 in Annexe 5). Amongst those that do contain some kind of recommendation, the views are diverse. While guidelines from Belgium and France recommend against the use of mapping in the reference case, several countries (Czech Republic, England, Ireland, Italy, Norway, Scotland, and CatSalut in Spain) accept mapping if no other data are available.

In the French guidelines(60), it is specified that “there are still doubts about the reliability of mapping functions, in particular for more severe health conditions (Rowen et al. 2009), and there is no study to show that these functions are valid in France.” As one of the countries with guidelines that accept mapping, Norway (73) specifies that if “pharmacoeconomic analyses come from clinical studies that also include relevant quality of life data or data that can be translated into quality of life scores using MAU-instruments (e.g. SF-36 data), then it is required to use these data”. In line with this, the Scottish guidelines (64) specify that utilities can be mapped from disease-specific QoL measure included in a clinical study. The guideline describes the best practice for conversion from condition-specific measures into preference-based (HRQoL weights that can be used for calculation of QALYs).

Other relevant guidelines

In the specific EUnetHTA guideline about HRQoL published in 2013 (40), mapping of disease-specific or generic instruments to preference-based instruments in order to obtain HRQoL weights for calculation of QALYs is generally not recommended for REA. Instead, authorities are recommended to encourage researchers to always include a preference-based instrument in their clinical trial protocol.

Conclusions concerning the use of mapping from disease-specific QoL measures to HRQoL weights that can be used for calculation of QALYs

Based on the current review of guidelines used by EUnetHTA partners, the results show that there are different views on the use of mapping from disease-specific QoL measures to HRQoL weights that can be used for calculation of QALYs.

2.3.9. Discounting of costs and effects

Results from the review of guidelines

All 25 countries that have guidelines provide some information about discounting (see Table A21 in Annexe 5). Eighteen of the countries recommend the use of the same discount rate for health effects and costs in the reference case while three recommend a lower discount rate for health effects than for costs (Belgium, The Netherlands, and Poland) and one recommends that the health effects are not discounted at all (Russia). The guidelines from Czech Republic, Slovenia, and Denmark recommend discounting but do not recommend specific discount rates.

Among the guidelines that recommend the same discount rate for health effects and costs, the recommended level for the discount rate varies between 3 and 5 percent. Most guidelines recommend 3 percent (Austria, Finland, Germany, Italy, Spain (CatSalut and Spanish recommendations), and Sweden) or 5 percent (Croatia, Estonia and Latvia, Ireland, Portugal, Russia, Slovakia, and Osteba in Spain) but others recommend 3.5 percent (England and Scotland), 3.7 percent (Hungary), and 4 percent (Norway). The French guidelines (60) recommend a rate of 4 percent for time horizons less than 30 years with a decline thereafter, down to a discount rate of 2 percent. It is however foreseen that the discount rate will be reduced from 4 to 2.5 percent in the revised version of the French guidelines. Several guidelines also include recommendations concerning sensitivity analyses with discount rates between 0 and 10 percent.

Of the four countries that have guidelines that suggest a lower discount rate (or no discounting) for health effects than on costs, two suggest a discount rate of 1.5 percent for health effects together with a 3 or 4 percent discount rate for costs (Belgium (63) and the Netherlands (70)). Poland (62), on the other hand, suggests a discount rate of 3.5 percent for health effects and 5 percent for costs. Some of the countries that suggest the same discount rate on health effects and costs, recommend using differential rates in sensitivity analyses. For example, guidelines from Sweden (57) and Spain (93) suggest that the discount rate for health effects is set to 0 percent in sensitivity analyses.

Investigating the effect of different discount rates may be especially important for economic evaluations of public health programmes such as vaccines. For example, the French guidelines (60) mention that when the time horizon of an economic evaluation is long, as is the case with vaccination programmes, it is recommended to reduce the discount rate after 30 years. This decline is continuous and bottoms out at a discount rate of 2 percent.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is recommended that decisions regarding discounting is reported with clear reasoning or justification and, where relevant, according to available country-specific guidelines. The use of thorough sensitivity analyses concerning variations in discount rates is particularly recommended when a time horizon of extended duration is used. In the presentation of the results, it is recommended that both the discounted results and results without the application of discounting are shown.

Conclusion for discounting of costs and effects in health economic evaluations

Most countries use a discount rate between 3 to 5 percent for both costs and effects. Based on the results of the current review of guidelines used by EUnetHTA partners and previous EUnetHTA guidelines, it is recommended that both costs and effects are discounted in the base case analysis with the same rate. Furthermore, sensitivity analyses that explore the effect of varying the discount rate and differential discount rates (that is a lower discount rate for benefits than costs) should be performed; setting both discount rates to zero is also recommended.

2.3.10. Updating of costs to the relevant year and currency

Results from the review of guidelines

Most guidelines do not contain any information about how to convert costs to relevant currencies and price years (Table A22 in Annexe 5). However, some guidelines give general recommendations saying that the costs should be expressed in values of the current (or most recent) year (Austria, Belgium, Finland, Hungary, Ireland, the Netherlands, Scotland, and Spain [Osteba and CatSalut]). For example, the guidelines from Belgium (63) specify that all costs should be expressed in values of the current or most recent year and that if older values are used, these should be adjusted for inflation using appropriate Health Index figure. For index figures, the guideline refers to the web-site of the ministry of Economic Affairs. Adjustment for inflation by the use of different price indices is also recommended by the guidelines from Finland (price index for public expenditure on municipal health services) (77), Germany (general price index published by the Federal Statistical Office) (59), Hungary (Consumer Price Index) (78), Ireland (Consumer Price Index for health or one of its sub-indices) (61), and Scotland (UK health service price index) (64). On a European level, indices of consumer prices for the euro area and other European countries can be found at the Eurostat webpage (97).

Concerning recommendations for conversion of currency, the Austrian (69) and the Irish (61) guidelines specify that all costs should be converted to euros using purchasing power parity (PPP) indices. The Irish guideline further specifies that all necessary assumptions to transfer this data must be explicitly reported. The Baltic guidelines (Estonia and Latvia (91)) explicitly state that all costs should be reflected in local currency.

Other relevant guidelines

In ISPOR’s guideline on good research practices for measuring drug costs in cost-effectiveness analyses from an international perspective (52) it is recommended that drug costs are measured in local currency per unit of active ingredient and is converted to other currencies using sensitivity analyses of purchasing power parities (PPP) and exchange rates. If using drug prices from different years, it is recommended that the consumer price index for the local currency is applied before the PPP and/or exchange rate conversion.

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), it is specified that it is useful to adjust all costs to a common price level, e.g. to the year of analysis, using appropriate price inflators or deflators. For details on how to handle currency, price date, and conversion, the text refers to national guidelines and other methodological texts such as guidelines by The Campbell and Cochrane Economics Methods Group (CCEMG) (98) as well as the books by Gray et al. (2010) (99), Glick et al. (2007) (37) and Gold et al. (1996) (36).

The CCEMG has developed a free web-based tool for adjustment of costs expressed in one currency and price year to a specific target currency and price year (100). This tool is based on data sets containing PPP conversion rates from the International Monetary Fund (IMF) in the World Economic Outlook and the OECD ‘Purchasing Power Parities for GDP’ dataset. The GDP deflator values are from the IMF World Economic Outlook Database ‘GDP deflator index’ dataset. It should be mentioned that the web-based tool is a generic tool that is intended to be used across a large number of different countries and sectors (including health care, social welfare, education and criminal justice) and that there are health care-specific, technology-specific and episode-specific PPPs that have been developed and applied for specific use in the health care sector.

Conclusions for updating costs to the relevant year and currency

Based on the results of the current review of guidelines used by EUnetHTA partners and previous guidelines, it is recommended to convert costs to the most recent price year by using relevant indices. The index used and the original price year should be clearly indicated.

2.3.11. Presentation of results

Results from the review of guidelines

Of the 25 countries with guidelines, almost all recommend or require an incremental analysis of costs and health effects (Table A23 in Annexe 5). Moreover, 20 of the countries with guidelines explicitly write that they recommend or require that the results are presented as an ICER. However, some guidelines clarify that if one of the alternatives being compared is dominant (has lower costs and better effects than the alternative), there is no need to calculate the ICER (Austria, Hungary, Italy, and Slovakia). Instead, it should be clearly stated which of the strategies is estimated to be dominant. Several guidelines do also recommend presenting the absolute costs and effects of each alternative strategy (Austria, Croatia, England, Estonia and Latvia, Finland, Hungary, Ireland, Poland, Portugal, Russia and Slovakia).

It is also recommended in several guidelines that costs and health effects are presented in an aggregated as well as a disaggregated form (England (12, 82), Denmark, France, Ireland, Italy, and Norway). For example, the Norwegian guidelines (73) specify that the costs should be broken down into categories of drug costs, hospital costs, care costs and any costs associated with the production effects. The French National Authority for Health (HAS) (60) also wishes to be able to identify changes in expenditure for each funder and “to identify any transfers of expenditure which would be generated by choosing one intervention instead of another”. Therefore, the costs borne by the patients, compulsory health insurance and supplementary health insurance are presented separately.

Guidelines from England (12, 82) state that in addition to ICERs, expected net monetary or health benefits can be presented by using values of a QALY gained of £20,000 and £30,000. It has also come to our knowledge that, calculations of net-health benefit are recommended in a recently revised version of the German guidelines (not yet published). Moreover, some guidelines recommend or require that the results are illustrated by an efficiency frontier (Austria, Belgium, France and Germany).

In summary, almost all countries with guidelines recommend or require an incremental analysis of costs and health effects with the results presented both separately and combined in the form of an ICER. Several guidelines also recommend that absolute costs and health effects be presented and that if one of the alternative strategies is dominant, this should be clearly stated.

Other relevant guidelines

In the Costs and Economic Evaluations (ECO) domain of the HTA Core Model (1), it is recommended that the results be presented in the form of an ICER and show the specific components of the cost and outcomes of each alternative. Moreover, it is recognized that different jurisdictions or health-care systems have different approaches for the reporting of results of economic evaluations, and that it therefore, is recommended that results should be presented in a simple, disaggregated form. For costs, it is suggested that the results

are presented in a way that allows for the separation of different perspectives (e.g., patient, third-party payer, hospital, or societal). It is also recommended to consider presenting costs and outcomes associated with different stages of a disease separately.

Conclusions for presentation of results in health economic evaluations

Based on the results of the current review of guidelines used by EUnetHTA partners and the recommendations in the EUnetHTA Core model text, it is in a CEA or a CUA recommended to present results in terms of absolute and incremental values, separately for both costs and health outcomes and in terms of incremental cost-effectiveness ratios (ICERs). It is also suggested that the results are presented in an as disaggregated format as possible to allow for interpretations of the results from different perspectives, such as the third-party payer or the societal perspective. If one of the alternative strategies is estimated to be dominant, this should be clearly stated.

2.3.12. Uncertainty

Results from the review of guidelines

All countries with guidelines recommend sensitivity analyses to explore stochastic, parametric and/or methodological uncertainty in the economic evaluation (Table A24 in Annexe 5). Several of the guidelines specify that one-way sensitivity analysis (Austria, Belgium, England, Finland, France, Germany, Hungary, Ireland, the Netherlands, Norway, Scotland, and Spain), multiple sensitivity analysis (Belgium, France, Germany, Hungary, Ireland, Norway, Scotland, and Spain) and/or scenario analysis (England, Finland, France, and Ireland) are recommended or should be performed.

For parameter uncertainty, various guidelines recommend probabilistic sensitivity analysis (PSA) (Austria, Belgium, Croatia, England, Finland, France, Germany, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Scotland, Slovakia, and Spain). The result is recommended to be presented with confidence intervals (CIs) around the ICER (Belgium, Estonia and Latvia, Italy, Poland, and Slovakia), in scatter plots in CE planes (Belgium, England, France, Ireland, The Netherlands, Poland, Scotland, Slovakia, and Spain) and/or in cost-effectiveness acceptability curves (CEAC) (Austria, Belgium, England, Ireland, Italy, Poland, Scotland, Slovakia, and Spain).

To assess model uncertainty, a few guidelines recommend building alternative models (Austria and France). The guidelines from France (60) mention model meta-analysis methods (model averaging), which can make it possible to weight different model scenarios explicitly.

The technology appraisal guidelines from England (12) give some advice on the usefulness of best- and/or worst-case sensitivity analysis. This is stated to be an “important way of identifying parameters that may have a substantial impact on the cost-effectiveness results and of explaining the key drivers of the model”. Nevertheless, such analyses become less helpful in exploring the combined effects of multiple sources of uncertainty as the number of uncertain parameters increase. In these cases, PSA is stated to be a better approach.

In summary, all countries with guidelines recommend sensitivity analysis to explore uncertainty. Several guidelines also specify that parameter uncertainty should be analyzed

by the use of PSA and recommend that the results are presented with CIs around the ICER, scatter plots in a CE plane or in a CEAC.

Other relevant guidelines

According to the Costs and Economic Evaluations (ECO) domain of the HTA Core Model® (1), the extent to which uncertainty analyses are included is likely to depend on the type of decision the economic evaluation seeks to support, or on the requirements defined in national guidelines. Nevertheless, univariate sensitivity analyses are stated to be particularly informative to identify parameters which may have substantial impact on the results of economic evaluations and both the use of DSA and PSA is recommended. For general guidance on uncertainty estimation, the text refers to a number of sources (see, e.g., (33), (32), (101) and (102)).

Conclusions concerning uncertainty

Based on the results of the current review of guidelines used by EUnetHTA partners and the recommendations in the HTA Core Model, uncertainty should be explored in sensitivity analyses. To be in accordance with the majority of the countries’ guidelines, deterministic as well as probabilistic sensitivity analysis should be conducted.

3. Conclusion and main recommendations

The work with the present guideline was initiated to set a general framework for EUnetHTA on how to conduct health economic evaluations and increase the transferability of economic evaluations between EUnetHTA partners. This is especially important in order to enhance the usefulness of economic evaluations conducted within EUnetHTA. Currently, economic evaluations conducted within the projects of EUnetHTA rely upon the availability of national guidelines for many issues. The hope is that a common framework will facilitate the production of economic evaluations that are more easily transferred from one local context to another. In addition, a common framework may also be useful for countries that do not have methodological guidelines for health economic evaluations.

This guideline is based on a review of methodological guidelines for health economic evaluations used in the countries represented in EUnetHTA. Reaching a 100 percent response rate, this review gives a highly complete picture of the methodological guidelines currently being used in the different countries involved in EUnetHTA. By describing the different standpoints of the EUnetHTA partners, it was possible to identify several methodological issues where the EUnetHTA countries have a common view. Based on these commonalities, recommendations for economic evaluations within EUnetHTA could subsequently be formed. On issues where no clear consensus was apparent, it was in some cases still possible to form recommendations on how the exchange of results between European countries could be facilitated by presenting different scenarios with alternative estimates.

Based on the existing guidelines used by the EUnetHTA partners, it is recommended that the economic evaluations are conducted both as cost-effectiveness analyses (CEA) and cost-utility analyses (CUA). It is also recommended that the chosen time horizon for the analysis is sufficiently long to reflect all important differences in costs and outcomes between the interventions being compared. Moreover, the use of decision models is encouraged by EUnetHTA partners. However, modelling should always be justified and presented as transparently as possible. Providing an electronic version of the model to users could enhance the transparency and usefulness further.

Concerning the choice of perspective for health economic evaluations, the recommendations are diverse. However, it may be concluded that the analysis should be performed at a minimum from a health care perspective. Since several countries recommend a societal perspective, supplementary analyses presenting resource use and effects related to other sectors of society may increase the usefulness of the economic evaluation for other countries.

One of the key difficulties in sharing economic evaluations between countries is related to costs often being context specific, which is clearly demonstrated by recommendations to use regional sources in the guidelines. The economic evaluations can be made more adaptable to local settings if the resource use is clearly presented in natural units.

Based on the preferences of the majority of the countries, it is recommended to present the outcome of the analysis in QALYs and in life years gained when relevant. The use of QALYs has been debated in the literature of health economic evaluation (see for example (103). It has been pointed out that the QALY does not comply with some of its methodological tenets (see for example Tsuchiya et al. (104) and Beresniak et al. (103)). Still, QALY is the most commonly used outcome measure in the countries involved in EUnetHTA since it combines two dimensions (gained life years and quality of life).

However, since not all countries prefer the use of QALY, it is also recommended that the health effects are presented in natural units (e.g. number of certain complications, number of certain side effects, symptom-free survival).

Concerning the presentation of results, it is recommended that cost and health outcomes be presented in incremental as well as absolute numbers. If a CUA or CEA is used, they should also be presented both separately and combined in the form of incremental cost-effectiveness ratios (ICER). To allow for the results to be interpreted from different perspectives, they should if possible be presented in a disaggregated format. To address the needs of the majority of the countries, deterministic as well as probabilistic sensitivity analysis is recommended to explore uncertainties surrounding the results.

This review has also identified aspects of conducting health economic evaluations where it is difficult to find a common view within EUnetHTA. For example, this concerns issues related to the acceptability of certain outcome measures, costs to be included, rates for discounting costs and effects, and methods for derivation of HRQoL weights for calculation of QALYs. A more thorough analysis of these issues would be of value to EUnetHTA. In such analyses, current methodological guidelines issued by organisations such as ISPOR could be helpful.

Despite the high response rate, this guideline has some limitations. First of all, the quality and timeliness of the guideline depends to a relevant extent on the documents provided by the EUnetHTA partners. Some of the guidelines are more than ten years old and they vary in scope, length and level of detail. As the practices and guidelines of the partners evolve, the relevance of this guideline may decrease. Frequent updates could help minimize this limitation. However, it is beyond the scope of the guideline to take into account any discrepancies between how health economic evaluations are conducted in practice and what has been outlined in the regional guidelines provided by the partners. Secondly, the accuracy of the data extraction also depends on the accuracy of the interpretations of the extractors. By relying on multiple people to extract data, there was a risk that the extractors did not interpret the information consistently, or that differing amounts of data were harvested. Further inaccuracy may have been introduced when data was extracted from guidelines not available in English. In these cases, it was necessary to rely on information from translated checklists based on the guidelines, ISPOR’s collection of country-specific pharmaco-economic guidelines and/or tools for translation. To address these limitations, a calibration exercise was performed before data extraction began. In addition, the extracted data were validated by contact persons for each country.

It could also be regarded as a limitation that the guideline does not take a standpoint on what is theoretically right or wrong. In this context, it should be emphasized that the focus of this guideline is to give an overview of the requests on economic evaluations faced by the EUnetHTA partners, and provide guidance on how economic evaluations can be conducted to make the results as useful and relevant as possible for the EUnetHTA partners. By doing so, it sheds light on the issues where the partners are in agreement but also where there are differences that may need further investigation.

There will probably always be a need for adaptations of economic evaluations to local settings due to different contexts and policies for how health care resources should be allocated (e.g. due to differences in health care systems, populations, local costs and clinical settings). However, many of the differences between the guidelines are related to strictly methodological issues and may reflect underlying differences in how HTA is understood by different researchers as well as decision-makers. For example, this concerns issues such as the discount rate, how to present the results and the uncertainty

around it, as well as the acceptance of mapping and the use of indirect comparisons. An interesting question is whether these methodological differences really depend on different views on what is methodologically correct, or whether they are merely a result of different processes for developing the guidelines. Although a consensus has yet to be agreed upon for some issues, the contents of this guideline will hopefully improve the usefulness of economic evaluations performed within EUnetHTA and move us closer to a common European framework for conducting health economic evaluations.

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Annexe 2. Documentation of literature search

No systematic literature search has been conducted for the elaboration of this guideline.

Annexe 3. Other sources of information

Table A1. Guidelines included in the overview

Country	Name of document and authoring organisation	Primarily used for	Documents and content of this guideline validated by
Austria	Methodenhandbuch für HTA Version 1.2012, Bundesinstitut für Qualität im Gesundheitswesen (BIQG) und Gesundheit Österreich GMbH, 2012 (69)	All type of technologies	Gesundheit Österreich (GmbH) Private Universität für Gesundheitswissenschaften (UMIT), Medizinische Informatik und Technik GmbH Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
	Hauptverband der österreichischen Sozialversicherungsträger, Der Hauptverband der österreichischen Sozialversicherungsträger verlautbart gemäß § 351g Abs. 1 ASVG:Verfahrensordnung zur Herausgabe des Erstattungskodex nach § 351g ASVG - VO-EKO (105)	Pharmaceuticals	
	Guidelines on Health Economic Evaluation, Consensus paper, Institute for Pharmacoeconomic Research (IPF), 2006 (106).	All type of technologies	
Belgium	Belgian guidelines for economic evaluations and budget impact analyses: Second edition, KCE Report 183C, Belgian Health Care Knowledge Centre (KCE), 2012 (63)	All type of technologies	Belgian Health Care Knowledge Centre (KCE)
Croatia	Chapter 6, Guide for the economic evaluation of health technologies, In: The Croatian Guideline for Health Technology Assessment Process and Reporting, Agency for Quality and Accreditation in Health Care, 2011 (65)	All type of technologies	Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ)
Czech Republic	SP-CAU-028 Postup pro hodnocení nákladové efektivity, Státní ústav pro kontrolu léčiv (SUKL), 2013 (107)	Pharmaceuticals	Ministry of Health of the Czech Republic (MoH Cz Rep)
	F-CAU-028-01-Check-list minimálních požadavků na kvalitu a úplnost hodnocení nákladové efektivity (Check-list for submitted pharmacoeconomic evaluation), Státní ústav pro kontrolu léčiv (SUKL), 2013 (108)	Pharmaceuticals	
Denmark	Chapter 9 The economy, In: Health Technology Assessment Handbook, Danish Centre for Health Technology Assessment, National Board of Health, 2007 (109)	All type of technologies	Danish Health and Medicines Authority (DHMA)
	Report on Guidelines for Health economic analyses of medicinal products, Sunhedsstyrelsen (initiated by the Danish Ministry of Health), 1998 (80)	Pharmaceuticals	
England	Guide to the methods of technology appraisal 2013, National Institute for Health and Care Excellence (NICE), 2013 (12)	All type of technologies	National Institute for Health and Care Excellence (NICE)
	Medical Technologies Evaluation Programme Methods guide, National Institute for Health and Care Excellence (NICE), 2011 (75)	Medical devices	
	Diagnostics Assessment Programme, 2011 manual, National Institute for Health and Care Excellence (NICE), 2011 (82)	Diagnostics	
Estonia	Baltic guideline for economic evaluation of pharmaceuticals (Pharmacoeconomic Analysis), Experts from health authorities of the	Pharmaceuticals	Department of Public Health of the University of Tartu (UTA)

	Baltic countries, 2002 (91)		
Finland	Preparing a health economic evaluation to be attached to the application for reimbursement status and wholesale price for a medicinal product, Application instructions TTS 10.6.2013, Lääkkeiden hintalautakunta, 2013 (77)	Pharmaceuticals	FinOHTA, National Institute for Health and Welfare (THL)
	Guidelines for preparing a health economic evaluation, Annex to the Decree of the Ministry of Social Affairs and Health on applications and price notifications made to the Pharmaceuticals Pricing Board (201/2009), Ministry of Social Affairs and Health, Pharmaceuticals Pricing Board, 2011 (110)	Pharmaceuticals	
	Taloudellinen arviointi (Economic evaluation). In: Menetelmien arviointi terveydenhuollossa. Duodecim, 2007 (111)	All type of technologies	
France	Choices in Methods for Economic Evaluation, Haute Autorité de Santé (HAS), 2012 (60)	All type of technologies	Haute Autorité de Santé (HAS)
Germany	Allgemeine Methoden, Version 4.2 , German national Institute for Quality and Efficiency in Health Care (IQWiG), 2015 (71)	Pharmaceuticals	German national Institute for Quality and Efficiency in Health Care (IQWiG)
	General Methods for the Assessment of the Relation of Benefits to Costs (Version 1.0 19/11/2009), German national Institute for Quality and Efficiency in Health Care (IQWiG), 2009 (59), expired since 24.04.2015!	Pharmaceuticals	
	Working Paper Modelling Version 1.0 – 19/11/2009, German national Institute for Quality and Efficiency in Health Care (IQWiG), 2009 (112), expired since 24.04.2015!	Pharmaceuticals	
	Working Paper Cost Estimation Version 1.0 – 19/11/2009, German national Institute for Quality and Efficiency in Health Care (IQWiG), 2009 (113), expired since 24.04.2015!	Pharmaceuticals	
Hungary	Methodological guidelines for conducting economic valuation of healthcare interventions in Hungary: a Hungarian proposal for methodology standards, Ministry of Health and academia, 2002 (78)	All type of technologies	National Institute for Quality and Organizational Development in Healthcare and Medicines (GYEMZI)
	Az Emberi Erıforrások Minisztériuma szakmai irányelve az egészség-gazdaságtani elemzések készítéséhez 2013. EüK. 3. szám EMMI közlemény 2 (hatályos: 2013.03.01 -), 2013 (114) (in Hungarian, the differences between this and the one from 2002 have been explained in English in an e-mail)	All type of technologies	
Ireland	Guidelines for the Economic Evaluation of Health Technologies in Ireland, Health Information and Quality Authority (HIQA), 2014 (61)	All type of technologies	Health Information and Quality Authority (HIQA)
Italy	Italian Guidelines for Economic Evaluation (only available in Italian: Proposta di linee guida per la valutazione economica degli interventi sanitari), Italian Association of health care economists, 2009 (83)	All type of technologies	Italian Medicines Agency (AIFA) Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS) Regione Emilia Romagna, Regional Agency for Health and Social Care (ASSR)
Latvia	Baltic guideline for economic evaluation of pharmaceuticals (Pharmacoeconomic Analysis), Experts from health authorities of the Baltic countries, 2002 (91)	Pharmaceuticals	The National Health Service of Latvia (NHS)

The Netherlands	Guidelines for Pharmacoeconomic Research in the Netherlands, Health Care Insurance Board, 2006 (70)	Pharmaceuticals	National Health Care Institute (ZIN)
	Update of the Dutch Manual for Costing in Economic Evaluations, Erasmus Universiteit Rotterdam, 2012 (115)	Pharmaceuticals	
	Guidelines for outcomes research (to assess the cost-effectiveness of inpatient drugs), Health Care Insurance Board, 2008 (116)	Pharmaceuticals	
Norway	Guidelines on how to conduct pharmacoeconomic analyses, Norwegian Medicines Agency (NOMA), 2012 (73)	Pharmaceuticals	Norwegian Knowledge Center for the Health Services (NOKC)
	Økonomisk evaluering av helsetiltak – en veileder, Helsedirektoratet, 2012 (74)	All type of technologies	
Poland	Guidelines for conducting Health Technology Assessment (HTA) (Polish guidelines), Agency for Health Technology Assessment, Version 2.1 (Part 4 & 5), 2009 (62)	All type of technologies	Agency for Health Technology Assessment in Poland (AHTAPol)
	REGULATION OF THE MINISTER OF HEALTH of 2 April 2012 on the minimum requirements to be satisfied by the analyses accounted for in the applications for reimbursement and setting the official sales price and for increasing the official sales price of a drug, a special purpose dietary supplement, a medical device, which do not have a reimbursed counterpart in a given indication (Polish regulation), Minister of health, 2012 (66)	Pharmaceuticals	
Portugal	Guidelines for Economic Drug Evaluation Studies, INFARMED, 1998 (81)	Pharmaceuticals	National Authority of Medicines and Health Products (INFARMED)
Russia	Protocol on the Procedure for Clinical and Economic Evaluation of Drugs which are submitted for inclusion into reimbursed drug lists, ISPOR Russian HTA Chapter, Russian State Medical University, 2010 (117)	Pharmaceuticals	National Center for Health Technology Assessment (ANO NC HTA)
	Regulation of the ministry of health of the Russian federation on the procedure of compiling essential drug list (Draft), Russian Ministry of Health (89)	Pharmaceuticals	
Scotland	Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF), Scottish Medicines Consortium, 2013 (64)	Pharmaceuticals	Scottish Medicines Consortium (SMC)
Slovakia	The announcement concerning pharmaco-economic analysis of drugs, Ministry of Health of the Slovak Republic, 2011 (67)	Pharmaceuticals	Ministry of Health of the Slovak Republic
	Methodological tool for the implementation economic analysis of pharmaceuticals and medical devices, Ministry of Health of the Slovak Republic, 2008 (118)	Pharmaceuticals & medical devices	
Slovenia	Regulation on classifying drugs onto positive list for public financing, Health Insurance Institute of Slovenia, 2010 (76)	Pharmaceuticals	Institute of Economic Research (IER)
Spain	Spanish recommendations on economic evaluation of health technologies (Spanish version: Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias), Canary Islands Health Services, Castilla La Mancha University, La Rioja University, Public Health Agency of Barcelona, Vic University, Alto Deba Hospital & Pompeu Fabra	All type of technologies	Andalusian HTA Agency (AETSA) Basque Agency for HTA, Department of Health (OSTEBA) Evaluation AND Planning Unit - Directorate of the Canary

	University, 2010 (93).		Islands Health Service (SESCS)
	Guía para informes de evaluación de medicamentos, Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA), 2013 (68)	Pharmaceuticals	
	Guía de Evaluación Económica en el Sector Sanitario. Osteba, 1999 (119)	All type of technologies	
	Guía y recomendaciones para la realización y presentación de evaluaciones económicas y análisis de impacto presupestario de medicamientos en el ámbito del CatSalut, Catsalut, 2014 (120)	Pharmaceuticals	
Sweden	General guidelines for economic evaluations from the Pharmaceutical Benefits Board, The Dental and Pharmaceutical Benefits Agency (TLV), 2003 (57)	Pharmaceuticals	The Dental and Pharmaceutical Benefits Agency (TLV) Swedish Council on Health Technology Assessment (SBU)
	Guide for companies when applying for subsidies and pricing for pharmaceutical products, Version 2.0, Decided 2/3/2012, The Dental and Pharmaceutical Benefits Agency (TLV), 2012 (79)	Pharmaceuticals	
	Allmänna råd för ansökan om pris och subvention för förbrukningsartiklar, TLVAR 2011:1, and "Handbok till Tandvårds- och läkemedelsförmånsverkets föreskrifter (TLVFS 2011:3) om ansökan om pris och subvention för förbrukningsartiklar, The Dental and Pharmaceutical Benefits Agency (TLV) (121)	Disposables	
	Utvärdering av metoder i hälso- och sjukvården – en handbok, Swedish Council on Health Technology Assessment (SBU), 2013 (122)	All type of technologies	
Switzerland	Handbuch betreffend die Spezialitätenliste (including Appendices), Bundesamt für Gesundheit, 2013 (72)	Pharmaceuticals	Swiss Federal Office of Public Health
	Handbuch zur Antragstellung auf Kostenübernahme bei neuen oder umstrittenen Leistungen, Erläuterungen zum Antragsformular „Medizinische Leistungen", Eidgenössische Kommission für allgemeine Leistungen und Grundsatzfragen (ELGK), 2009 (92)	All type of technologies	
	Operationalisierung der Begriffe Wirksamkeit,: Zweckmässigkeit und Wirtschaftlichkeit Arbeitspapier, Workingpaper, Version 2.0, Bundesamt für Gesundheit, 2011 (123)	Pharmaceuticals	
	Antragsformular (application form), Eidgenössische Kommission für allgemeine Leistungen und Grundsatzfragen (ELGK), 2009 (124)	All type of technologies	

Annexe 4. Additional information about included guidelines

Table A2. Status of the guideline[1]

Country	Status of the economic guideline
Austria	Recommendation
Belgium	Mandatory, deviations need to be justified in detail
Croatia	Mandatory, deviations need to be justified in detail
Czech Republic	Recommendation
Denmark	Mandatory (Sunhedsstyrelsen) Deviation from the guideline is accepted if a well-founded reason exists
	Recommendation (Danish Centre for Health Technology Assessment)
England	Mandatory (NICE Technology Appraisals)
	Mandatory (NICE Medical Technologies Evaluation Programme Methods guide)
	Mandatory (NICE Diagnostics Assessment Programme)
Estonia	Not explicitly stated
Finland	Mandatory (Lääkkeiden Hintalautakunta)
France	Mandatory (but some guidelines are only recommendations)
Germany	Mandatory
Hungary	Recommendation
Ireland	Mandatory
Italy	Recommendation
Latvia	Mandatory
The Netherlands	Mandatory, deviations need to be justified in detail
Norway	Mandatory (Norwegian Medicines Agency, 2012)
	Recommendation (Helsedirektoratet)
Poland	Recommendation (Guideline)
	Mandatory (Regulation)
Portugal	Mandatory
Russia	Mandatory (ISPOR)
	Mandatory (REGULATION OF THE MINISTRY OF HEALTH)
Scotland	Mandatory
Slovakia	Mandatory
Slovenia	Mandatory
Spain	Recommendation (Spanish recommendations, OSTEBA, AETSA, CatSalut)
Sweden	Mandatory (TLV parmaceuticals and articles of consumption)
	Recommendation (SBU)
Switzerland	Mandatory (for the administration)

[1] This refers only to the application of the guidelines, not to the question whether health economic evaluations as such are mandatory.

Table A3. Purpose of conducting the health economic evaluations that the guideline is written for

Country	The purpose of the economic evaluations that the guideline is written for
Austria	Reimbursement
Belgium	Reimbursement
Croatia	Recommendation
Czech Republic	Reimbursement
Denmark	Reimbursement (Sunhedsstyrelsen)
	Recommendation (Danish Centre for Health Technology Assessment)
England	Reimbursement (NICE Technology Appraisals)
	Recommendation (NICE Medical Technologies Evaluation Programme Methods guide)
	Recommendation (NICE Diagnostics Assessment Programme)
Estonia and Latvia	Reimbursement
Finland	Reimbursement
France	In general, recommendation but for price negotiation for pharmaceuticals and medical devices
Germany	Reimbursement
Hungary	Reimbursement
Ireland	In general information but also for reimbursement
Italy	Information
The Netherlands	Reimbursement
Norway	Reimbursement (NOMA)
	Recommendation (Helsedirektoratet)
Poland	Information (Guideline)
	Reimbursement (Regulation)
Portugal	Reimbursement
Russia	Recommendation (ISPOR)
	Reimbursement (REGULATION OF THE MINISTRY OF HEALTH)
Scotland	Recommendation
Slovakia	Reimbursement
Slovenia	Reimbursement
Spain	Information (OSTEBA, AETSA), Information and recommendation (CatSalut)
Sweden	Reimbursement (TLV)
	Information (SBU)
Switzerland	Reimbursement

Annexe 5. Tables

Table A4. Choice of comparator/s for the health economic evaluation

Country	Choice of comparator/s for the economic evaluation
Austria	Na
Belgium	Selected by help of an efficiency frontier
Croatia	Therapies routinely used in the Croatian health system, including technologies regarded as current best practice
Czech Republic	Therapies routinely used and reimbursed in the Czech health system. The comparator should be selected and justified properly.
Denmark	Na
England	Technologies or tests that are current practice or are recommended in current NICE guidance (Technology Appraisals and NICE Medical Technologies Evaluation Programme Methods guide)
Estonia and Latvia	Standard treatment or the usual treatment in daily practice
Finland	Therapeutically the most appropriate alternative. Based on Finnish clinical practice
France	All interventions that compete with the intervention evaluated
Germany	All therapeutic alternatives
Hungary	Standard/ most common treatment
Ireland	Routine care, i.e. the technology(ies) most widely used in clinical practice in Ireland
Italy	Current practice
Norway	The treatment (drug(s) or health program(s)) that the new pharmaceutical will most likely replace. If currently used treatment not cost-effective, the efficiency frontier.
The Netherlands	Standard treatment
Poland	Existing practice – procedure that will likely be replaced by assessed health technology in medical practice (Guideline) Reimbursed technology that is the existing practice should be the first choice (Regulation)
Portugal	Current practice, i.e. the most common treatment
Russia	Drugs that are already included in the reimbursement list or, if there is no such drugs, common drugs with similar indications
Scotland	Treatments considered to be in routine use or represent best practice in NHS Scotland, and are the treatments that are most likely to be replaced.
Slovakia	The treatment that is most likely to be replaced by the new treatment or, in case of add-on treatments, the current treatment without the add-on product
Slovenia	The drug with the same therapeutic indication (other drugs can be included as well)
Spain	The standard technology used in current health care practices (AETSA, Osteba, CatSalut, Spanish recommendation). If possible also the most effective alternatives (Osteba, CatSalut)
Sweden	The most appropriate alternative treatment in Sweden (e.g. the most used)
Switzerland	The current treatment standard in Switzerland

Na: No information available.

Table A5. Subgroup analyses in health economic evaluations

Country	Are there recommendations for subgroup analyses in health economic evaluations?
Austria	Yes. Recommended for populations with high heterogeneity
Belgium	Yes. If the intervention's safety, effectiveness, costs and/or baseline risk for events differ between subgroups, separate subgroup analyses should be performed.
Croatia	Yes. Estimates of clinical and cost effectiveness separately for each *relevant* subgroup of patients
Czech Republic	Subgroup data may be presented additionally in case of potentially important differences in clinical effectiveness or costs
Denmark	Na
England	Yes. Subgroup analyses should be presented separately for each relevant subgroup where appropriate.
Estonia and Latvia	Yes. Subgroup data may be presented additionally in case of potentially important differences in clinical effectiveness or costs
Finland	Yes. A separate evaluation should be prepared for each indication
France	Yes. Subgroups analyses may be necessary in case of documented heterogeneity of the health effects or the costs
Germany	Yes. There can be subgroup analyses, which need to be documented
Hungary	Yes. When the clinical effectiveness or cost-effectiveness in particular patient subgroups differ significantly
Ireland	Yes. Stratified analysis of sub-groups is appropriate when there is biological or clinical support for heterogeneity in the target population
Italy	Yes. Subgroup analyses should be derived from proven differences in the parameters
Norway	Yes. When/if the intervention is expected to differ significantly in cost and/or efficacy for different groups
The Netherlands	Yes. With respect to assumptions in the discount rate, unit costs, subgroups, patient characteristics and possible model structures, it is possible to conduct an extra analysis.
Poland	Yes. If the analysis of subgroups has been carried out, the cost-effectiveness in the sub-group should be indicated in comparison to the total population.
Portugal	Yes. The target population can be divided into subgroups
Russia	Na
Scotland	Yes. A clear definition of subgroup analysis (when appropriate) and a justification of a differential effect within patient subgroups are required
Slovakia	Yes. Subgroup analysis should be performed
Slovenia	Na
Spain	Yes. Use data that will determine whether differences in age, gender, disease severity, and risk factors have a significant impact on either effectiveness or costs (Spanish recommendations, Osteba). If there is clinical evidence that there are differences between subgroups, the results should be analyzed separately for these different subgroups (CatSalut).
Sweden	Yes. Separate calculations should be made for different patient groups where the treatment is expected to have different cost-effectiveness
Switzerland	Na

Na: No information available

Table A6. Systematic review of previous health economic evaluations

Country	Is it requested to present a systematic review over previous health economic evaluations of the technology?
Austria	Not requested
Belgium	Recommended
Croatia	Yes, requested
Czech Republic	Na
Denmark	Na
England	Yes, requested
Estonia and Latvia	Not requested.
Finland	Na
France	Yes, requested
Germany	Recommended
Hungary	It is recommended to compare the results with the previous economic evaluations.
Ireland	Na
Italy	Na
The Netherlands	No, a systematic review is not explicitly requested, but results have to be compared with other studies.
Norway	Na
Poland	Guideline: It is not specified that a systematic review is required, just a convergence validation is recommended. Regulation: Yes, requested
Portugal	Na
Russia	Na
Scotland	Na
Slovakia	Yes, requested
Slovenia	Na
Spain	Yes (AETSA)
Sweden	Na
Switzerland	Na

Na: No information available

Table A7. Time horizon

Country	Preferred time horizon of the economic evaluation
Austria	Choice of time horizon depends on research question and study subject
Belgium	Sufficiently long to reflect all important differences in costs and outcomes
Croatia	Sufficiently long to reflect all important differences in costs and outcomes
Czech Republic	Sufficiently long to reflect all important differences in costs and outcomes
Denmark	Sufficiently long to reflect all important differences in costs and outcomes
England	Sufficiently long to reflect all important differences in costs and outcomes
Estonia and Latvia	Not indicated, but it is stated that “…modelling techniques can be applied when trial data provide too short a time frame…”
Finland	Sufficiently long to reflect all important differences in costs and outcomes
France	Sufficiently long to reflect all important differences in costs and outcomes
Germany	At least length of RCTs, yet the appropriate time horizon depend on the nature of the disease
Hungary	Sufficiently long to reflect all important differences in costs and outcomes
Ireland	Sufficiently long to reflect all important differences in costs and outcomes
Italy	Sufficiently long to reflect all important differences in costs and outcomes
The Netherlands	Sufficiently long to reflect all important differences in costs and outcomes
Norway	Sufficiently long to reflect all important differences in costs and outcomes
Poland	Sufficiently long to reflect all important differences in costs and outcomes
Portugal	Sufficiently long to reflect all important differences in costs and outcomes
Russia	Na
Scotland	Sufficiently long to reflect all important differences in costs and outcomes. Results (in net cost per QALY gained) should also be reported at different time horizon intervals e.g. at end of study follow-up, at 5 years follow-up and at 5-year intervals thereafter.
Slovakia	Sufficiently long to reflect all important differences or 5 years
Slovenia	Time horizon must be specified in economic analysis
Spain	Sufficiently long to reflect all important differences in costs and outcomes (Spanish recommendations, CatSalut) A shorter horizon which only includes primary data and a longer horizon that includes modelling (Osteba) It is recommended to do a complimentary analysis with a time perspective of 3-5 years (CatSalut)
Sweden	Sufficiently long to reflect all important differences in costs and outcomes
Switzerland	Na

Na: No information available, RCT: randomized controlled trial

Table A8. Preferred type of analysis

Country	Preferred type of analysis
Austria	No preferred type
Belgium	CUA, CEA or CMA.
Croatia	CUA or CEA
Czech Republic	CUA
Denmark	Not explicitly stated. CEA and CUA seem to be accepted.
England	CUA (Technology Appraisals and NICE Diagnostics Assessment Programme) CCA (NICE Medical Technologies Evaluation Programme Methods Guide)
Estonia and Latvia	CEA or CMA
Finland	CUA, CEA, CMA or CBA
France	CUA and CEA
Germany	CEA (several endpoints= several efficiency frontiers)
Hungary	CUA, CEA or CMA,
Ireland	CUA or CEA
Italy	CUA or CEA
The Netherlands	CUA, CEA or CMA
Norway	CUA, CEA or CMA.
Poland	CUA (preferred according to the regulation), CEA or CMA and a CCA. CBA is possible only as an additional analysis (according to the guidelines).
Portugal	CUA, CEA, CMA or CBA (CUA is preferred)
Russia	CEA or CMA (Ministry of health) CMA, CEA, CUA or CBA (ISPOR Russian HTA Chapter)
Scotland	CUA or CMA
Slovakia	CUA, CEA or CMA
Slovenia	CUA, CEA or CMA and Cost Analysis.
Spain	CUA, CEA, CMA or CBA. CUA is preferred. (Spanish recommendations, Osteba) CUA, CEA or CMA (AETSA) CUA or CMA (CEA only if a CUA cannot be conducted) (CatSalut)
Sweden	CUA, CEA, CMA or CBA
Switzerland	CEA

CBA: Cost-benefit analysis, CCA: Cost-consequence analysis, CEA: Cost-effectiveness analysis, CUA: Cost-utility analysis, CMA: Cost-minimization analysis.

Table A9. Use of models

Country	Acceptance of modeling and specific requirements
Austria	Modelling accepted All kinds of models Internal and external validation should be analysed
Belgium	Modelling accepted Markov and decision trees are mentioned as major categories Extrapolation should be presented in scenarios Internal and external validation requirements
Croatia	Modelling accepted No further information available
Czech Republic	Modelling accepted All kinds of models
Denmark	Modelling accepted No further information available
England	Modelling accepted Microsoft Excel, DATA, Winbugs or R is recommended (process guide).If extrapolation, compare several alternative scenarios The methods of quality assurance used in the development of the model, and model validation should be detailed
Estonia and Latvia	Modelling accepted No further information available
Finland	Modelling accepted No further information available
France	Modelling accepted Many types of model can be used Effect of extrapolation tested in scenarios The ability of a model to produce results that are consistent and suited to the reality of the decision-making process is tested.
Germany	Modelling accepted All kinds of models Requirements on validation
Hungary	Modelling accepted All types of models are accepted Modelling software is not specified
Ireland	Modelling accepted Available modelling techniques including decision-tree analysis, state transition or Markov models, and discrete-event simulation. No requirement on methods for extrapolation Validation requirements exist
Italy	Modelling accepted All types of models are accepted, requirements on documentation and motivation No specific program or modelling methods recommended Models should be carefully validated
The Netherlands	Modelling accepted In general: Markov, decision trees, discrete-event simulations (template for applicants)Only models in MS Excel or TreeAge are accepted (template for applicants) Internal and external validation is required
Norway	Modelling accepted The choice of approach should be justified. Requirements on documentation of extrapolation Models should be carefully validated
Poland	Modelling accepted Markov model is accepted. Other models are not mentioned. If data in the model are extrapolated over time horizon of the primary trials, the following scenarios should be analyzed: optimistic, pessimistic and neutral. Internal and external validation, as well as convergence validation, are required
Portugal	Modelling accepted The following types of models are accepted: Decision trees, Markov's Model, Extended revision of literature relevant to the clinical and economic analysis of the problem There is no specific program recommended. External validation is recommended.
Russia	Modelling accepted No further information available
Scotland	Modelling accepted

	There is no requirement on methods for extrapolation Requirements on internal or external validation are not stated
Slovakia	Modelling accepted No further information available
Slovenia	Modelling accepted No further information available
Spain	Modelling accepted (Spanish recommendations, Osteba, AETSA, CatSalut) All types of models (only decision trees and Markov models addressed in Osteba) No additional information concerning programs or methods for extrapolation or internal/external validation.
Sweden	Modelling accepted No further information available
Switzerland	Modelling accepted No further information available

Table A10. Perspective on costs and outcomes

Country	Perspective on costs	Perspective on outcomes
Austria	The choice of perspective must be justified.	The choice of perspective must be justified.
Belgium	Health care payers	Effects on patients primarily
Croatia	Perspective of the Croatian Institute for Health Insurance (public payer)	All health effects on individuals. Health effects in informal caregivers and/or family members can be reported separately
Czech Republic	Health care payers	Na
Denmark	Socio-economic perspective	Na
England	The NHS and personal social services	All direct health effects, whether for patients or where relevant for caregivers.
Estonia and Latvia	Health care	Na
Finland	Societal	Na
France	Collective perspective. All the resources used in the production of interventions.	Collective perspective. All the health effects relevant of the individuals concerned (patients, informal carers, general population)
Germany	SHI insurants primarily according to Social Code	SHI insurant primarily according to Social Code
Hungary	Na	Na
Ireland	The perspective of the publicly-funded health and social care system	All health benefits accruing to individuals
Italy	Health care	Effects on patients primarily
The Netherlands	Societal	Societal
Norway	Societal	Societal
Poland	Two variants are required: Public health care payer and public health care payer and the patient.	The patients. Societal perspective (health effects to other members of the society) in specific cases.
Portugal	Societal. This means considering the costs for the patient, for his or her family and also for third parties, i.e. public and private payers in particular. Society's perspective should be broken down into other relevant points of view, with special attention to the third payers if they are the users of the study.	Societal. This means considering the consequences for the patient, for his or her family and also for third parties, i.e. public and private payers in particular. Society's perspective should be broken down into other relevant points of view, with special attention to the third payers if they are the users of the study.
Russia	No priority for any perspective; it is only recommended that researchers declare clearly the perspective of the study (any: societal, healthcare, etc). For drugs submitted into the lists either societal or health care perspective are recommended.	No priority for any perspective; it is only recommended that researchers declare clearly the perspective of the study (any: societal, healthcare, etc). For drugs submitted into the lists either societal or health care perspective are recommended.
Scotland	A healthcare perspective is required, but a societal perspective can be explored through sensitivity analysis.	A healthcare perspective is required, but a societal perspective including effects on other individuals than patients (principally carers) can be explored through sensitivity analysis.
Slovakia	Health care payers	Societal
Slovenia	Health insurance; societal perspective can be performed as well	Patients only
Spain	Societal and third-party National Health System (NHS) Societal and that of the decision-maker (OSTEBA) The perspective of the financer – CATSALUT and as a complement a societal perspective (CATSALUT)	Societal and third-party National Health System (NHS) Societal and that of the decision-maker (OSTEBA) The perspective of the financer – CATSALUT and as a complement a societal perspective (CATSALUT)
Sweden	Societal	Societal
Switzerland	Health care	Only health effects on patients (not utility)

Na: No information available, NHS: National health service, SHI: Social health insurance.

Table A11. Costs to include

Country	What types of costs should be included?
Austria	Health-care payer perspective: all direct medical costs (e.g. for inpatient care, diagnostic test, drugs). If direct non-medical costs are relevant (e.g. costs for transportation), they need to be considered as well. Societal perspective: include productivity costs (Methods handbook). Costs for the Social Insurance (Regulation for pharmaceuticals/outpatient sector (VO-EKO).
Belgium	Direct health care costs in the reference case, while direct costs outside the health care sector, productivity costs and health care costs associated with unrelated diseases reported as a separate analysis.
Croatia	Direct cost relevant to Croatian Institute for Health Insurance. All cost and benefits outside the health care system, may be presented in addition, if considered relevant.
Czech Republic	Only costs related to the payer perspective should be included.
Denmark	All relevant costs, regardless whether they are direct, indirect or intangible. Indirect and intangible costs must be reported separately.
England	Direct costs should be included. Productivity costs are not included. Future costs that are considered to be unrelated to the condition or technology of interest should be excluded. Costs borne by patients that are not reimbursed by the NHS and personal social services may be presented separately. When care by family members, friends or a partner might otherwise have been provided by the NHS or personal social services it may be appropriate to consider the cost of the time of providing this care in a separate analysis.
Estonia and Latvia	Depends on the perspective. Health care perspective: all direct costs inside the health care system should be considered. If additional economic analysis is performed from the societal perspective, other non-medical costs can be included (both direct and indirect costs outside the health care system).
Finland	All direct health care and comparable social welfare costs related to the therapies. If productivity losses are included, the results must also be presented so that those are excluded.
France	Direct costs. All indirect costs (including productivity loss) are excluded from the ICER but may be presented in additional analysis. Unrelated future costs are excluded.
Germany	Direct health care costs and patient borne cost. Only future related costs should be considered in the base case. Any other costs can be included from other perspectives (productivity losses in societal perspective) and in other scenarios (unrelated future costs).
Hungary	Direct medical and direct non-medical costs. Costs not associated with the original intervention or costs emerging during one's life prolonged by the therapy should not be taken into account in the evaluation.
Ireland	Only direct costs relevant to the publicly-funded health and social care system should be included in the reference case. Resource use in physical units and unit costs should be presented in addition to total costs. Potential costs (or savings) to other government departments should not be included in the reference case, but may be included separately.
Italy	Direct costs. Indirect costs may be included in a separate analysis.
The Netherlands	Direct and indirect costs inside and outside the healthcare system; productivity loss should be included in a separate analysis; unrelated future costs due to prolonged survival must be excluded.
Norway	Direct costs should be included. Productivity effects (gains or losses) may be included in the standard analysis but then the results of the analysis must be shown both with and without these effects. Unrelated medical and non-medical costs in life years gained are not included.
Poland	The analysis should differentiate the following: (i) direct medical costs, (ii) direct non-medical costs, (iii) indirect costs.
Portugal	All direct and indirect costs should be identified. It is also advisable to include intangible costs (e.g. the pain suffered by the patient due to the use of invasive surgical techniques). Indirect costs should be reported in net terms, i.e. as costs calculated and deducted from gains, and be reported separately.
Russia	Direct and indirect costs should be presented.
Scotland	Only direct costs related to resources that are under the control of the NHS in Scotland and social work should be included in the reference case. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, these should be reported in a sensitivity analysis.
Slovakia	Direct health care costs should be included. Productivity loss and unrelated future costs due to prolonged survival may be included, but separated from the direct health care costs.
Slovenia	Direct health costs for all relevant future years.
Spain	It depends on the chosen perspective. Health care costs, labour losses, time loss, and informal care should be readily distinguished to ensure that such costs are not counted twice (Spanish recommendations, CatSalut, and Osteba). Indirect costs should be included in the societal perspective (Spanish recommendations, CatSalut).
Sweden	All relevant costs associated with treatment and illness should be included. The production loss for treatment and sickness should also be included. Unrelated future costs due to prolonged

	survival should be included. However, SBU recommends that the results are presented both with and without indirect costs.
Switzerland	Direct health care costs are decisive. Significant savings in indirect costs should be documented. Unrelated future costs due to prolonged survival should be included in the budget impact post.

ICER: incremental cost-effectiveness ratio, Na: No information available, NHS: National health service.

Table A12. Sources for data on costs

Country	Recommendations concerning sources for data on costs
Austria	No hierarchy
Belgium	No official hierarchy, but conditions are mentioned for situations when certain sources should be used; specific Belgian sources are mentioned, for instance Belgian unit prices for reimbursed and non-reimbursed drugs, unit prices for ambulatory and hospital health care services, and APR-DRGs
Croatia	The resources should be valued using the prices relevant to the Croatian Institute for Health Insurance. No hierarchy of sources is defined.
Czech Republic	Empirical costs are preferred rather than expert opinions. Sources of data used to estimate costs should be provided.
Denmark	Clinical and epidemiological data may be supplemented by ad hoc data on use of resources, which may be retrospective, although prospective designs are recommended.
England	The sources that best reflect the price relevant to the NHS are preferred (for the Technology Appraisal Programme: public list prices, nationally available price reductions, prices paid for some generic drugs, patient access scheme, national average unit cost of an HRG). Data based on HRGs may not be appropriate in all circumstances (for example, when the new technology and the comparator both fall under the same HRG, or when the mean cost does not reflect resource use in relation to the new technology under appraisal) and other sources of evidence, such as micro-costing studies, tariff or unit costs, may be preferred.
Estonia and Latvia	Sources of data used to estimate costs should be provided. Costs should be adapted to the local health care circumstances.
Finland	A detailed account must be presented of the resources used and unit costs, giving the grounds and source references. The health economic evaluation must be based on as up-to-date information on the costs in Finland as possible.
France	As far as possible, the valuation of a resource must be based on the production cost of this resource. In the absence of data on the production costs, tariffs are a priori an acceptable basis for valuation.
Germany	No hierarchy of sources
Hungary	In the case of studies which adapt resource use data from foreign clinical studies or health economic evaluations clinical practice in the foreign setting should be compared (and recalculated) with the Hungarian one.
Ireland	Sources include RCTs, meta-analysis (synthesizing data from several sources), clinical practice guidelines, local administration and accounting data, and expert opinion. Currently, there are no agreed Irish cost models available.
Italy	Preferably from RCTs, observational studies or registries. For costs with little impact on results, expert opinions may be used. There is a preference for costs that are representative for the Italian health care system but prices and fees may be used as estimates for costs.
The Netherlands	Recommendation to use the official 'Manual for cost research'; research data preferred over expert opinion.
Norway	When reporting resource use, market prices should be used as proxies for unit costs / calculation prices. The size of the resource and calculation price used must be presented and justified separately.
Poland	Sources of data: collecting primary data within a properly designed research, or by collecting secondary data from existing databases. The choice of data sources depends on the required degree of detail to be analysed.
Portugal	The information on the use of resources should be based on clinical practice in the country. If this is not possible, it is necessary to use foreign data, they should be validated by local health care providers.
Russia	Official sources of data on rates for services for public health are preferred. For medicine costs, official registered process adjusted for regional mark-ups, retail process for medicines with analysis of expenses for in-patient treatment should be used.
Scotland	A first point of reference in identifying costs and prices should be any current official listing. Where cost data are taken from literature, the methods used to identify the sources should be defined. For resource use, data from elsewhere in the UK are acceptable. Resource use data from other countries or estimated by a panel of experts should be avoided if possible, or at least validated for the Scottish setting and included in a sensitivity analysis.
Slovakia	The identification, measurement and valuation of costs should be consistent with the perspective of the Slovak health care payer. Relevant sources should be used for unit costs. Hierarchy of sources is not mentioned.
Slovenia	As reference sources are considered data from professional and scientific publications, therapeutic guidelines, findings and assessments of reference professional associations, data and guidelines of the WHO and other institutions and bodies responsible for the prices of medicines and public funding, as well as data from other publicly available sources.

Spain	Costs should be evaluated based on opportunity cost (i.e., the best available alternative) (Spanish recommendations, CATSALUT, and OSTEBA). Due to imperfections on the health care market, it is probably more useful to rely on official publications, accounts of health care centres, and the fees applied to NHS service provision contracts. Non-health-care costs should be identified individually and in detail using surveys designed for this purpose (Spanish recommendations).
Sweden	The Sales Price for pharmaceuticals must be used. No hierarchy of sources.
Switzerland	A database provides lump-sum and/or standard prices, otherwise costs have to be given for each treatment/service.

APR-DRGs: All Patient Refined Diagnosis Related Groups, HRG: Healthcare Resource Group, Na: No information available, NHS: National health service, RCT: randomized controlled trial.

Table A13. Sources for clinical effectiveness and quality of data

Country	Sources for clinical effectiveness and quality of data
Austria	RCTs and meta-analyses
Belgium	Systematic reviews of RCTs, preferably active control studies. No specifications of requirements on the level of quality and certainty of data on effectiveness.
Croatia	Systematic review with/or without meta-analysis of RCTs. Already published Core HTA and/or HTAs from other countries. Best available quality with appropriate measures of uncertainty.
Czech Republic	Best available and valid evidence.
Denmark	Additional studies of long-term consequences can be based on different data sources
England	Technology Appraisals: In the reference case, evidence on outcomes should be obtained from a systematic review. RCTs are considered to be most appropriate for measures of relative treatment effect. Data from non-randomised studies may be required to supplement RCT data, but are at a higher risk of bias. Any potential bias arising from the design of the studies used in the assessment should be explored and documented. Diagnostics Assessment Programme: Studies that follow patients from testing, through treatment, to final outcomes are included in the systematic review. These end-to-end studies may be of varying quality and design and could include randomised controlled trials (RCTs), cohort studies and observational studies. Diagnostic test accuracy studies which are generally prospective cohort or cross-sectional studies, or retrospective case-control studies in design could also be included in the systematic review. Medical Technologies Evaluation Programme: For medical technology evaluations, the systematic review may include published and unpublished studies measuring patient outcomes in response to the technology under consideration and comparator technologies. Lower level evidence such as comparative observational studies and case series can be included as well as RCT studies.
Estonia and Latvia	Published clinical trial data. Meta-analyses, double-blind RCTs, or open trials where these are appropriate.
Finland	All the relevant studies that have been carried out on the therapies compared. Systematic reviews and meta-analyses are often the best way of combining the results of different studies. Good scientific practices must be followed.
France	Evidence on health effects is obtained from RCTs, or meta-analysis of RCTs. Comparative observational studies might be used in the case of added value. No detailed requirement on the level of quality.
Germany	RCTs, MTC-meta-analysis. Calculations based on studies of lower quality will be accepted but the certainty of the conclusion will be affected. Studies not showing significant results will be taken into account.
Hungary	If it is possible, all health-related data should come from RCTs.
Ireland	Systematic review of all high-calibre, relevant data. Meta-analysis may be used to synthesize outcome data provided the homogeneity and quality of the studies included justifies this approach.
Italy	Systematic reviews and meta-analysis. Head-to-head-studies. Observational studies may be used.
The Netherlands	Preferably meta-analysis and RCTs. Expert panels can be used as an alternative.
Norway	A systematic review must be carried out. Data from RCTs with adequate internal and external validity are preferred. Data from observational studies may constitute an appropriate supplement. The assessment of data's internal and external validity must be done using checklists.
Poland	Systematic reviews (with or without a meta-analysis) are at the top of the hierarchy of credibility. Could be completed by observational studies of good quality. The quality evaluation of the data allows to determine its reliability.
Portugal	RCTs and meta analyses are preferred to other type of studies.
Russia	RCTs are preferable. Specialists analyze the quality of each clinical study and use a classification of level of evidence. Systematic reviews and meta-analyses are regarded as the highest level of evidence.
Scotland	RCTs, meta-analyses and other studies provide evidence.
Slovakia	Systematic review of the existing clinical and economic studies on the intervention, including unpublished studies and studies with negative results.
Slovenia	Based on the results of publicly available meta-analyses or high-quality randomized trials. Additional information, if needed, can be taken from observational studies.
Spain	Systematic reviews and meta-analysis are preferred but other studies could be relevant. (Spanish recommendations and Osteba) Systematic reviews and meta-analysis (CatSalut)
Sweden	Na

Switzerland	Systematic review of RCTs, having the highest level of evidence. Grey literature should be searched for. The quality of studies will be rated by the Consort-Statement.

MTC: multiple treatment comparison, Na: no information available, RCT: randomized controlled trial.

Table A14. Indirect comparisons

Country	Are indirect comparisons accepted?
Austria	Yes
Belgium	Yes
Croatia	Yes
Czech Republic	Yes
Denmark	Na
England	Yes
Estonia and Latvia	Yes
Finland	Yes
France	Yes
Germany	Yes
Hungary	Yes
Ireland	Yes
Italy	Yes
The Netherlands	Yes in case no better data is available (based on information about the practice in pharmacoeconomic assessments, personal communication).
Norway	Yes
Poland	Yes
Portugal	Na
Russia	Na
Scotland	Yes
Slovakia	Na
Slovenia	Na
Spain	Yes (AETSA and CatSalut)
Sweden	Yes
Switzerland	Na

Na: No information available

Table A15. Preferred outcome measure/s

Country	Preferred outcome measure/s
Austria	QALYs
Belgium	QALYs and LYG
Croatia	Both QALYs and natural units are possible.
Czech Republic	QALYs are preferred, then LYG and validated surrogates.
Denmark	QALYs or LYG, but also response rate, number of successful treatments, measure of time without symptoms, pains etc.
England	Technology Appraisals and Diagnostics Assessment Programme: QALYs Medical Technologies Evaluation Programme: clinical benefits for individual patients and its impact on clinical and system outcomes
Estonia and Latvia	Prevention of death, reduced incidence of complications, reduced incidence of side-effects, incidence of well controlled therapy symptoms, etc. QALYs only presented in additional analyses.
Finland	Primarily QALYs
France	QALYs or LYG
Germany	Primarily mortality, morbidity, HRQoL and validated surrogates
Hungary	CUA: QALYs Effectiveness: appropriate outcome for the selected condition, and final (long-term) outcome (morbidity, mortality) and changes in QoL
Ireland	QALYs
Italy	QALYs
The Netherlands	QALYs or life years gained
Norway	QALYs
Poland	Depends on type of economic analysis In CUA: QALY (preferred outcome) In CEA: LYG In CCA: costs and health consequences.
Portugal	The following are generally used: (1) Measurements related to the disease (2) Measurements related to the patient (e.g. reduction in the number of cardiovascular events or life years gained) (3) Measurements of the QoL (4) Monetary units.
Russia	QALY, LYG, serious complications, hospital admissions etc.
Scotland	QALYs. This should include adverse effects.
Slovakia	Chronic conditions: QALYs or LYG. Acute conditions: other relevant outcome variables, as in the clinical file
Slovenia	QALYs
Spain	QALYs (Spanish recommendations, CATSALUT and OSTEBA. Separate data on changes in both quantity and QoL (Spanish recommendations, CATSALUT, and OSTEBA).
Sweden	QALYs. In treatments that mostly affect survival: both QALYs and LYG
Switzerland	No specifications of preferred outcome, but CUA ratios are explicitly mentioned as not so important

CCA: cost-consequence analysis, CEA: cost-effectiveness analysis, CUA: cost-utility analysis, HRQoL: health-related quality of life, LYG: life years gained, QALY: Quality-adjusted life years, QoL: quality of life

Table A16. Intermediate/surrogate outcomes

Country	Is the use of intermediate/surrogate outcomes accepted?
Austria	Yes, intermediate endpoints and surrogate endpoints can be used as a measure of outcome if these have a high degree of predictability of a hard clinical endpoint but hard clinical endpoints should be preferred.
Belgium	Yes, outcomes should be expressed in terms of final endpoints instead of intermediary outcomes but extrapolation from surrogates to final endpoints in models is permitted and sometimes necessary.
Croatia	Unclear, outcomes can be expressed in natural units such as reduced incidence of complications, reduced side-effects etc.
Czech Republic	Yes, in case QALYs and LYGs cannot be provided.
Denmark	Unclear, acceptable outcome measures include response rate, number of successful treatments, measure of time without symptoms, pain etc.
England	Technology Appraisals and Diagnostics Assessment Programme: Yes, clinical endpoints are preferred but surrogate outcomes may be used to infer the effect of treatment on mortality and HRQoL. Evidence in support of the surrogate-to-final endpoint outcome relationship must be provided together with an explanation of how the relationship is quantified for use in odelling.
Estonia and Latvia	Unclear, the final outcome can be reduced incidence of complications, reduced incidence of side-effects, incidence of well controlled therapy symptoms, etc.
Finland	Yes, effectiveness can also be measured by surrogate endpoints.
France	Yes, but LYG and QALYs are preferred. Decision models can be used to simulate the relationship between surrogate and final outcomes.
Germany	Yes, but Intermediate outcomes are only accepted if validated.
Hungary	Yes, reporting of surrogate outcomes only should be avoided but may be used if there is a strong association between the surrogate outcome and the final outcome (morbidity, mortality, QoL) and/or the surrogate outcome is clinically significant, and this improvement is long standing
Ireland	Yes, the benefit measure may be an intermediate (surrogate) marker rather than a final outcome. There must be a well-established, validated link between this marker and an important patient outcome.
Italy	Na
The Netherlands	Yes, but intermediate outcomes, should preferably be translated into final outcomes, such as LYG.
Norway	Yes, data for intermediate endpoints may be used even though hard endpoints are preferred.
Poland	Yes, but it is recommended to convert the data regarding the surrogates to the probabilities of clinically significant endpoints (provided a reliable conversion method exists).
Portugal	Yes, measurements related to the disease (e.g. lower blood pressure, reduction in cholesterolemia or increased nervous conduction speed) are mentioned as one of the types of outcomes that are generally used.
Russia	Yes, if final outcomes are missing, intermediate (surrogate) criteria can be used.
Scotland	Yes, but models are required when intermediate outcomes measures are used rather than effect on HRQoL and survival. Details of any association between surrogate markers and health benefits or disadvantages to patients should be provided.
Slovakia	Yes, surrogate endpoints can be used if there is a significant association between the surrogates and the final outcomes.
Slovenia	Yes, intermediate outcomes (such as blood pressure, cholesterol, glycosylated haemoglobin, hospitalization) can be accepted
Spain	Yes, but the connection to final outcomes must be clear and scientifically proven (Spanish recommendation and CatSalut). Yes (Osteba).
Sweden	Yes, but if so-called surrogate end-points are used, the account should also include modelling from these end-points to illustrate the effects on mortality and morbidity, i.e. QALY's gained.
Switzerland	Na

HRQoL: health-related quality of life, LYG: life years gained, Na: No information available, QALY: Quality-adjusted life years, QoL: quality of life.

Table A17. The use of willingness-to-pay (WTP) to assess the value of health outcomes

Country	The use of willingness-to-pay (WTP) to assess the value of health outcomes
Austria	Na
Belgium	Na
Croatia	Na
Czech Republic	Na
Denmark	WTP can be used as a complementary measure of outcome by asking a segment of the population to value the outcomes in monetary units. The direct method is contingency valuation.
England	Na
Estonia and Latvia	Na
Finland	CBA can be used.
France	WTP can be used as a complementary source of information.
Germany	Na
Hungary	The use of CBA is currently discouraged.
Ireland	Na
Italy	CBA is in general not recommended.
The Netherlands	Na
Norway	CBA is generally not recommended due to the ethical and technical challenges associated with setting a monetary value on health improvements (Guidelines). CBA can be used in the analysis of cross-sectorial public health interventions (Helsedirektoratet).
Poland	Na
Portugal	If CBA is performed, the gains associated with treatments should be valued in monetary units. WTP should be assessed using the contingent valuation method.
Russia	Na
Scotland	If submitting companies present methods as WTP studies or a discrete choice experiment, these must be fully described and the uncertainty in results fully explored.
Slovakia	Na
Slovenia	Na
Spain	CBA is a valid type of analysis. In a CBA, WTP methodology should be included. (Spanish recommendation, CatSalut and OSTEBA)
Sweden	If it is difficult to use QALY's (e.g. with heavy pain over a short time in connection with treatment), WTP may be used as a measure of effect.
Switzerland	Na

CBA: cost-benefit analysis, Na: No information available, WTP: willingness-to-pay.

Table A18. Preferred method to derive HRQoL weights for calculation of QALYs

Country	Preferred method to derive HRQoL weights for calculation of QALYs
Austria	Indirect methods (HUI, EQ-5D)
Belgium	Indirect methods (EQ-5D)
Croatia	Indirect methods (EQ-5D)
Czech Republic	Indirect methods (EQ-5D)
Denmark	Direct methods (TTO or SG)
England	Indirect methods (EQ-5D in adults). A set of preference values elicited from a large UK population study using a choice-based method of valuation (the TTO method) is available for the EQ-5D health state descriptions.
Estonia and Latvia	Indirect methods (EQ-5D and HUI).
Finland	A validated generic QoL measure
France	Indirect methods (EQ-5D and HUI-3 since validated value sets for France are available)
Germany	No preferred method.
Hungary	Indirect methods (utility-based HRQoL questionnaires).
Ireland	Indirect methods (Generic preference-based measure (EQ-5D or SF-6D))
Italy	Indirect methods (EQ-5D)
The Netherlands	EQ-5D is the preferred QoL measure, but other measures are also sufficient (based on information about the practice in pharmacoeconomic assessments, personal communication).
Norway	Indirect methods (EQ-5D, SF-6D and 15D)
Poland	Indirect methods (EQ-5D, validated in Polish. Polish value set based on TTO method).
Portugal	Any of them, provided that it has been validated for Portugal and it can be justified that the choice is appropriate for the study.
Russia	Na
Scotland	Indirect methods (EQ-5D with value sets for general public based on choice-based methods, such as TTO or SG but not rating scale).
Slovakia	Indirect methods (EQ-5D)
Slovenia	Na
Spain	Indirect methods (Spanish recommendations and CATSALUT). Direct or indirect methods (OSTEBA). EQ-5D and SF-6D (CATSALUT).
Sweden	Direct methods (SG or TTO).
Switzerland	Not applicable

EQ-5D: EuroQol 5 dimensions, HRQoL: health-related quality of life, HUI: Health Utilities Index, MAU: Multi-attribute utility, Na: No information available, QoL: quality of life, SF-6D: Short-form 6D, SG: Standard gamble, TTO: Time trade-off, 15-D: The 15-D instrument.

Table A19. If QALYs are used, whose preferences should the HRQoL weights represent?

Country	If QALYs are used, whose preferences should the HRQoL weights represent?
Austria	Na
Belgium	General public (preferably Flemish tariff)
Croatia	General public (tariff based on a choice-based method and representative sample of the Croatian population)
Czech Republic	General public (implicitly since EQ-5D is recommended)
Denmark	General public
England	Technology Appraisals and Diagnostics Assessment Programme: General public
Estonia and Latvia	Na
Finland	Na
France	General public (French tariff)
Germany	Preferably from the target population
Hungary	General public
Ireland	General public
Italy	General public
The Netherlands	General public
Norway	Na (but from a Norwegian population)
Poland	General public (tariff based on the TTO method and Polish population)
Portugal	People that are familiar with the evolution of the disease
Russia	Na
Scotland	General public
Slovakia	Na
Slovenia	Na
Spain	General public (Spanish recommendations and CatSalut)
Sweden	Persons in the health condition in question
Switzerland	Not applicable

EQ-5D: EuroQol 5 dimensions, HRQoL: health-related quality of life, Na: no information available, QALY: quality-adjusted life years, TTO: time trade-off.

Table A20. Mapping from disease-specific QoL measures to HRQoL weights that can be used for calculation of QALYs

Country	Is mapping from disease-specific QoLmeasures to HRQoL weights that can be used for calculation of QALYs accepted?
Austria	Na
Belgium	The direct use of a generic utility instrument is recommended. Mapping is only allowed if such primary data cannot be obtained and mapping functions are based on and validated with empirical data.
Croatia	Na
Czech Republic	Yes
Denmark	Na
England	Yes, when EQ-5D data are not available and an appropriate, validated mapping function is available, these data can be estimated by mapping other HRQoL measures or health-related benefits observed in the relevant clinical trial(s) to EQ-5D.
Estonia and Latvia	Na
Finland	Na
France	No, mapping is not recommended for the reference case analysis.
Germany	Na
Hungary	Na
Ireland	Yes, in the absence of relevant utility data from one of these generic techniques, alternative methods may be used including mapping data from other HRQoL measures to one of the generic instruments.
Italy	Yes
The Netherlands	In case utility data from generic instruments is not available mapping of disease specific QoL measures is accepted (based on information about the practice in pharmacoeconomic assessments, personal communication)..
Norway	Yes, if data from MAU-instruments or TTO or SG techniques does not exist, then mapping the available health state valuation data over to MAU-instruments is allowed.
Poland	Na
Portugal	Na
Russia	Na
Scotland	Yes, if utility data from generic validated instruments is not available, utilities can be mapped from a disease specific QoL measure included in a clinical study.
Slovakia	Na
Slovenia	Na
Spain	Yes (CatSalut)
Sweden	Na
Switzerland	Not applicable

EQ-5D: EuroQol 5 dimensions, HRQoL: health-related quality of life, Na: No information available, MAU: Multi-attribute utility, QALY: quality-adjusted life years, QoL: quality of life, SG: Standard gamble, TTO: Time trade-off.

Table A21. Discounting of costs and effects

Country	Discounting of costs and effects
Austria	Both costs and health effects discounted at 3%. Sensitivity analyses: 0, 5 and 10%
Belgium	Costs at 3%, future benefits at 1.5%. Sensitivity analyses with 0, 3 and 5 % on both costs and benefits.
Croatia	Discounting of costs and outcomes should be taken into account in case of a time horizon longer than 1 year. Both costs and health effects discounted at 3%. Sensitivity analyses: 0 and 5%
Czech Republic	Discounting of costs and outcomes should be taken into account in case of a time horizon longer than 1 year
Denmark	Yes to discounting, but no recommendation on level
England	Technology Appraisals and Diagnostics Assessment Programme: Both costs and health effects discounted at 3.5%. Sensitivity analyses: 1.5% for both costs and health effects
Estonia and Latvia	Both costs and health effects discounted at 5%.
Finland	Both costs and health effects should be presented discounted and undiscounted. Discount rate: 3%.
France	Both costs and health effects discounted at 4% for time horizons of less than 30 years with a reduction of up to 2% thereafter.
Germany	Both costs and health effects discounted at 3%, sensitivity analyses at 0 and 5%
Hungary	Both costs and health effects discounted at 3.7%.
Ireland	Both costs and health effects discounted at 5%
Italy	Both costs and health effects discounted at 3%. Sensitivity analyses: 0 and 5%.
The Netherlands	4% for costs, 1.5% for future benefits
Norway	Both costs and health effects discounted at 4 %.
Poland	5% for costs and 3.5% for health care results Sensitivity analyses: 5% for costs and health care results, 0% for costs and health care results, 0% for health care results and 5% for costs
Portugal	Both costs and health effects discounted at 5 %.
Russia	Costs discounted at 5% per year.
Scotland	Both costs and health effects discounted at 3.5%
Slovakia	Both costs and health effects discounted at 5 %.
Slovenia	Yes to discounting, but no recommendation on level.
Spain	Both costs and health effects discounted at 3% (Sensitivity analyses with 0% for health effects and 5% for health effects and costs) (Spanish recommendations, CatSalut). Both costs and health effects discounted at 5 % (Sensitivity analyses with 0 % for both costs and health effects and 3 % for health effects) (OSTEBA).
Sweden	Both costs and health effects discounted at 3% (Sensitivity analyses with 0% for health effects and 3% for costs as well as 0-5% for both health effects and costs)
Switzerland	Same rate for costs and benefits, no rate given

Table A22. Updating of costs to the relevant year and currency

Country	Updating of costs to the relevant year and currency
Austria	Costs should be adjusted to reference year and converted into Euro using PPP.
Belgium	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 inflated using the appropriate Health Index figures, if relevant.
Croatia	Na
Czech Republic	Na
Denmark	Na
England	Na
Estonia and Latvia	All costs should be reflected in local currency.
Finland	Unit costs shall also, as needed, be converted into present value. The price index for public expenditure on municipal health services is used in converting health care unit costs into present value and the suitable price indexes in regard to other costs. The index used must be reported.
France	Na
Germany	General price index (published by the Federal Statistical Office) is used
Hungary	Prices shall be converted to the same date (possibly present date). Consumer price index (inflation) should be chosen as conversion rate, irrespectively of where the costs (or savings) arise, within or outside the healthcare sector. The official publications of the Hungarian Central Statistical Office should be consulted on annual price index.
Ireland	Retrospective input costs should be inflated to the most recent calendar year using the CPI for health or one of its sub-indices where reasonable justification is given for its use. Where costs are applied from other countries, the assumptions necessary to transfer this data must be explicitly reported, with all costs converted to their Irish equivalent in Euro using PPP indices. When converting historical cost data from one country to another, costs should first be inflated to current costs using the CPI data from the origin country, before converting to local currency using the PPP index.
Italy	Na
The Netherlands	All costs should be converted into present value using Dutch Statistics Bureau price index.
Norway	Na
Poland	Na
Portugal	Na
Russia	Na
Scotland	It is mentioned that capital costs should be updated to the current year using a UK health service price index.
Slovakia	Na
Slovenia	Na
Spain	Costs should be adjusted to reference year (OSTEBA and CatSalut)
Sweden	It should be clear what year prices represent
Switzerland	If future price changes are known, they should be accounted for.

CPI: Consumer Price Index, Na: No information available, PPP: Purchasing Power Parities

Table A23. Presentation of results

Country	Presentation of results
Austria	ICERs, absolute and incremental costs and effects, efficiency frontier
Belgium	ICERs. Mean values and CI for both incremental costs, incremental benefits and ICERs.
Croatia	ICER and absolute costs/effects. The expected value of each component of cost and expected total costs as well as expected QALYs.
Czech Republic	ICER.
Denmark	Results reported at a disaggregated level.
England	Technology Appraisals and Diagnostics Assessment Programme: ICER (expected additional total cost to expected additional QALYs. Expected mean results (costs and outcomes). The expected value of each component of cost and expected total costs should be presented. The probability that the treatment is cost-effective at maximum acceptable ICERs of £20,000–£30,000 per QALY gained. Medical Technologies Evaluation Programme: Estimates of resource use and of clinical benefits as separate domains of the evaluation
Estonia and Latvia	ICER. Incremental analysis, total annual cost of the treatments to the health care system and total benefit, cost savings in the health care system.
Finland	ICER. Total benefits and costs as well as incremental benefits and costs.
France	ICER. Costs and health effects for all comparators are tabulated to demonstrate all the dominance situations (strict or extended). The results are illustrated by the efficiency frontier.
Germany	Benefit/net costs per patient is presented for each intervention in a diagram, an efficiency frontier.
Hungary	ICER. Results for total costs and total health gains of interventions under comparison should be clearly reported.
Ireland	ICER, expected mean costs, total costs and QALYs should be documented for the comparator technologies. All results should be presented in both their disaggregated and aggregated form.
Italy	ICER, incremental costs and effects.
The Netherlands	ICER, incremental effects and costs
Norway	Results presented both at an aggregated level and broken down into categories for both costs (drug costs, hospital costs, care costs and any costs associated with the production effects) and health effects (QALY and LYG)
Poland	ICER (the estimation of the cost of gaining an additional QALY or additional LYG). Costs/effects presented both in absolute and incremental terms. Total clinical results and total costs should be presented separately.
Portugal	ICER, incremental costs and consequences of each alternative. The total values should also be calculated so that the decision maker can analyse the costs and consequences of each alternative.
Russia	ICER and absolute cost-effectiveness ratios.
Scotland	ICER (the ratio of expected cost to expected QALY).The expected value of each component of cost and expected total costs should be presented; expected QALYs for each option compared in the analysis should also be detailed.
Slovakia	Incremental analysis and total C/E. Results should contain the discounted costs, outcomes, incremental costs and outcomes in a disaggregated form and separately for the study intervention and the comparator.
Slovenia	ICER
Spain	ICER comparing relevant alternatives, and separating the perspectives (if analyzed from the perspective of society and that of a third-party payer) and subgroups. Present the main outcomes (cost and health outcomes) both separately and together (Spanish recommendatiosn, CatSalut, and Osteba).
Sweden	ICER (cost per QALY). Unit costs and quantities should be presented separately as far as is possible so that a distinction can be made between price and quantity.
Switzerland	Description of costs only

C/E: cost per effect, CI: confidence intervals, ICER: incremental cost-effectiveness ratio, LYG: life years gained, QALY: quality-adjusted life years

Table A24. Uncertainty

Country	Description of uncertainty
Austria	DSA presented in tornado diagrams. PSA with CEAC. To assess uncertainty in model structure: use different pathways through the model or even build another model, yet the authors admit that the second solution is too time- and resource-consuming in most instances. Structural and other assumptions and their limitations should be described.
Belgium	One-way or multiple sensitivity analyses. For parameter uncertainty: PSA with CE plane and CEAC. Uncertainty around the incremental costs, incremental effects and ICERs should be provided by means of confidence or credibility intervals. The most important contributors to the uncertainty of the estimated ICER should be shown.
Croatia	Sensitivity analyses. Parameter uncertainty preferably using PSA.
Czech Republic	Sensitivity analyses. All uncertainty which may have direct and substantial impact on the results should be identified (particularly uncertainty that may have a negative effect on the results (higher ICER)) Parameter uncertainty preferably using PSA.
Denmark	Sensitivity analysis to evaluate the robustness of the conclusions to changes of assumptions, valuation, costs, outcome and discounting.
England	Technology Appraisals and Diagnostics Assessment Programme: Univariate and best- or worst-case sensitivity analysis to identify parameters that may have a substantial impact on the cost-effectiveness results. The use of PSA to perform a more comprehensive characterization of the parameter uncertainty associated with all input parameters. The results of PSA may be presented in confidence ellipses and scatter plots on the CE plane and CEAC. Uncertainty should also be presented in tabular form. The probability that the treatment is cost effective at maximum acceptable ICERs of £20,000–£30,000 per QALY gained and the error probability (that the treatment is not cost effective) should also be presented. Medical Technologies Evaluation Programme: Uncertainty analysis techniques (relating to chance, evidential and model uncertainty) should be undertaken. The level of complexity should be appropriate for the specific technology and its comparator healthcare pathway. Various analyses of different complexity may be used, such as scenario-based DSA, threshold analysis or PSA.
Estonia and Latvia	Sensitivity analysis and CIs around the main variables.
Finland	DSA, scenario analyses and/or PSA. Results of sensitivity analysis must be given in a table form. Attention should be paid to the most significant uncertainty factors in view of the final results.
France	Univariate or multivariate DSA on parameters likely to influence the results of the model. Scenario analysis to characterise structural uncertainty. A PSA is preferred to characterise uncertainty about parameters when the theoretical or empirical distributions of the parameters are known or can be estimated.
Germany	Univariate and multivariate analyses (with results reported in both tabular form and as a tornado diagram) and PSA (presented as the cumulative distribution of results). Also structural sensitivity analyses to explore the impact of varying structural model assumptions. With respect to a DSA, parameter values should be identified, for which the new technology is cost-saving, or is above or below the efficiency frontier. In PSA, the proportion of simulations generating cost-savings or leading to a position above or below the efficiency frontier should be provided.
Hungary	One-way sensitivity analysis should be performed. Two-way sensitivity analysis and PSA is recommended to provide more information about the uncertain parameters in the model.
Ireland	One-way and multivariate sensitivity analysis to identify the key model inputs/assumptions contributing most to uncertainty. PSA should be used to assess parameter uncertainty. Uncertainty should be presented graphically (tornado plot, scatter plot and CEAC) and in tabular form to facilitate interpretation. The expected value of perfect information (EVPI) can be determined directly from the results of the PSA. The effects of model uncertainty (i.e. structure, methods and assumptions) and parameter uncertainty on the outcome of the economic evaluation must be systematically evaluated using sensitivity analysis and scenario analyses.
Italy	Sensitivity analysis and PSA (presented for example with ellipses, confidence intervals and CEAC).
The Netherlands	Univariate sensitivity analysis to determine the effect of assumptions, such as the discount rate, estimated cost prices etc. and PSA with results displayed as a CEAC and/or a CE plane.
Norway	Univariate (presented in tornado diagrams), and multivariate sensitivity analysis (mainly scenario analyses) for handling methodological, model, structural and extrapolation/generalization uncertainty. PSA for handling parameter uncertainty.
Poland	Sensitivity analysis to explore assumptions of the model and PSA. Results of PSA presented in CE plane and by confidence intervals (e.g. 95%), CEAC or incremental Net Monetary Benefit (NMB).

Portugal	Sensitivity analysis calculating lowest and highest values to which the order of the alternatives changes (threshold analysis) or specifying alternative values for the parameters and comparing the results we have obtained with those of the initial scenario. Sensitivity analysis considering the confidence intervals for each estimate.
Russia	Sensitivity analysis
Scotland	One and two-way sensitivity analyses supported by graphical representation including threshold values. PSA may be submitted but are not considered mandatory. Appropriate ways of presenting uncertainty are confidence ellipses and scatter plots on the CE plane and CEAC.
Slovakia	Sensitivity analysis (tornado diagrams). PSA (CIs around the ICER; CE plane and CEAC).
Slovenia	Sensitivity analysis.
Spain	One-way or multi-way sensitivity analysis, threshold analysis (Spanish recommendations. CatSalut, and Osteba). Whenever possible, carry out a PSA. When a PSA is carried out, include a CE/CU plane and the CEAC in the findings (Spanish recommendations and CatSalut).
Sweden	Sensitivity analysis of central assumptions and parameters.
Switzerland	No details given except for sensitivity analysis for differential discounting.

CE: cost-effectiveness, CEAC: cost-effectiveness acceptability curve, CI: confidence interval, CU: cost-utility, DSA: deterministic sensitivity analysis, ICER: incremental cost-effectiveness ratio, PSA: probabilistic sensitivity analysis.

Annexe 6. Letter to EUnetHTA partners

Dear EUnetHTA partners,

As part of EUnetHTA SG3 of Joint Action 2 – Work Package 7, methodological guidelines are being developed in various HTA areas. SBU in Sweden has been given the first author responsibility of the methodological guideline concerning Economic evaluations. The work is done together with HAS (France), IER (Slovenia), INFARMED (Portugal) and IQWIG (Germany).

The purpose of this guideline is to identify relevant differences and similarities in the national concepts and methods for economic evaluations, if possible to describe a common denominator, and to increase the transferability of economic evaluations between EUnetHTA members. As a first step to achieve the purpose, available methodological guidelines for economic evaluations in the European countries will be analysed and integrated into a structured overview.

To make sure we have the correct and most recent guidelines for economic evaluations in each country or region, we need your help. We have put together a list with all the guidelines we are aware of (see attached file) and would be very grateful if you could help us by answering the following questions based on the information we have for your country/region:

1. Is the guideline/-s in the list the latest version of the guideline/-s that is being used for economic evaluations in your country/region?

2. Are there other guidelines on methods for economic evaluation in your country/region? Please indicate which these are!

3. If there is no guideline, are there other documents forming some kind of praxis concerning economic evaluations?

4. If the documents are not in English, do you know if it has been translated to English, in part or in full?

5. If it is not stated in the list that we already have the full versions of the document, we would be very grateful if you could provide us with a copy of the guideline in its original language and in English (if available).

We would appreciate if you could send the answers to these questions and the guidelines (or other relevant information) to Emelie Heintz (heintz@sbu.se) by 30 November 2013. Don’t hesitate to contact us if you have any further questions.

Many thanks in advance,

Best regards

Emelie Heintz, Thomas Davidson and Måns Rosén, SBU

Annexe 7. Template for collection of information

Template for extraction of information from methodological guidelines for economic evaluations among EUnetHTA partners

The purpose of this template is to serve as a tool for extraction of information from methodological guidelines concerning economic evaluations. This information will later be used to summarize the differences and similarities between methodological guidelines of different countries within EUnetHTA. The template should in a first step be completed by two independent reviewers for each guideline. In the next step, the two reviewers compare their completed templates and decide on a common version that will be the official final version. Every answer in the template should start with a short summary (1-2 lines) and then continue with more detailed information if necessary. The template should be used only for information concerning economic evaluations and not budget impact analyses. Budget impact analyses are only dealt with in the last question. If no information is available this should be indicated with the text "No information available" in the box for the relevant question. For questions please contact Emelie Heintz (Heintz@sbu.se) at Swedish Council on Health Technology Assessment (SBU).

Information about the review	***1.1 Country/region of the document***	
	1.2 Name and organization of the person who reviews the guideline	
	1.3 Date of the review of the guideline	
Information about guideline	2.1 Reference to the document (with information about name of document, name of organization that has authored it and if available, name of the authors, version etc. Provide a link if possible)	

	2.2 a) What types of technologies does the guideline primarily aim to be used for (i.e. pharmaceuticals, medical devices, interventional procedures or all technologies etc.)? b) Can it be used for other technologies as well?		
		Reference (page and section)	
	2.3 Target audience of the guideline (i.e. submitters of dossiers, HTA-agencies etc.)		
		Reference (page and section)	
	2.4 What is the status of the economic guideline (i.e. mandatory, recommended or voluntary)?	Mandatory	
		Reference (page and section)	
	2.5 What will the resulting economic evaluation be used for (reimbursement, recommendation, information only etc.)?		
		Ref (page and section)	
1.2 Information about the technolgoy	3.1 Indication?		
		Reference (page and section)	
	3.2 Target population?		
		Reference (page and section)	
	3.3 Are there		

	recommendations for subgroup analyses (e.g. separate analyses for groups of different ages, genders, disease severities etc.)?		
		Reference (page and section)	
	3.4 Choice of comparator/s?		
		Reference (page and section)	
Methods for economic evaluation	4.1 Is it requested to present a systematic review over previous economic evaluations of the technology?		
		Reference (page and section)	
	4.2 Time horizon of the economic evaluation (i.e. life time, time horizon for clinical data etc.)?		
		Reference (page and section)	
	4.3 Preferred type of economic evaluation?		
		Reference (page and section)	
	4.4 Perspective on outcomes (e.g. only health benefits or utility in general, effects on patients only or on other individuals in society as well?)		
		Reference (page and section)	
	4.5 Perspective on costs (e.g. societal, health care provider etc.)?		
		Reference (page and section)	
	4.6 Are models accepted and if so, in what cases?		
		Reference (page and section)	

	4.7 What types of models are accepted (e.g. markov, decision trees, discrete event simulation, dynamic models etc.)? Does the guideline recommend a specific program for modelling? Requirements on methods for extrapolation? Requirements on internal or external validation?		
		Reference (page and section)	
	4.8 What costs should be included? Indicate all types of costs that should be included (e.g. direct health care costs, direct non-health care costs, indirect costs). Do not forget to answer if productivity loss and unrelated future costs due to prolonged survival should be included!	.	
		Reference (page and section)	
	4.9 Is there recommendations concerning sources of data on costs? Is there a hierarchy of sources (e.g. are empirical costs preferred to, say, expert opinion)? If detailed information on which databases to use, please indicate only where in the guideline these are mentioned.		
		Reference (page and section)	
	4.10 What data sources are required/acceptable for the clinical evidence (e.g. systematic reviews, RCTs, observational studies, grey literature etc.)?		
		Reference (page and section)	

	4.11 a) Are there requirements on the level of quality and certainty concerning the data on effectiveness (e.g. are calculations based on studies of low quality accepted? b) Are calculations based on effect differences that are not statistically significant accepted? c) Are indirect comparisons accepted?)		
		Reference (page and section)	
	4.12 Is real world data, i.e. data/effects outside of RCTs, mentioned? And with regard to outcomes what kind of sources are permitted (supplements to RCTs, large practical clinical trials, registries, administrative data, health surveys, (electronic) health records)? How is each source valued?		
		Reference (page and section)	
	4.13 What is the preferred outcome measure/s (e.g. QALYs, life years)? Are intermediate outcomes accepted?		
		Reference (page and section)	
	4.14 If QALYs are used, what is the preferred method to derive QALY weights (e.g. SG, TTO, EQ-5D, SF-6D etc.)? Is mapping from other QoL-instruments accepted?		
		Reference (page and section)	

	4.15 If QALYs are used, by whom should the QALY weights be valued (e.g. patients or general public)? If indirect methods are used, is a specific tariff recommended?		
		Reference (page and section)	
	4.16 Are estimates of the patients'/general population's willingness-to-pay (WTP) for interventions accepted for estimation of the value of interventions and if so, under what circumstances?		
		Reference (page and section)	
	4.17 Are there any equity issues that should be taken into account in the economic analysis?		
		Reference (page and section)	
	4.18 Discounting of costs and effects (yes/no and what rates are used?)		
		Reference (page and section)	
	4.19 How are costs being updated to the relevant year of prices and currency?		
		Reference (page and section)	
	4.20 How are results being presented (e.g. absolute or incremental costs/effects, ICER, productivity frontier etc?)?		
		Reference (page and section)	
	4.21 How should structural uncertainty (e.g. uncertainty concerning model structure, assumptions about extrapolation etc.) and uncertainty concerning the choice of data sources for the key parameters in the		
		Reference (page	

	analysis be described?	and section)	
	4.22 How should parameter uncertainty (i.e. the uncertainty around the mean effect and cost inputs) be described?		
		Reference (page and section)	
	4.23 Is budget impact analysis required?		
		Reference (page and section)	

