

IFEDH

Innovative Framework for
Evidence-based Decisionmaking in
Healthcare

Standardised working in HTA
(WP1.2)



Ludwig Boltzmann Institut
Health Technology Assessment

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Ludwig Boltzmann Institut
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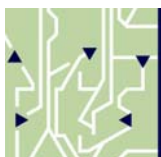
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1 Background

The extraordinary high amount of 20-25 billion Euros of annual turnover in the Austrian health system has increasingly raised the questions of cost-effectiveness and evidence based decision making in health care. Health technology assessment is already intensively dealing with these issues, especially on the level of single interventions. Still, due to lack of data, assessments often include modelling or simulation techniques in order to analyse long-term effects. This, in turn, requires increasing cooperation of experts from different fields of science such as HTA, statistics, data management, modelling & simulation as well as visualisation. A common understanding on contents, methodology and terminology needs to be developed. In Austria, such a common understanding has hardly been elaborated in a systematic way so far.

It is the main aim of the Innovative Framework for Evidence-based Decisionmaking in Healthcare/IFEDH project to support evidence based decision making in health care by a service tool which helps profiting from existing potentials in HTA, modelling, simulation, statistics and data analysis. Therefore common standards will be defined in order to facilitate cooperation and interdisciplinary work. Along three practical examples the tool will be tested regarding its applicability.

This report addresses work package 1.2 that focuses on quality standards of HTA in general and on the evaluation of vaccination programmes in particular. It aims to answer the following research questions:

What are general basic principles of standardised working in HTA?

Which standards exist in order to assess data validity for HTA?

Which standards exist in health economic research within HTA?

Which standards exist in modelling within HTA?

Which standards explicitly refer to evaluating vaccination programmes?

Which are the limitations of HTA?

high turnover in Austrian health system calls for interdisciplinary expert cooperation in evidence-based decision making

service tool for evidence-based decision making in healthcare

research questions WP1.2

2 Methods

2.1 Literature search

Hand search was made for international manuals for HTA in German and English language. Methodological manuals and websites of leading international institutions were screened. Beyond that, an international call via the International Network of Agencies for Health Technology Assessment/INAHTA was launched. This network encompasses 46 institutions in 24 countries. Within six weeks 12 institutions replied of which three were not able to deliver any material. The manuals and papers of two institutions were exclusively available in other languages than German or English and therefore could not be included. The seven remaining answers contained own papers of the institutions and links to other sources of information. Apart from institutions answering to the call, websites of all INAHTA countries were scanned.

hand search and international call

12 replies

Additionally, the databases of the Cochrane Collaboration and the Centre for Reviews and Dissemination/CRD were screened, following a simple search strategy. Together, both searches added up to 177 hits after deduplication. The search strategies are added in the appendix.

small systematic search in Cochrane database and CRD

2.2 Selection of literature and terms

Throughout literature screening, several manuals and many other documents were identified. In order to decide which of them were the most relevant the following inclusion criteria were defined:

inclusion criteria

We included reports that cover

- ✿ explicit standards of HTA
- ✿ standards of health economic evaluations
- ✿ standards of modelling
- ✿ information on the evaluation of vaccination programmes

Furthermore, we limited the documents to those from institutions that have demonstrated an HTA tradition and that are accepted among the HTA community. In addition to these institutions there are several edited books and articles dealing with the topic of standardised procedures in HTA, mainly from authors who work in institutions cited above and/or contribute in networks such as INAHTA, the European Network for Health Technology Assessment/ EUnetHTA or the International Society of Pharmacoeconomic and Outcome Research/ ISPOR. These documents were not explicitly considered in our overview.

selection criteria

We did not search for methodological papers in the field of modelling or health economic evaluation either, but only on those HTA-manuals which include the standards of these topics within HTA.

no methodological papers but HTA-manuals on standards

**method to summarise
the literature**

Selected core documents were summarised in tables according to the following criteria

- ✿ main characteristics of methodologies in international HTA institutions including structure and content of different types of HTA reports and the core methodological approaches stated
- ✿ modelling approaches provided by the documents
- ✿ approaches for modelling vaccination programmes

For the field of vaccination the scope of search was widened. For reason of extremely limited evidence in classical HTA manuals we included guidelines or recommendations published by international institutions (e.g. WHO) or documents that were commissioned by public institutions (e.g. Gemeinsamer Bundesausschuss in Germany).

3 Results

The following list (table 3-1) shows institutions which published methodological work on HTA in general or in particular on health economic evaluations, modelling or standardised vaccination programme evaluation:

list of HTA-institutions included

Table 3-1: List of HTA institutions included

Institution	Country
INAHTA - International Network of Agencies for Health Technology Assessment	International
EUnetHTA - European Network for Health Technology Assessment	EU
ISPOR - International Society of Pharmacoeconomic and Outcome Research	International
WHO – World Health Organisation	International
Austrian Ministry of Health/GÖG – Gesundheit Österreich GmbH	Austria
LBI-HTA – Ludwig Boltzmann Institut für HTA	Austria
DAHTA@DIMDI - German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
IQWiG – Institute for Quality and Efficiency in Health-care	Germany
KCE - Belgian Federal Health Care Knowledge Centre	Belgium
DACEHTA - Danish Centre for Health Technology Assessment	Denmark
INFAMED - National Authority of Medicines and Health Products	Portugal
HIQA - Health Information and Quality Authority	Ireland
NETSCC, HTA - NIHR Coordinating Centre for Health Technology Assessment	United Kingdom
CADTH – Canadian Agency for Drugs and Technology in Health	Canada
CDC – Centers for Disease Control and Prevention	USA
MSAC - Medical Services Advisory Committee of the Department for Health and Ageing - DHA	Australia
PBAC – Pharmaceutical Benefits Advisory Committee of the Department for Health and Ageing - DHA	Australia

3.1 General principles of standardised work in HTA

overview of HTA characteristics in table

In order to provide an overview of standards in HTA, table 3-4 lists the main characteristics of HTA methodologies of the relevant documents at a glance. The core characteristics and similarities as well as differences between different manuals are described in the following chapters.

3.1.1 General principles of scientific work and particular characteristics of HTA

general principles of good scientific practice combined with EbM and interdisciplinarity

Like in any other scientific field general principles of scientific work such as traceability in methods and transparency in data gathering and presentation, correct citation and logic consistency are core requirements in HTA. HTA is a method of providing systematic, transparent, unbiased and scientifically based policy advice in health care. Since HTA tries to state a counter-movement to the kind of policy which is based on so called “eminence-based medicine”, and therefore a lack of methodological transparency, the general principles of transparency and unbiased work play a key role in HTA-research.

special need of transparency

Additionally, the interdependence of different scientific sub-disciplines and the need of a clear distinction between critical scientific appraisal and a political decision are other reasons for the strong focus that is put on transparency in HTA.

dependency on regional and cultural contexts

The immanent nature of HTA as a multidisciplinary approach implies a certain context-dependence. E.g. the choice of a type of an economic evaluation depends on the setting of financing and on the acceptance of specific theories in the national or regional context. The best known examples is the concept of quality adjusted life years/ QALYs, a concept that expresses the benefit of an intervention which is based on a utilitarian theory of social value. This concept is a standard tool in many countries such as the United Kingdom, Australia or the Netherlands. Other countries such as Austria and Germany (see chapter 3.3) do not accept major theoretic implications of this approach for ethical or political reasons. Therefore they either modify it, or do not use it at all in standardised healthcare decision making.

3.1.2 Different types of HTA products

(full) HTA reports, based on clinical and cost-effectiveness + further issues

The main product in HTA is the classical HTA report. It is based on a systematic literature search and, besides a clinical and economic assessment of the health technology under investigation may contain assessments on several other fields such as organisational, social or legal aspects related to the technology. A classical HTA-report usually finishes with a discussion of the results and limitations and (in some countries) with a recommendation for decision makers.

A core methodological document in that context has been developed during the EUnetHTA project. EUnetHTA is an EU-based cooperative initiative which aims to define and to develop standards and tools for HTA users and producers. The so called “EUnetHTA Core Model” [1] which has been developed until December 2008 gives a general understanding of contents and structures of HTA reports by defining “issues”, subordinated to “topics” which again are parts of “domains”. It is providing one of the most exhaustive and structured definitions of HTA.

The domains covered by the core model are: the current use of technology, description of technical characteristics, safety, effectiveness, costs, economic evaluation, ethical aspects, organisational aspects, social aspects and legal aspects. One example for a safety topic would be the identification of harms. This is treated in issues in the form of questions such as “What is the scope of the harms to be assessed?”, or “What types of harms are of interest for the assessment?”

The other institutions stated in table 3-1 are basically focusing on similar domains such as clinical effectiveness, safety, economic analysis, as well as ethical, organisational or legal aspects. Hence, the methods of HTA are highly compatible and do not differ very much between the countries. The contents of full HTA reports are similar (see: table 3-4, column 2).

Nevertheless there are some differences in the approach of doing HTA between countries. Some countries are investing important parts of public resources in primary data collection by commissioning randomised controlled clinical trials. Simultaneously economic data may be collected for doing an economic evaluation alongside a clinical trial. In the majority of manuals, however, secondary clinical and economic data are gathered and may be combined for doing economic evaluations. The former such as the United Kingdom, the United States of America or Australia usually do not see a clinical added value as a precondition for a health economic evaluation (see chapter 3.3) while others (e.g. IQWiG) do economic evaluations only if clinical benefits of a technology have been demonstrated.

A second often produced report within HTA is the so called “rapid assessment”. It is a way of covering the main aspects of an HTA report with limited resources. Clinical and (sometimes) economic assessments are still the dominant, but not the only parts treated in such a format. Different institutions define rapid assessments according to their needs and priorities. Some HTA institutes such as those in Germany or Austria have defined an explicit framework for rapid assessments. Others such as the DACEHTA, the KCE or EUnetHTA only define so called “full HTAs” and their different areas’ special relevance and context-dependency. According to this description, in a rapid assessment, some of these domains have to be treated in more detail than others.

3.2 Clinical assessment

The assessment on clinical effectiveness and safety is the main item of an HTA. The methodology relies strongly on principles of evidence-based medicine (EbM) and clinical epidemiology. Since the manuals generally rely on international standards of EbM, they are quite coherent with respect to clinical assessment, compared to other domains of the assessment.

“Core Model” by EUnetHTA cooperation, defining full HTA reports via domains, topics and issues

methods in HTA highly compatible

different traditions especially in economic evaluations

rapid assessments – brief version

**clinical effectiveness and safety is core item
consensus on EbM standards**

RCTs as preferred source of evidence, hierarchy of evidence

In order to avoid any possible kind of systematic error (bias), in clinical epidemiology (double-blinded) RCTs are the preferred study design to evaluate the clinical benefit of a technology. Usually this refers to the ‘efficacy’ of a technology. Depending on the nature of the technology, the current state of art and the availability of evidence, other studies (e.g. pragmatic CTs, cohort studies or case-control studies) can also be used to assess clinical questions. This is particularly the case for evaluating adverse events but may also be relevant for other questions such as effectiveness (performance of a technology under real-life conditions).

3.2.1 The research question

PICO - question

The main framework in any clinical assessment in the manuals analysed is the “PICO”-question. This methodology is the standard method in clinical epidemiology and therefore as well used in many HTA manuals, such as the GÖG, KCE, EUnetHTA, CADTH or IQWiG [1-5]. PICO is a standardised way of designing the research question, dealing with the following sub-questions:

- ✿ Population / patients with the disease of interest
- ✿ Intervention(s), i.e. the technology under assessment
- ✿ Comparison(s), that should serve as reference
- ✿ Outcomes which encompass the endpoints for assessing effectiveness and safety

3.2.2 Literature search

systematic literature search sometimes completed by handsearch

Once the research question is formulated, relevant literature needs to be searched. There is an important distinction between a systematic literature search and a so called “handsearch”. Following an explicit search strategy which defines the type of studies to search for a systematic literature search is conducted in relevant databases. Articles are then selected according to pre-defined inclusion- and exclusion-criteria [4]. Manuals recommend that literature selection should be done by two independent researchers first after abstract and second after full text lecture.

transparency in literature search and selection by PRISMA table

All manuals point out the importance to do the selection in a transparent way and to publish the documentation of literature selection. One common tool of documentation is the PRISMA framework. This framework is a flow chart that pictures the process of literature search and selection. It shows which papers were identified, ordered and finally in- or excluded for what reason and at what stage of the selection process. Together with the search strategies of the databases screened the PRISMA table gives the main information of the search protocol [6]. For an example see Warmuth, Johansson 2010 [7] and table 7.3-1 in the appendix.

search for grey literature sometimes more efficient by handsearch

A non systematic literature search, also known as handsearch, is generally seen as a way of second choice or as an add-on. Still there might be good reasons for doing a handsearch, such as the lack of a certain type of literature in databases (e.g. grey literature, web-site information,...) or the need of including very recent information which has not found the way through journal review procedures. In such cases a quality assessment is especially relevant.

Some institutions e.g. the National Institute for Health and Clinical Excellence/ NICE have included other ways of literature search and information gathering into their assessment procedures. Within stakeholder involvement procedures patient representatives, producers or other commentators are systematically invited to add information to the assessment on the technology or other relevant contextual issues at well specified points in time [8, 9].

**stakeholder
involvement**

3.2.3 Literature assessment

For a clinical research question literature assessment includes a judgement on the following questions [3]:

**primary selection
criteria**

- ✿ Is the article relevant to the subject?
- ✿ Are the article's results valid?
- ✿ Are the article's results important for answering the question?

Once a study is identified as relevant data have to be extracted into an evidence table (see chapter 3.2.5).

3.2.4 Data quality assessment

Internal validity is the precondition of a study to be included in the assessment. A good judgement on internal validity requires identification of potential systematic errors. The main limitations for the quality of an RCT are:

internal validity of data

- ✿ Incorrect randomisation
- ✿ Incorrect allocation concealment
- ✿ Clinical dissimilarities between the groups
- ✿ Lack of power
- ✿ Incorrect blinding
- ✿ High drop-out rate
- ✿ Lack of intention-to-treat analysis

Types of potential bias can differ with different types of studies. Most common forms are confounding, selection bias and information bias. There is nothing such as a complete list of biases for one or a group of study types. Even though there is not complete consensus whether validity of studies should be assessed with checklists, they still exist and are widely used. Some manuals such as the Austrian [10] or the manual by KCE [3] add them as an appendix to their manuals. Widely used checklists are the Cochrane checklist [11] for assessing RCTs or the QUADAS [12] tool for quality assessment of diagnostic studies. DIMDI has recently also provided checklists on "methodological quality of primary and secondary studies in HTA reports" [13]. Once a study has been checked and included with respect to its internal validity, data on effectiveness and safety can be extracted and assessed. The results from the quality assessment of the studies are either used to include or exclude studies or they are incorporated into the overall rating of the evidence as it is for example the case in the GRADE-methodology.

**identifying and avoiding
systematic errors such
as confounding,
selection bias,
information bias**

3.2.5 Data extraction

clinical data extraction procedure

Data extraction should be executed by one author and double-checked by an independent person.

A clinical data extraction should contain the following issues [4]:

- ✿ General information on the study (author, year, country/health system, aim of the study, details of study funding)
- ✿ Specific Information on the study (design, duration, no. of patients, inclusion criteria of the population, characteristics of the population, intervention/exposition, outcomes parameters)
- ✿ Results (relevant outcomes, effect size, confidence interval and p-value including not significant results)
- ✿ Internal validity (quality)
- ✿ Comments

For an example of data extraction see [14].

3.2.6 Analysis and critical appraisal

different grade of quantitative approach in appraisals

The actual assessment and the critical appraisal of literature can be executed in different ways. These ways particularly differ in the extent of their quantitative approach.

GRADE-tool for qualitative evidence synthesis

A qualitative way of analysing clinical evidence is the methodology of the GRADE-working group [15]. It is based on evidence tables that summarize the effect sizes of different studies in a qualitative manner including a tool to grade the evidence according to its quality. GRADE is explicitly recommended by the Austrian, Danish, Belgian and German manuals.

meta-analysis for quantitative evidence synthesis

The prototype of quantitative analysis is to conduct a meta-analysis. In a meta-analysis the statistical data of several studies on the same topic are combined and analysed as if it was data from one study. It is evident that such a type of analysis can only be conducted if it is for sure that there is no contextual interference which has a systematic influence on the overall results. In order to avoid heterogeneity, studies that are similar in setting and parameters addressed are to be included in a meta-analysis. The Cochrane Collaboration offers a free software called “Review Manager” to execute meta-analyses which is also used by the Belgian KCE and other institutions.

Some manuals describe details of meta-analyses

Apart from the Cochrane Collaboration, meta-analyses are treated in the Austrian manual, by IQWIG, DACEHTA, KCE, NICE, CADTH and HIQA. In all these manuals meta-analyses are seen as the ideal way to assess existing clinical evidence, but as a dangerous method if data are not well assessed in order to be sure that they are standardised and comparable.

modelling approach for evidence synthesis

Not least the clinical question can be approached by a decision analytical model where several data sources are combined in a mathematical model in order to analyse benefits and risks of alternative interventions. Methodological standards for modelling within HTA are described in chapter 3.5.

3.3 Economic analysis

The relevance of economic analysis in an HTA varies considerably between different institutions and countries. In general it is common understanding that economic analysis is seen as a part of HTA. Still some countries such as the United Kingdom, Australia or Canada emphasise its relevance a lot more than others. Additionally, some manuals focus on how to conduct an economic analysis while others restrict the economic analysis to a summary of secondary literature and describe how to include this information into an HTA-report. All in all, the methodology of economic evaluation is – with some exceptions as described down below - highly standardised and well known in the international community of HTA.

varying relevance of economic analysis

3.3.1 Economic evaluation

The most widely used types of economic analysis are health economic evaluations (see table 3-2). Health economic evaluations are generally defined as studies comparing two or more treatment options in terms of their costs (in monetary terms) and their benefits. There are four standard types of economic evaluations which are characterised by the way of expressing benefits of an intervention [16, 17]:

standard: health economic evaluations

compares different treatment options in terms of benefits and costs => 4 types

Table 3-2: Types of health economic evaluations

Type of analysis	Costs measured in	Benefit measured in
Cost-minimisation analysis / CMA	monetary units	equal benefits assumption
Cost-effectiveness analysis / CEA	monetary units	natural units (e.g. live years gained)
Cost-utility analysis / CUA	monetary units	utilities transferred into generic units (e.g. QALY)
Cost-benefit analysis / CBA	monetary units	monetary units

In a CMA it is assumed that both therapies have exactly the same clinical effects. Obviously this is true very rarely and therefore is hardly used, but can still be a helpful tool. A CBA is limited by the strong constraint of monetary validation of every single medical benefit or harm. Therefore usually a willingness-to-pay approach as considered by CADTH is chosen [2]. CEA and CUA are the most commonly used evaluations. The CEA measures the benefit of an intervention in natural units in order to create a cost-effectiveness ratio e.g. cost per life years gained / LYG. The CUA uses generic units such as the quality adjusted life year / QALY which is a combined index of quality of life and mortality.

CMA, CEA, CUA and CBA differ in benefit measurement

Australia or UK different approach than Germany	The manuals differ with respect to the evaluation type recommended. Most countries recommend cost-utility analysis as one option. Some such as Australia [17] or the United Kingdom [8] explicitly focus on this evaluation type. On the contrary, Germany rejects cost-utility analyses in public decision-making and follows a different route: In the IQWiG manual, comparison between alternative types of treatment is restricted to technologies within the same indication (e.g. medication for elevated blood pressure) while technologies across indications (e.g. cancer therapy versus therapies in cardio vascular diseases) must not be evaluated economically. Within an indication, new technologies are assessed according to their ratio between incremental costs and their additional benefit. Assuming that the most cost-effective technology is used as long a possible, followed by a more cost-effective technology, a new technology has to be at least more efficient than any other technology in use. This is expressed by the so called “efficiency-frontier”.
IQWiG: economic comparison only for treatments in the same field of indication; “efficiency frontier”	
differences in cost analysis	Manuals additionally differ in methodological details. Some institutions do exclude any indirect costs [18]. Others consider indirect cost as an essential source of information which closes the gap between a theoretic pricing framework and real life. Main practical steps in the determination of costs are [18]: <ul style="list-style-type: none"> ✿ Identification of resource consumption ✿ Entry of quantities of resource consumption ✿ Valuation of quantities ✿ Calculation of total costs of treatment alternatives
different perspectives ask for different cost analyses	The description of cost-analysis in the manuals is closely related to the perspective from which economic evaluations are to be conducted. The Australian and the Irish manuals [17, 19, 20] e.g. are examples for a public payers’ perspective. Other manuals such as the Danish or the Belgian [3, 16] do not explicitly specify which perspective should be chosen for an evaluation to be useful.
realistic time horizon relevant for clinical and economic assessment	Another essential element of economic calculations is the discounting-process. This weighting has to be executed in order to validate all investments according to one and the same point in time. The longer the time horizon of a calculation the more important this aspect becomes. Some manuals recommend a discounting rate of 3%. Others do not give any specification on this topic. Since treatments have different harms end benefits in short and long term, the choice of the time horizon can also have an impact on the clinical benefit of a treatment. Therefore it can influence the result of a health economic evaluation in more than one way. Manuals such as the HIQA or the CADTH manual primarily recommend being transparent about the choices of perspective and timing horizon. CADTH especially recommends choosing a time horizon that is clinically relevant. Depending on causal relationships CADTH considers the possibility of multiple modelling for different time horizons.
patient relevant outcomes recommended	It is not always evident which clinical outcome is the best to choose in an economic evaluation. As in clinical evaluation, the majority of manuals recommend to choose patient relevant indicators. Therefore in CEAs one frequent ratio is the cost per live years gained, and in CUAs the cost per QALY. The predominant outcome of CEAs and CUAs is the incremental cost-effectiveness ratio / ICER. It expresses the ratio of change in costs and out-

comes of the compared treatments. Several manuals from Canada, Ireland, United Kingdom, Portugal or Australia [2, 19-22] formulate guidelines to use ICERs as outcome measures.

To validate results most manuals recommend performing sensitivity analyses. The Canadian model gives the most detailed guidelines on how to deal with uncertainty and variability (table 3-3). Depending on the type of uncertainty or variability there are different approaches recommended [2]:

CADTH guidelines on uncertainty

Table 3-3: Handling variability and uncertainty

Category	Type of Variability or Uncertainty	Recommended Approach
Variability	Differences in clinical practice patterns between geographic areas or settings	Sensitivity analysis
	Variability in patient population (patient heterogeneity)	Stratified analysis
Model-based uncertainty	Model uncertainty <ul style="list-style-type: none"> • analytical methods • model structure • assumptions • data sources 	DSA using alternative assumptions, one-way, multi-way, threshold, or extremes analysis; and model validation methods
	Parameter uncertainty	DSA using one-way, multi-way, threshold, or extremes analysis; PSA using Monte Carlo simulation is encouraged

Such a framework can probably not be seen as the international standard every HTA institution is following, but since CADTH is a highly prestigious institution and covers leading positions in INAHTA and ISPOR it can be considered as one of the main methodological guidelines existing in the field of HTA.

3.3.2 Other types of economic analysis

Apart from health economic evaluations there are business-economic analyses and budget-economic analyses. They play a minor role in the manuals and are primarily described in the Danish and German manuals [16, 18].

Business-economic analyses are mainly performed to support service providers such as hospitals in their planning. Therefore they also deal with the questions of financing, maintaining, operating, and gaining savings from a technology.

others: business economic analyses...

Budget-economic analyses are a support tool for health care financing institutions such as insurance companies or public authorities. They are used to assess the impacts of investment for a technology/programme on long-term costs and potential cost-containment. Therefore it is a support in priority-setting [18].

... and budget-economic analyses

3.3.3 Secondary data of economic analyses within HTAs

some manuals include methods on review of economic evidence

Often it is not possible to execute primary economic evaluation for every HTA. The Canadian agency CADTH [2] and the Austrian HTA manual [23] give a methodological guideline for reviews of economic studies. The research process of conducting a review of economic evidence is similar to reviewing clinical evidence in that transparency in literature search, definition of selection criteria and selection method, data extraction, the strategy of data assessment of the studies (e.g. use of checklists [3] of quality assessment scales), and information on the data analysis methods are described.

sensible research question required

However, the research question itself needs to be defined clearly in advance in order to benefit from a review on economic evidence. Differences between health care systems, in terms of service provision as well as in terms of funding, have major impacts on the generalisability of economic parts of HTAs. Hence, the question whether some technology is cost-effective compared to another can hardly be answered sensibly via a review of economic evaluations. Yet, a review can be useful in other circumstances (e.g. if information is needed for conducting ones own study).

checklists for data assessment available

Just like clinical data, economic data in a review has to be assessed in terms of validity before it can be included in any analysis. Therefore checklists have been developed as well. Two important examples are the one of Drummond and Jefferson and the one of Siebert et al. [24, 25].

summarising evidence less standardised

For summarising the economic evidence several approaches have been recommended [10], however, they are much less standardised than for clinical evidence. Not least, economic analyses can be supported by decision analytic modelling which will be described in chapter 3.5.

3.4 Ethical, social and legal issues within an HTA report

other aspects than clinical and cost-effectiveness relevant

Besides clinical and economic analysis there are several issues which are generally seen as important parts of HTA methodology. Still these issues are not approached in the same comparably unanimous way as the two main areas. Ethical considerations are a good example for a field that is commonly mentioned by every HTA manual. It is treated in detail by some institutions such as the EUnetHTA, DACEHTA, or within the Austrian manual but almost ignored by some others such as the manual by NICE or by the Australian PBAC. Even considering that some manuals such as those of CADTH or KCE are much shorter than these, they still contain more information and guidance on how to deal with ethical considerations.

mainly ethical, organisational, social and legal issues

QALY questioned from ethical point of view

In terms of ethics, most manuals mention the discussion on the concept of Quality Adjusted Life Years. This concept is sometimes criticised for discriminating the elderly. Another ethical discussion addresses the issue if patient relevance of clinical outcomes is most important or if individual satisfaction should be considered as well.

In some manuals [1, 2, 10, 22] the discussion of efficiency versus equity and the utilitarian approach of health economic evaluation is at the core of the ethical issues covered. The Anglo-Saxon approach of NICE and PBAC seems very utilitarian, whereas European continental countries such as Austria or Germany seem to be more critical. The Belgian paper is rather brief and does not break down concepts on a very detailed level. Still it contains a relevant part on the patient and the societal level of patient and ethical issues and indicates different scientific approaches to analyse such aspects within an HTA.

Ethical aspects do also occur in the clinical analysis and even earlier in the setup of a study design. To a certain extent this field is covered by legal rules, regulations and procedures. Apart from ethical aspects the field of legal aspects mainly influences the important question on applicability of technologies, implementation of service provision or transferability of technologies from one regional or national context to another.

The terminus of “psychosocial considerations” is only used by the EUnetHTA, the Canadian and the Austrian manual. The Canadian agency defines it as “intangible” factors for those affected by a technology. The Austrian manual enhances the factor of the individuals’ perception of a technology and its influence on an efficient implementation. This meets the consideration of different perspectives, and in the end the involvement of stakeholders which is rather represented in the Anglo-Saxon culture.

The scope of topics existing apart from clinical and cost effectiveness seems to be beyond important dispute, but the extent to which institutions are really including these topics in their HTA manuals and finally in their HTAs varies considerably.

utilitarianism in Anglo-Saxon countries

brief Belgian manual includes patient and societal level

ethical aspects also meet legal issues;

legal issues strongly connected with transferability

psychosocial considerations rare, sometimes dealt with by stakeholder involvement

consensus on topics but not on execution

Table 3-4: Main characteristics of methodologies in international HTA institutions

Country, agency	STRUCTURE AND CONTENTS OF REPORTS		METHODS		
	HTA reports	Rapid assessments	Clinical assessment	Economic analysis	Other aspects
EU: EUnetHTA [1]	9 Core domains: 1. current use of technology 2. description of technical characteristics 3. safety 4. effectiveness 5. costs, economic evaluation 6. ethical aspects 7. organisational aspects 8. social aspects 9. legal aspects	The extent of an HTA can considerably vary as long as it follows the methodology and the interest of the topic;	Evidence-based approach; Good epidemiological practice /GEP ¹ [26]; Ideally but not compulsory based on RCTs; focus on effectiveness and patient relevant questions such as side effects or ethical considerations;	Target population, intervention, comparators, outcomes, time frame and perspective are essential aspects of a health economic evaluation;	Detailed framework on ethical, organisational, societal and legal aspects as well as on the context of the technology assessed;
Austria: LBI-HTA, GÖG [4, 10]	Methodology, literature search, literature selection, data assessment, data extraction, analysis and synthesis; focus on clinical effectiveness and safety;	Explicit framework for rapid assessments	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	n.a.	Framework for systematic analysis of socio-cultural implications including psychosocial, ethical, legal and organisational aspects;
Germany: IQWiG [5, 18]	Effectiveness, safety, economic analysis, patient relevance, patient information;	Explicit framework for rapid assessments	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	Health economic evaluation and modelling if clinical benefit is proven; efficiency-frontier approach	Implicit expression of legal and organisational aspects through definition of contexts of clinical and economic analyses;
Germany: DAHTA@DIMDI [27]	Societal background, medical aspects, health economic aspects, ethical and social aspects, legal aspects;	Explicit framework for rapid assessments	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	International evidence with regard on applicability;	General guidance on how to present ethical, social and legal aspects;

¹ “Good Epidemiological Practice” / GEP [4] is defined by the International Epidemiologic Association as in the IEA GUIDELINES FOR PROPER CONDUCT IN EPIDEMIOLOGIC RESEARCH. These Guidelines include procedural rules for good research behaviour as well as ethical principals, or the role of ethics committees.

Country, agency	STRUCTURE AND CONTENTS OF REPORTS		METHODS		
	HTA reports	Rapid assessments	Clinical assessment	Economic analysis	Other aspects
Belgium: KCE [28]	Clinical effectiveness, cost-effectiveness, patient issues, organisational issues;	n.a.	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	Cost-effectiveness analyses and cost-benefit analyses and their quality control;	Guidelines on ethical and patient issues on individual and societal level
Denmark: DACEHTA [16]	Literature search and assessment, data, technology and patient issues, organisation, economic evaluation, synthesis and utilization, quality assurance and presentation;	Documentation of different types of HTA products	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	Health economic evaluations including modelling approaches as well as other types of health economic studies;	Exhaustive description of ethical considerations, patient aspects, organisational aspects and the question of how to use an HTA
Portugal: INFARMED [21]	PICO (see 3.2.1), time horizon, analysis techniques, identifying costs, measuring and valuing costs, measuring consequences, total and incremental analysis, discount rate, uncertainty, ethical aspects;	n.a.	n.a.	Guidelines for economic drug evaluation studies	n.a.
Ireland: HIQA [19]	Evaluation types, perspectives of costs and outcomes, choice of comparator, synthesis of effectiveness, outcome measurement, discounting, sensitivity analysis, equity rating;	n.a.	n.a.	Detailed structured guidelines on economic evaluations;	Equity considerations referring to the QALY concept (see 3.3)
UK: NETSCC [8, 9, 22]	Clinical effectiveness is not a precondition for the economic assessment of a technology; strong focus on clinical and cost effectiveness, scoping and stakeholder involvement;	n.a.	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	Cost-effectiveness analyses and cost-utility analyses as a precondition for reimbursement decisions, economic analysis alongside randomised controlled clinical trials;	Very limited and general statement on the usefulness of ethical considerations and on feasibility, impact, equity and equality;

Country, agency	STRUCTURE AND CONTENTS OF REPORTS		METHODS		
	HTA reports	Rapid assessments	Clinical assessment	Economic analysis	Other aspects
Canada: CADTH [2]	PICO (see 3.2.1), perspective, effectiveness, time horizon, modelling, valuing outcomes, resource use and costs, discounting, variability and uncertainty, equity, generalisability;	n.a.	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	General guidelines, resource identification guidelines, resource measurement guidelines and resource valuation guidelines;	“Health services impact” considerations including population, budget, implementation, laws, psychosocial and ethical issues;
Australia: PBAC, MSAC [17]	Description of intervention, evaluation for indication, economic evaluation;	n.a.	GEP; hierarchy of clinical study designs; internal and external validation of identified literature	Detailed guidelines for preparing health economic evaluations and analyses;	Focus on legal and administrative aspects, hardly any ethical considerations;

n.a.: not available. Such fields express the lack of an explicit methodological paper in this field. Institutions may use standards of institutions from other countries or expert groups.

3.5 Modelling standards in HTA manuals

In order to deal with a lack of data and to get an idea of how an actual situation might change in the future, certain circumstances given, mathematic modelling is in many fields of HTA a practical approach. In HTA, modelling can be used in the clinical as well as in the economic part of the assessment. Briggs et al. describe the necessity of decision modelling for health economic evaluations with “...the need to synthesize all relevant evidence and to compare all options over an appropriate time horizon” [29].

Most of the national agencies do not provide detailed methodological guidance on modelling in HTA (see table 3-5). Some of them provide basic information. Important capacity lies in individual knowledge, academia and the network of the International Society for Pharmacoeconomic and Outcome Research/ ISPOR. Some agencies have started over the years to update their guidelines with remarks on modelling, such as CADTH.

The most common types of models in HTA mentioned in the manuals are decision tree models, Markov models, cohort- or individual simulation, as well as more recently discrete event simulation/ DES, agent-based simulation and transmission models [30]. The main steps in creating a model are described by the IQWIG as follows:

- ✿ Precise definition of research question
- ✿ Diagram of influence factors
- ✿ Model concept
- ✿ Systematic search for data available, if needed primary data survey
- ✿ Definition of functional relations in the model
- ✿ Choice of model type in order to structure the model
- ✿ Implementation and programming of the model
- ✿ Validation of the model as well as sensitivity analyses
- ✿ Writing a report including a transparent description of the model and a critical discussion of assumptions and limitations

This punctuation can already be seen as a basic guideline for “how to do modelling in HTA”. On an international level, standards are discussed and developed by members of the International Society of Pharmacoeconomics and Outcome Research/ ISPOR. Another important paper has been published by Philips et al., including a checklist for good practice in decision-analytic modelling in HTA [31]. Similarly, the Australian Pharmaceutical Benefits Advisory Committee/ PBAC claims a high level of transparency and documentation regarding the methods used in modelling [17]. It explicitly asks to present any details of the model such as decision trees, transition diagrams, or to answer if a Markov-model includes constant transition probabilities or not, and if the ‘memorylessness’ assumption of the model is valid. Such requirements are not formulated in an explicit guideline on modelling, but they are part of the overall requirements a submission to the PBAC has to fulfil.

modelling useful in cases of uncertainty

main information in UK, Canada and ISPOR

most common types of modelling in HTA

guidance vs. checklist...

real “guidance’s” rare	One of the most detailed general guideline for modelling in the manuals is provided by the CADTH-manual. Since 2006 it mentions the following considerations which are supported by more detailed guidelines on each point [2]:
modelling considerations	<p>Modelling considerations:</p> <ul style="list-style-type: none"> ✿ Follow good modelling practices when constructing the model used to conduct the evaluation. Analysts are encouraged to consult good modelling practice guidelines as required. ✿ Describe the model, including its scope, structure, and assumptions. Provide justification for assumptions and choices. ✿ Use a model structure that is appropriate for addressing the study question. Build the model in such a way to permit updating of results as more data become available. ✿ Explain and justify any causal relationships and extrapolation techniques used in the model. Base the extrapolation of data on valid techniques that reflect reasonable scientific evidence, and test through sensitivity analysis. ✿ Formally validate the model, and state how this was done.
data considerations	<p>Data considerations:</p> <ul style="list-style-type: none"> ✿ Systematically identify, collect, and assess the data used in the model ✿ Report and identify all data sources. Explain and justify all parameter choices and assumptions. ✿ Describe the quality (e.g., strength of evidence) of the data used in the model. Be explicit about data limitations and how they were dealt with. Try to quantify the impact of the limitations on the uncertainty of the evaluation results. ✿ Gather the best available evidence on key model parameters for which the model results are most sensitive. Justify any failure to gather the best available evidence of such parameters. ✿ Use caution when expert opinion is used to establish parameter values. Justify its use; and describe the source of the opinion, the method of elicitation, and the results of the exercise. Assess such estimates through a sensitivity analysis. ✿ Use appropriate methods to analyze or combine data from different sources. Explain and justify the methods used, and report the results of the analysis. Report limitations in the methods or data used, and where feasible, test through a sensitivity analysis. ✿ Incorporate data into the model using appropriate techniques, and explain the methods used. If data are incorporated as point estimates, use mean estimates of parameters in the base case. If estimates are incorporated as probability distributions, state and justify the form of the distributions.

Compared to this general guideline, Philips et al. [31] and the IQWIG [30] guidelines actually guide through the process of doing quality-assured modelling in HTA by providing concrete checklists.

Although the checklist by Philips et al. [31] is not an HTA manual itself it is mentioned in manuals and can be regarded as accepted standard. Grouped in “Structure”, “Data”, and “Consistency”, the authors define 16 elements of quality and areas of disagreement in previous guidelines. They provide recommendations on how to deal with disagreements and a framework for quality assessment of decision-analytic models in HTA. In this framework the dimensions of quality – e.g. the statement of the decision problem or the time horizon – is described by attributes of good practice and questions for critical appraisal – e.g. “Is there a clear statement of the decision problem?” or “Is the time horizon of the model sufficient to reflect all important differences between options?” Finally Philips et al. give an example for a quality assessment of a model, answering and commenting the assessment questions.

NICE and CADTH less concrete than Philips or IQWIG

Philips et al. define framework of 16 elements of structure, data and consistency

Table 3-5: Modelling guidelines in international HTA institutions

Country, agency	Type of publication	Type of information	Quality criteria described
EU: EUnetHTA [1]	n.a.	n.a.	n.a.
Austria: GÖG, LBI-HTA [4, 10]	Manual	n.a.	n.a.
Germany: IQWIG [5, 18]	working papers	Main steps and requirements for good modelling practice in HTA	Structured step-by-step approach; appropriateness of modelling tool;
Germany: DAHTA@DIMDI [27]	n.a.	n.a.	n.a.
Belgium: KCE [28]	n.a.	n.a.	n.a.
Denmark: DACEHTA [16]	HTA-textbook	General information on the use of modelling in economic evaluations in HTA	n.a.
Portugal: INFARMED [21]	Guidelines for economic drug evaluation studies	General requirements of modelling documentation	Transparency, discounting, documentation and discussion of limitations
Ireland: HIQA [19]	Guidelines for the Economic Evaluation of Health Technologies	Short description of good modelling requirements	Transparent documentation, validation, sensitivity analyses;
UK: NETSCC [8, 9]	Manual	Short description of good modelling requirements	Justification of structural assumptions, good documentation and justification of data inputs, avoiding selection of outlying values, high transparency;
Canada: CADTH [2]	Guidelines for the economic evaluation of health technologies	12 modelling principles and data considerations	Following good practices, transparency and clearness, appropriateness, validation, documentation, critical appraisal;
Australia: PBAC, MSAC [17]	Submission guidelines to the PBAC	Requirements of modelling documentation	Transparency;
Additional document on standards in modelling:			
Philips et al. [31]	Scientific journal paper	Good practice guidelines for decision analytic modelling in HTA	Standards and assessment questions on structure, data and consistency
Weinstein et al. [32]	Scientific journal paper	Good practice guidelines for decision analytic modelling in HTA	Standards on model quality

n.a.: not available

3.6 Standards in evaluating vaccination programmes

**infectious diseases
potentially highly
dynamic and uncertain
=> need for modelling**

In searching for a case study topic for work package 8 in the IFEDH project, vaccination to prevent infectious diseases was identified as a relevant field of application. The dynamic of infection, the uncertainties linked to long-term effects of vaccination programs and the high number of vaccines that is expected to enter the market make this subject interesting for modelling. Consequently, in WP1.2 we tried to identify manuals on standards of evaluating vaccination programmes and the role of modelling in this context.

**limited methodological
standards on
vaccination modelling**

Unfortunately systematic documentation on evaluation and modelling standards in this field is very limited. Table 3-6 lists the four main sources of information which could be identified. Their main concern is an optimal assessment of vaccination programmes. Still they are all approaching the topic from different angles.

Table 3-6: Modelling in HTA for vaccination programmes

Country, agency	Type of author	Type of document	Focus
Australia: PBAC 2008 [17]	service provider submitting a technology to national authority	guideline for submitting vaccination programme	focus on clinical effectiveness, safety and cost-effectiveness; best information available;
International: SMDM 2008 [33]	academia	journal article	sensitivity analyses and uncertainty
International: WHO [34]	International public authority	report	standardization of economic evaluations of vaccine programmes
Germany: IGES et al. 2010 [35]	academia commissioned by public authority	report	focus on cost-effectiveness of vaccination programmes

**Australia: information
guideline for
reimbursement
application**

The PABAC document [17] provides a very general guideline on the type of information that is required when vaccines are submitted for reimbursement considerations. Concerning evaluation in general and modelling in particular it does not specify specific methodological requirements but rather outlines which type of information needs to be submitted:

- ✦ Details of the proposed vaccine and its intended use
 - Pharmacological class and action
 - Indications and requested restrictions
 - Treatment details
 - Main comparator
- ✦ Clinical evaluation for the main indication
 - Assessing noninferiority between a vaccine combination product and its components
 - Outcome measures
 - Assessment of comparative harms

- ✿ Translating the clinical evaluation to the listing requested for inclusion in the economic evaluation²
- ✿ Economic evaluation for the main indication
 - Type of economic evaluation
 - Population and circumstances of use reflected in the economic evaluation
 - Structure and rationale of the economic evaluation
 - Type of model
 - Joint analysis
 - Duration of a model
 - Modelling of consequences
 - Variables in the economic evaluation
- ✿ Estimated extent of use and financial implications
 - Estimated financial implications for the National Immunization Plan
 - Estimated extent of use and cost of the proposed vaccine
 - Estimated financial implications for government health budgets
 - Estimated extent of use and cost of the proposed vaccine
 - Estimated financial implications for government health budgets

While details on methodological recommendations are missing, the documents identified address some general methodological issues, often related to the correct choice of models.

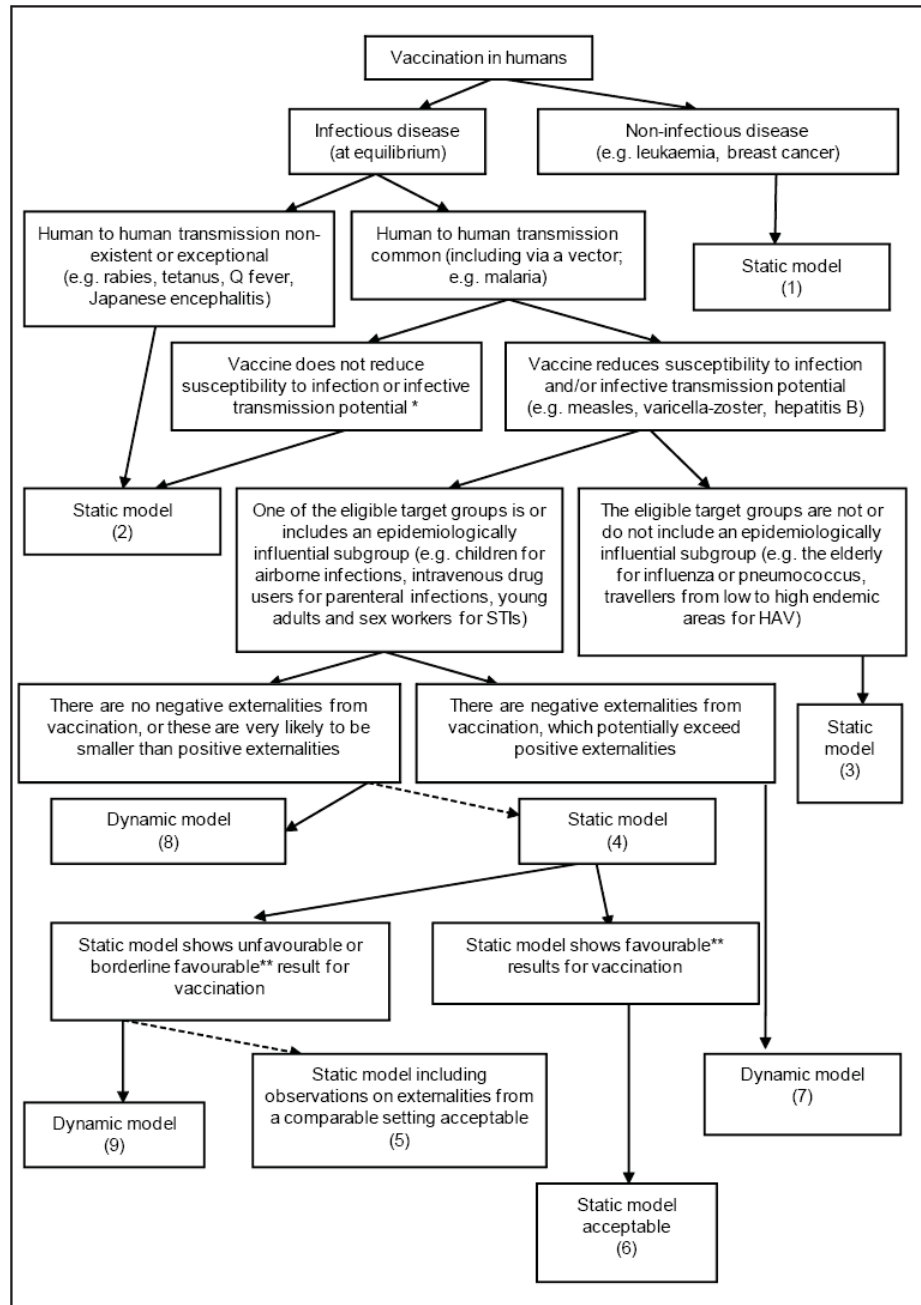
For example the WHO created an algorithm called “WHO guide for standardization of economic evaluations of immunization programmes” [34]. This flow chart shows in which case what kind of model seems to be the most appropriate to calculate either a static or a dynamic model of a vaccination initiative.

**in some documents:
support in choice of
modelling**

**WHO algorithm to
choose between static
and dynamic model**

² The results of trials might need to be translated into a decision analysis appropriate for the intended clinical use of the proposed drug on the PBS (pharmaceutical benefits schedule) in Australia

Figure 3: Flow chart to help determine when dynamic or static models are appropriate



Source: WHO guide for standardization of economic evaluations of immunization programmes (WHO 2008) [34]

As to the mathematical model of a vaccination programme the WHO [34] recommends to be:

- ✿ Transparent in that the structure and implicit or explicit assumptions are all clearly described.
- ✿ Static, if vaccination is unlikely to change the force of infection in susceptibles or as a means to make a conservative estimate when externalities from herd-immunity cannot on the whole be adverse.
- ✿ Dynamic, if vaccination is likely to change the force of infection in susceptibles, and a static model would not yield a conservative estimate, or if the conservative estimate from a static model does not lead to an outcome which would be considered favourable by decision makers.
- ✿ Stochastic if chance plays an important role in the transmission process of the pathogen
- ✿ Validated, in as many facets of validation (verification, calibration, face validity, predictive validity) as possible, but at least verified.

WHO recommendations on mathematical models

Furthermore, Klein et al. [32] recommend keeping a model:

- ✿ as simple as possible,
- ✿ transparent,
- ✿ dynamic (adaptable in case of a change in the rate of infection)
- ✿ stochastic, and
- ✿ validated in any possible dimension;

Klein et al. recommendations

Additionally, it has been acknowledged that vaccines are to be evaluated differently than other health care technologies such as drugs. Klein et al. [35] show that vaccination programmes evaluations are different from other health technologies because they imply specific characteristics such as:

- ✿ Positive externalities (lower infection risk of non-immunised people)/herd-immunity
- ✿ Uncertainty about duration of protection
- ✿ Time gap between investment and potential benefit gained
- ✿ Evaluation of dynamic cohorts
- ✿ Transmission models for acute diseases
- ✿ Markov models for chronic diseases
- ✿ Big size of target population

acknowledgment that vaccination implies specific characteristics

Herd immunity is seen as the most relevant factor for modelling vaccination programmes. It describes the phenomenon of non immunised people being protected in the group of immunised people and therefore is one major source of uncertainty.

different types of uncertainty: herd immunity,

Another source of uncertainty is the problem of an uncertain time horizon, since for most new vaccines the period of immunisation protection cannot be defined exactly. Therefore modelling has to choose an approximate time horizon. A wrong choice – as mentioned in chapter 3.5 – mainly affects the clinical effect.

time horizon,

discounting of costs and benefits

With respect to economic evaluations of vaccination, some attention has been paid to discounting of benefits and costs. Since benefits of vaccinations may be accrued in the far future a high discounting factor results in zero benefits after a certain time period. Consequently cost-effectiveness ratios become unfavourable. In that respect the WHO [34] gives the following recommendations:

- ✿ Discount costs and effects initially using the rate in the country in question (for studies to inform local decision-makers) and then using a 3% discount rate (consistent with WHO-CHOICE and DCP2);
- ✿ Conduct sensitivity analysis using discount rates of 0%, near-zero, 5% and 10% to reflect the (probably) higher real risk-free cost of capital in developing countries;
- ✿ A non-constant (declining or ‘slow’) discounting procedure may be applied where the effects begin only long after the intervention, e.g. vaccination against HBV or HPV, or last for an exceptionally long time, e.g. polio eradication.

sensitivity analysis:

SMDM: dynamic economic evaluation models specifically sensitive to choice of methods

Finally, the documents address the issue of sensitivity analysis in modelling of vaccination programmes. On behalf of the Society for Medical Decision Making/ SMDM Duintjer Tebbens et al. [33] highlight the fact that in the context of a dynamic economic evaluation model for vaccination programs, the choice of methods is especially important when it comes to uncertainty and sensitivity analyses. Therefore they compared the results of different methods of sensitivity analysis and present the trade-offs in a table. The aim was to show that the choice of method should not be made without considering influence factors such as complexity of the model, number of uncertain inputs and desired types of insights from the sensitivity analysis.

recommendations:

discount rates 0%-10%

one-way sensitivity analyses

probabilistic sensitivity analyses and cost acceptability curves

scenario analyses

Klein et al. recommend that discount rates in modelling cost-effectiveness of vaccination programmes should be varied between 0%-10% in sensitivity analysis. Further, they recommend one-way sensitivity analyses for any parameter which is relevant from a vaccination perspective, probabilistic sensitivity analyses and cost-acceptability-curves in order to examine the influence of parameter uncertainty on the overall result and scenario-analyses according to the specific vaccination programme with and without herd immunity effects, varying time horizons, discount rates, etc. in order to examine the influence of methodological assumptions.

4 Limitations of HTA

HTA can be considered as a scientific approach to support evidence-based decision making in healthcare by considering various relevant aspects, mainly clinical and economic ones.

None of the manuals explicitly lists limitations of the method of HTA in the form of a proper chapter. The DACEHTA Handbook probably has the most self-reflexive approach, listing limitations of single aspects within HTA along through the whole book. The main strategy these limitations are faced with is one of the main virtues in HTA: transparency; wherever restrictions in sub-disciplines are identified the researchers are asked to explain them and their impact on the overall result.

Even though the general topic of ethics is an essential part of every manual, in some manuals, some ethical aspects actual do not seem to be judged as topics to be analysed, but rather as limitations to be mentioned in HTAs. This is the way some manuals particularly deal with the issue of “equity vs. equality” [17, 22]. Other manuals’ authors show much more awareness for actually working on ethical problems.

Every sub-discipline has its own limitations where specific standards have been developed to deal with them. For example uncertainty in modelling is to be addressed by doing sensitivity analyses [18, 30].

One important limitation of HTA is mentioned but still far away from solved by EUnetHTA. Many results are very hard to transfer into other regional contexts. Sometimes it is because of a simple language barrier that the same assessment is done twice or even more often, sometimes there are other barriers, often due to context-specific administrative and legal regulations.

hardly any explicit limitations in manuals

ethical topics sometimes stated as limitations of HTA instead of separate topic

limitations in sub-disciplines

transferability is limitation for all types of HTA

5 Conclusion

Despite the young age of the discipline and the interdependencies between various sub-disciplines, HTA can be considered as a methodology which is properly defined in its methodological fundamentals. There are clear roots in evidence-based medicine, health economics, public health and other fields, and the literature is quite consistent about how these disciplines contribute to HTA.

Concerning the different domains in HTA, most detailed standards are available for the clinical assessment of technologies. When it comes to economic analyses and evaluation of legal, ethical or social issues manuals are much less congruent and vary in methodological details provided.

Manuals deal only to a small extent with standards on modelling. Even though there are references and the issue of modelling is often mentioned, the degree of standardisation is lower than in the fields of literature search, clinical effectiveness and economic evaluation. Only a few documents identified were dealing with standards in the evaluation of vaccination programmes. Perspectives are very different and vary from simple data collection to the question of systematic differences between modelling in vaccination programmes and other fields of healthcare decision making.

young discipline – well established methods

roots in EbM, health economics and public health

clinical domain highly standardised

less standards on modelling, very few documents on vaccination

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35. Klein, S., et al., *Gutachten zur Verbesserung der Wirtschaftlichkeit von Impfstoffen in Deutschland*, G-BA, Editor. 2010, IGES, Germany; Universität Duisburg-Essen, Germany; Office of Health Economics, England; UMIT, Austria: Berlin.

7 Appendix

7.1 Search strategy 1: The Cochrane Library

Search Name: IFEDH
Comments: Philipp R.
Save Date: 2010-12-16 07:26:55.503

ID	Search
#1	MeSH descriptor Technology Assessment, Biomedical explode all trees
#2	MeSH descriptor Decision Support Techniques explode all trees
#3	modelling
#4	(#2 OR #3)
#5	(#1 AND #4)

180 Hits

7.2 Search strategy 2: Centre for Reviews and Dissemination

MeSH Technology Assessment, Biomedical EXPLODE 1 2
MeSH Decision Support Techniques EXPLODE 1 2
modeling
modelling
#2 OR #3 OR #4
#1 AND #5

56 Hits

16.12.2010

7.3 Examples

Abbildung 7.3-1: Example for study selection according to PRISMA-Tree

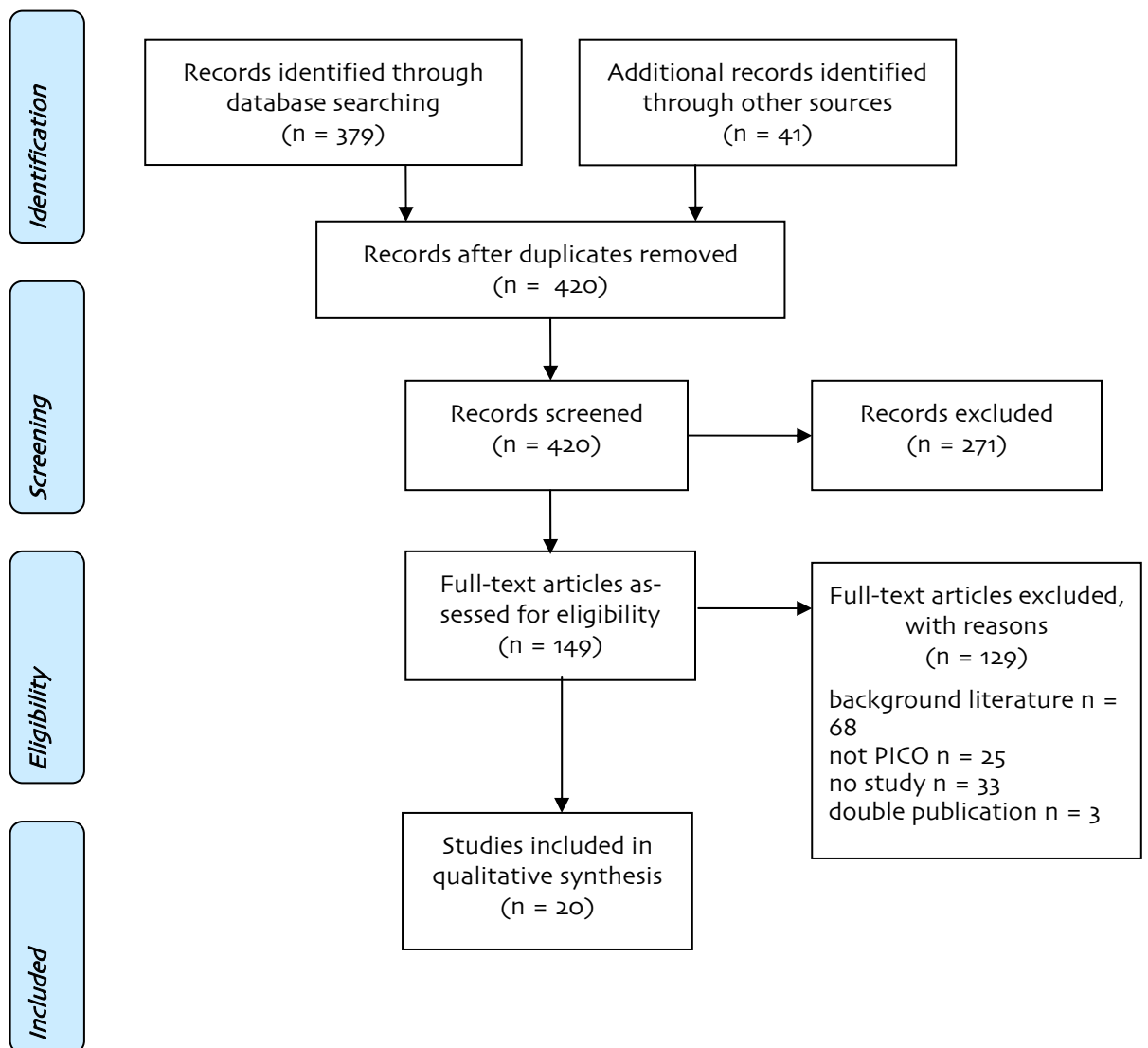


Table 7.3-1: Methods of sensitivity analyses recommended in dynamic economic evaluation models for vaccination [33]

Table 7 Recommended Sensitivity Analysis Methods among the Methods Presented in This Article, for Different Types of Models and Desired Insights				
Desired Insights	Few Inputs, Low Computational Cost per Model Run	Few Inputs, High Computational Cost per Model Run	Many Inputs, Low Computational Cost per Model Run	Many Inputs, High Computational Cost per Model Run
Ranking of individual inputs in the reference case	OWSA ^a	OWSA ^a	OWSA ^a	OWSA ^a
Overall ranking of individual inputs	CR, PMC, RC	Morris' method ^b CR, PMC, RC	CR, PMC, RC	Morris' method ^b CR, PMC, RC
Overall ranking of individual inputs and interactions ^b	2 ^k design ^b	Fraction of 2 ^k design ^b	Two-level design on most important inputs as identified by one of above methods ^c	Two-level design on most important inputs as identified by one of above methods ^c
Importance of curvature and/or increased understanding of the model	2 ^k design with center point, 3 ^k or mixed design (or more) ^b All probabilistic measures considered jointly, conditional expectation plots, cobwebs	Fraction of 2 ^k design with center point (or more) ^b All probabilistic measures considered jointly, conditional expectation plots, cobwebs ^d	Fraction of 3 ^k or mixed design on most important inputs as identified by 1 of above methods ^c All probabilistic measures considered jointly, conditional expectation plots, cobwebs	MWSA for selected inputs ^e

Note: CR = correlation ratio; MWSA = multiway sensitivity analysis; OWSA = 1-way sensitivity analysis; PMC = product-moment correlation; RC = rank correlation.
a. To obtain ranges in case of an uncertainty characterization using nonuniform distributions, one could use the mean plus and minus 2 standard deviations.
b. In the case of an uncertainty characterization using dependent or nonuniform distributions, using this method violates its implicit assumption of independent, uniform distributions.
c. May require a highly aliased design if the prior analysis identified many inputs as important. Design-of-experiments software commonly includes 2-level and 3-level designs for up to 15 inputs.
d. Refer to the technical appendix available from <http://mdm.sagepub.com/supplemental/>.
e. In the case of uncertainty characterization using nonuniform or dependent input distributions, MWSA will not factor in this information.