
# Mapping of HTA methodologies in EU and Norway

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Directorate-General for Health and Food Safety

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# EXECUTIVE SUMMARY

## Introduction

### European HTA cooperation

The Health Technology Assessment Network (HTA Network) is a policy network that has its basis in Article 15 on European HTA cooperation in the EU Directive on Patients' rights in Cross-border Healthcare and its secretariat is ensured by the Directorate General for Health and Food Safety (DG SANTE) of the European Commission. The HTA Network was set up in 2013 and includes all EU Member States and provides strategic guidance and policy orientation, by developing policy papers and discussing areas of potential collaboration.

HTA is now institutionalised in a majority of EU Member States with growing scientific and technical cooperation across borders. With the support of the EU Health Programme, EUnetHTA was established initially as project (2006-2009) and later, time-limited sustainability was ensured through a series of Joint Actions having scientific and technical cooperation on HTA as primary objective. Joint Action 1 (2010-2012) and 2 (2012-2015) focused on developing common methodologies, piloting and producing joint early dialogues and HTA reports, developing and maintaining common tools. All these activities contributed to building HTA capacity and trust among HTA bodies. Joint Action 3 (2016-2020) aims to "create an effective and sustainable network for HTA across Europe".

### HTA institutions' choice of scientific and technical methodologies

A primary requirement that HTA institutions are expected to meet is to provide trusted timely HTA reports in their country context. Their products should be considered relevant by the decision makers that determine e.g. the use / procurement / reimbursement of technologies or implementation of public health interventions (their primary clients). The scope of assessments that the institutions address, i.e. the span of assessment questions from effectiveness to, say, organisational and economic issues, influences their relevance. Some decision makers may ask for clinical assessment only while other may request economic and patient aspects covered as well.

Behind the present study lies the assumption that methodology choices which are made by HTA institutions have consequences for the way concrete assessments are done and with what quality. However, as argued above, not only the scientific quality of the assessments but also their relevance, value and usefulness to be a help in reaching a decision hinge on methodology choices.

At this stage of the development of network cooperation it seems relevant to map the situation in Europe and consider how to more actively address outstanding differences in the choice of scientific and technical methodologies between HTA institutions.

A mapping of HTA methodologies should aim at revealing discrepancies in choice of methodology to answer frequently asked questions in assessments and contribute to a discussion on possibilities of alignment in Europe. Methodology choices made by HTA institutions may be directly influenced by legislation or by formal agreements between an HTA institution and a decision maker. Thus, it is also relevant to map the extent of formal arrangements that may be in place in the Member States to govern methodology choices in HTA.

### Aim of the study

This study aims to

- provide a concise and accurate overview of the scientific methodologies implemented by the European Union Member States' HTA bodies
- inform a better understanding of the current methodological framework in each country
- identify the potential needs and limitations of the HTA collaboration

# Methods

## Desk research

The themes and topics for this study were derived from a combination of published HTA methodology guidance, particularly by EUnetHTA, studies of applied HTA methodology and experience from national, European and global HTA practice.

HTA methodology guidance was reviewed to identify pertinent research questions for this study, in practice meaning EUnetHTA guidance from guidelines, the HTA Core Model®, EUnetHTA procedures for Relative Effectiveness Assessment (REA) of pharmaceuticals, and other technologies, and comprehensive HTA).

Published studies of methodologies applied by HTA institutions were searched and reviewed to further refine research questions and identify additional items that should be addressed by this mapping study.

## Survey to obtain data

A survey approach involving the relevant target group of institutions was decided. The geography and jurisdictions of the study are European Economic Area (EEA) countries, i.e. all 28 EU Member States and Norway (the remaining two EEA countries Iceland and Lichtenstein having no specific HTA activity).

The institutions of interest in this study are those that play an official role of producing HTA reports and information in the relevant countries, and the nomination in 2015 by ministries of health of EU Member States and Norway to partake in EUnetHTA Joint Action 3 was assumed to be an indicator of such a role.

Items for a self-administered survey were developed to collect information on scientific and technical methodologies applied together with background items to facilitate description and analysis of these methodologies at institution and country level.

The items were developed and selected based on methodology topics mentioned in the HTA Core Model's several applications and published surveys of applied methodology. A few normative questions stemming from a good HTA practice article were added.

One of the aims of the study was to identify the potential needs and limitations of the HTA collaboration. To contribute to meeting this aim, background questions on types of technologies assessed, the administrative level (national, regional, institutional) and formal background (legislation, formal agreement, internal guideline) of certain methodological requirements in the institutions were also included in the survey. An established survey tool (EUSurvey) was provided by the European Commission.

## Survey data collection

A total of 78 institutions in 27 EU countries and Norway that had been designated by Ministries of Health to participate in EUnetHTA Joint Action 3 in 2015 were contacted with the help of the Directorate in the coordinating organisation, ZIN, Netherlands. In addition, the Ministry of Health of Luxembourg was contacted directly. Thus, the total sample invited to participate in the survey was 79 institutions from all 28 EU countries and Norway.

Data were collected between December 2016 and February 2017. The total number of respondents by end of February 2017 was 61 and a total of 48 institutions in 27 EU countries and Norway con-

firmed having a defined role of directly informing a decision maker by way of HTA reports or structured HTA information. Thus, the survey study population consists of 48 institutions with a confirmed role of informing a decision maker.

### Analysis of the survey results

In a first step, the 48 institutions with a confirmed role of informing a decision maker were selected for analysis. The dataset was validated for completeness of responses.

The study dataset was used to produce country profiles that are structured in primary tables which report various issues in scientific and technical methodology applied in the HTA institutions' work. Other tables describe the formal context where HTA methodology is applied. Eight appendix tables provide additional detailed information on each institution relating to the primary tables, e.g. where any background in legislation of a methodology choice of an institution can be found.

The analysis was descriptive in nature and a multitude of illustrations and tables are used to illustrate similarities and discrepancies in the application of methodology across the 48 institutions. Tables within the report list organisations by their choice in relation to each issue, e.g. methods in synthesis of clinical evidence and pre-specified plans for assessments. Information in the report and in the country profiles point towards formal backgrounds that HTA institutions may have for methodology choices.

### Limitations of the study

The empirical data in this study were collected with a survey to institutions. Factors such as interpretation of questions by the respondent, amount of assessment practice in the responding institution to build the response on, transparency of its methodology, and the attention to the matter and the knowledge possessed by the respondent may all play a role.

## Results

### Country HTA Profiles

The country profiles map 28 countries and their 48 HTA institutions that directly inform a decision maker. The survey study results are reported in standardised country profiles consisting of 9 tables and 8 appendix tables per country.

The country tables are organised to first report *issues in research methodology* applied in the HTA institutions moving from the general to the more specific starting with tables on issues that are essential for a decision maker: Which technology or technologies is the technology (pharmaceutical, medical device, or e.g. diagnostic) in focus going to be compared with in the assessment, which kind of questions will be addressed. The next tables address issues of methodology choice that also have, perhaps indirectly, influence on the applicability of assessment reports to inform a decision maker's questions, e.g. study design, sources of evidence, and method of synthesis of evidence. The *formal context* where HTA methodology is applied in the HTA institutions is reported in additional tables covering the institution in relation to decision making, technologies assessed, legal requirements and guidelines, recommendations in reports and their relation to decision-making, and contribution to HTA from outside the institution.

The report includes figures with percentage distributions of HTA institutions in Europe on methodology choice and tables that list institutions by their choice.

## Observations - similarities and differences in methodology choices between HTA institutions

- All 48 institutions in 27 Member States and Norway that inform a decision maker address the 4 REA domains (Health problem and current use of technology, Technical characteristics, Clinical effectiveness, and Safety) that are included in the HTA Core Model for REA
- The study shows that 3 in 4 institutions consider issues of transferability in their assessments - e.g. to/from populations studied or to/from other clinical, organisational, economic, social contexts
- More than half of the institutions explicitly indicated that their "clinical" assessment mostly or completely overlaps with the methodology features of the HTA Core Model for REA in all technologies (53 % in pharmaceuticals and 58 % in medical technologies and other non-pharmaceutical technologies). Only 3 institutions indicated that there was no overlapping
- About 1 in 5 institutions could not respond on the degree to which their methodology overlaps with the features of REA, and about 20 % found only methodologies in the clinical assessment "somewhat" overlapping
- In addition to showing complete overlap in the priority given to the content of REA, this study makes clear that applying the wider scope of HTA (economic, patient, organisational, ethical, social, legal aspects) - which is reflected in the domains of the full HTA Core Model - is indeed practiced by a large majority of countries/institutions when it is relevant for the technology assessed
- In pharmaceuticals 26 of 38 HTA institutions (68 %) reported that they include the comparator technology or technologies most likely to be replaced by the assessed technology if proven inferior to it as a criterion or among criteria for choice of comparator(s) in their assessments. Contrary to this, 4 institutions (11 % of all 38) indicated a comparator supported by evidence of its efficacy and safety profile as the only criterion for choice of comparator. However, 18 (47 %) pointed to both the comparator most likely to be replaced and a comparator supported by evidence of its efficacy and safety profile
- A total of 40 (83 %) of the 48 institutions explicitly apply indirect comparison when estimating effectiveness or safety in their assessments. Among these 40 institutions that use indirect comparisons 34 institutions explicitly also apply the methodology of network meta-analysis in their estimations (83 % of these institutions or 71 % of all institutions). Three institutions explicitly do not apply this methodology
- There was no noteworthy difference in the frequency of use of non-randomised prospective studies and other kinds of observational studies in assessment of pharmaceuticals and assessment of medical technology and other non-pharmaceutical technologies. In both cases it was relatively high, about 80 %
- In the case of using surrogate endpoints, 43 Institutions (90 %) explicitly indicated that they use this measure when estimating effectiveness or safety in their assessments. Only 1 of the 48 institutions explicitly does not use surrogate endpoints
- All institutions use randomised clinical trials (RCT) as sources of evidence for all technologies when they are available. A small minority of institutions only include RCTs in the clinical assessment (11 % in pharmaceuticals and 14 % in non-pharmaceutical technologies)
- In the case of using surrogate endpoints, 43 Institutions (90 %) explicitly indicated that they use this measure when estimating effectiveness or safety in their assessments. Only 1 of the 48 institutions explicitly does not use surrogate endpoints
- A total of 37 of the 48 institutions (77 %) include a pre-specified plan on methodology to be applied in their assessments, and thus are in harmony with the practical guidance developed by EUnetHTA

- A large majority of the institutions (87 %) indicated that they have written guidelines for the production of HTA reports
- At least one institution in 23 of the 28 countries responded that they receive submission dossiers
- Some degree of explicit general requirements on how assessments should be produced exist in 42 % of institutions for pharmaceuticals and 33 % for medical technologies (including all types of medical devices and in vitro diagnostics)
- A third of the institutions have legislation or a formal agreement with a decision maker as a background for their choice of comparator in assessment of pharmaceuticals
- Half of the institutions have legislation or a formal agreement with a decision maker included as a background for inclusion of cost, budget impact or economic evaluation in the assessment of pharmaceuticals
- Aspects related to the research designs to be included in the assessment of pharmaceuticals are formally governed by either legislation or a formal agreement with a decision maker in nearly a third (29 %) of the institutions. Formal requirements in these areas are less frequent in non-pharmaceutical technologies

## Discussion

The finding that all institutions address the 4 REA domains suggests that going ahead with production of REA (at both national and EU level) based on the HTA core Model is feasible. There is a sufficient number of institutions with a high degree of overlap between their clinical assessment and REA to go ahead with joint assessments to be then used at national level (generally known as "national uptake"). Because all institutions assess topics covered by the HTA Core Model for REA they and their decision makers and stakeholders can get direct value from joint assessments – and from sharing REAs done by a single or a group of institutions.

The lack of knowledge of REA and lack of sufficient overlap in methodology with The HTA Core Model for REA presents a serious challenge to the scientific and technical HTA cooperation in Europe and could be a potential serious limitation in the current HTA cooperation. This should be systematically addressed by the HTA Network and Joint Action to increase the value of working together. The need to implement and use the Model in HTA production should have the attention of all stakeholders.

The study shows that the institutions go beyond the four domains included in REA which fits with a generally shared view on what an assessment could comprise in its scope to meet the needs of the decision makers – depending on the topic of the assessment. This fits with the HTA Core Model that was developed to serve this purpose, and even though information may need to be analysed at national level, there is still an argument for cross-border cooperation in identifying issues that would generally be relevant to address nationally.

Finding the balance on best available evidence should be practiced according to the decision-makers' request to have evidence-based input that meet good methodology standards and that can be a direct help when the decision is made. After more than 10 years of finding practical solutions the European HTA cooperation is mature, and it should take upon itself to find the balance in this ever-present challenge through joint work. For example, the version of the HTA Core Model for Rapid REAs developed by Work Package 5 in Joint Action 2, and the Procedure Manuals for rapid REA of pharmaceuticals and for other health technologies such as medical devices, surgical interventions or diagnostics developed in Joint Action 2 have paved the way for finding a balance.

RCT design is the standard in regulatory requirements of clinical studies in pharmaceuticals, and often, but not always, these studies are available among the sources of evidence in HTA. For exam-

ple, in orphan drugs and targeted therapies in stratified medicine, for various reasons the RCT design is currently infrequently applied which is a challenge shared with regulators. This situation is well-known in the medical technologies sector. The evidence available for the clinical assessment in institutions that only accept RCTs as evidence will be limited or missing, particularly in medical technology and other non-pharmaceutical technologies.

Manufacturers that typically bring their drugs, devices, and other technologies to market in many or all countries in Europe may be met with a request to provide information in a certain structured way in submission dossiers. These may vary slightly or substantially between institutions and country, yet may basically ask for the same information from an assessment point of view. It can be very work intensive to tailor information into documents that meet national requirements which are similar or even identical content-wise, but have to be structured in a different way from one organisation/country to another. Since 2016 there are non-country specific Evidence Submission Templates for pharmaceuticals and for medical devices developed by EUnetHTA .

In general, for European cooperation to be successful in spearheading national involvement and uptake it seems important that the relation between HTA and decision making in each country is clear for all those involved and that the relation is transparent to stakeholders.

An institution having focus on one type of technology only, may meet challenges associated with cross-technology comparisons, e.g. pharmaceuticals with medical technology and vice versa – which is often precisely the choice the decision maker may be presented with. It may be appropriate to develop national strategies for covering relevant technologies according to health policy goals and to avoid “silos” by establishing a national framework of institutions that together can cover all the relevant types of technologies if indeed the decision is not to have a single national institution to cover all technologies.

The survey results show that approaches to many specific research methodology issues are shared by a large majority of institutions and aligned with the HTA Core Model, EUnetHTA guidelines and procedures. This fact should lead to constructive discussion on best practices with a view to even more alignment between institutions of methodologies that fit to cross-border cooperation. The discussion should not only be between researchers. It seems important for further alignment that a discussion of applied methodologies be stimulated by, and involve institution managements, decision makers, and stakeholders as well.

The information in the report and in the Country Profiles on underlying requirements in the form of legislation or formal agreement with a decision maker can contribute to clarification of any formal backgrounds for methodology choices in the institutions. In addition, the mapping of formal requirements from methodology can facilitate discussion of how legal texts translate into methodology guidance in institutions, and how helpful it is to set the framework for scientific and technical methodology by way of legislation.

## Conclusions

When it is relevant, a large majority of institutions and countries apply a wider scope than what is covered with the clinical domains of the HTA Core Model for REA. To cover the scope of assessment of a range of different technologies the full HTA Core Model should be continued as the basic framework from which tailored fit for purpose applications can be drawn.

There seems in practice to be a general methodological approach spanning across different types of technologies today which is shared by the majority of institutions. Several written procedures for the implementation of HTA methodology that are tailored to type of technology and address the specific

characteristics of the technology already exist for REA of pharmaceutical and non-pharmaceutical interventions and for several applications of the full HTA Core Model. As the group "non-pharmaceutical technologies" covers a wide range of technologies, additional fit for purpose procedure documents should be developed, e.g. for in vitro diagnostics, imaging and information and communication technologies. Involvement of relevant stakeholders and testing for usefulness of assessments to inform concrete decisions should be applied.

Further alignment of methodologies can grow out of joint practical assessment work within a committed scientific and technical cooperation. This must go hand in hand with national processes facilitated by the country partners in Joint Action 3 which was given a remarkable priority in the EU Health Programme. With a sizable four-year grant, EUnetHTA Joint Action 3 should create the results that will bring about methodology alignment. For European cooperation to be successful in national involvement and uptake it seems important that the nature and properties of the relation between HTA and decision making in each country is clear for all parties involved and that it is transparent to stakeholders.

If there is a wish to align the scientific and technical practices with other HTA institutions to increase the quality, quantity and efficiency in the production of assessments, the first step could be to encourage the institution to review, revise or to develop their internal guidelines or procedure descriptions. Guidance to assist HTA "doers" from EUnetHTA includes the procedure manuals for applying the HTA Core Model for Rapid REAs of pharmaceuticals and for medical technology and other technologies, the full HTA Core Model in several applications, such as diagnostic and screening Technologies, the Submission Templates, and 15 guidelines. These documents can help a coordinated process of alignment between the HTA institutions in the HTA cooperation and bring other institution closer. The distance is not far to having good scientific and technical solutions in using best available evidence for valid and reliable comparative assessments of technology options. After more than a decade of EU cooperation on HTA, reaching consensus on a common HTA methodology, to be used at both national and EU level is getting closer than ever to becoming a reality.

# 1 INTRODUCTION

## 1.1 Background

Over the last 20 years Health Technology Assessment (HTA) has taken the stage in European health policy as a science-based policy tool to facilitate appropriate use of limited resources in health policy and decision making. HTA is increasingly applied as a means of informing decisions on the application / payment / reimbursement of health technologies, particularly pharmaceuticals, medical devises and public health interventions. In parallel to this, variation in methodologies used in HTA across countries and institutions has drawn attention from stakeholders such as policy makers, academia, scientific societies, patient organisations, industry and international organisations.

In relation to uptake, procurement, or reimbursement of health technologies, decision makers will tend to seek contributions from HTA institutions with a clear role in relation to the decision making process. Requests of assessments are associated with an expectation that the reporting of the assessments will provide relevant, valid and reliable information into a concrete policy process that leads to a decision. To meet this expectation, the HTA institutions must keep focus on the intent of HTA to inform decisions, and the methodology choices should be appropriate, transparent and scientifically coherent.

## 1.2 European HTA cooperation

European HTA cooperation has nearly 25 years of history (Banta et al, 2002). From a dispersed and fragmented situation with only a few institutions having a formal role of providing a defined decision maker with HTA information, the HTA institutions have grown in number and have come closer in terms of a more shared understanding of the role of HTA in relation to decision making and in terms of understanding which methodologies to apply. The network cooperation between institutions in Europe is unquestionably the most developed in the world. The European projects supported by the EU Health Programme have had a critical role in facilitating this process of alignment between institutions (Liberati, 1997, Jonsson, 2002, Kristensen, 2017).

## 1.3 EUnetHTA and the HTA Network

HTA is now institutionalised in a majority of EU Member States with growing scientific and technical cooperation across borders. With the support of the EU Health Programme, EUnetHTA was established initially as project (2006-2009)[1] and later, time-limited sustainability was ensured through a series of Joint Actions having scientific and technical cooperation on HTA as primary objective. Joint Action 1 (2010-2012)[2] and 2 (2012-2015)[3] focused on developing common methodologies, piloting and producing joint early dialogues and HTA reports, developing and maintaining common tools. All these activities contributed to building HTA capacity and trust among HTA bodies. Joint Action 3 (2016-2020)[4] aims to “create an effective and sustainable network for HTA across Europe”.

[1] http://www.eunethta.eu/activities/EUnetHTA%20Project%20%282006-08%29/eunethta-project-2006-2008

[2] http://www.eunethta.eu/activities/eunethta-joint-action-2010-12/eunethta-joint-action-2010-12

[3] http://www.eunethta.eu/activities/EUnetHTA%20Joint%20Action%202%20%282012-15%29/eunethta-joint-action-2-2012-2015

[4] http://www.eunethta.eu/activities/joint-action-3/jointaction31/eunethta-joint-action-3-2016-2020

The Health Technology Assessment Network (HTA Network) is a policy network that has its basis in Article 15 on European HTA cooperation in the EU Directive on Patients' rights in Cross-border Healthcare[5] and its secretariat is ensured by the Directorate General for Health and Food Safety (DG SANTE) of the European Commission[6]. The HTA Network was set up in 2013 and includes all EU Member States and provides strategic guidance and policy orientation, by developing policy papers and discussing areas of potential collaboration.

## 1.4 The scientific disciplines that contribute to HTA methodology

The scientific disciplines that contribute to HTA methodology are, for example, comparative effectiveness research, clinical research (e.g. clinical trials methodology), population and clinical epidemiology, evidence synthesis, health economics and qualitative research. Deciding methodologically sound approaches that ensure quality in the scientific practices of these various fields is facilitated by well-known academic means such as formal education, awarding higher degrees, peer supervision and peer review. This way, over time, good or best research practices within the various disciplines emerge through theory, studies, scientific debate and consensus. There may be discussion, sometimes even controversy within the various disciplines, and generally, no full consensus among researchers about best research practice within a specific of the disciplines relevant for HTA can be claimed to exist.

Methodologies that are applied in day-to-day HTA are significantly influenced by specialised researchers in the scientific disciplines that contribute to HTA. The methods are also influenced by HTA methodologists within the institutions and in academic institutions that have a stake in HTA through teaching or commissioned research. The HTA researchers and management of HTA institutions influence the institutions' research practice because they have the scientific responsibility to practically apply research methodologies in the actual assessments of, say, drugs and medical devices to inform a decision and assure quality of the output.

Compared to the contributing scientific disciplines, there is an important dimension specific to good research practice in HTA: The fact that the research must be relevant for the decision-maker to meet its intent. In turn, this implies that the research methodologies need to be practically applied in assessments so that the results fulfil the intent to contribute useful quality assured information based on science to decision-making.

## 1.5 What influences an HTA institution's choice of scientific and technical methodologies?

A primary requirement that HTA institutions are expected to meet is to provide trusted timely HTA reports in their country context. Their products should be considered relevant by the decision makers that determine e.g. the use / procurement / reimbursement of technologies or implementation of public health interventions (their primary *clients*). The scope of assessments that the institutions address, i.e. the span of assessment questions from effectiveness to, say, organisational and economic issues, influences their relevance. Some decision makers may ask for clinical assessment only while other may request economic and patient aspects covered as well.

[5] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF

[6] http://ec.europa.eu/health/technology_assessment/policy_en

The scientific and technical methodologies that are applied in HTA arise from research, and it should be acknowledged that decisions made by the HTA institutions on which principles and practices to apply in assessments have consequences for the decision makers and stakeholders. For example, the decisions on appropriate methodologies influence which research questions can be addressed in assessments by including or excluding certain groups of comparators or study designs. The exclusion of non-randomised prospective studies from the evidence base in comparative assessment research may exclude most or all the available evidence on current (best) technology: the comparator likely to be replaced if the technology under assessment proves superior. Consequently, methodology choices influence to which degree a concrete HTA report reflects the options of choice that the decision maker is presented with in reality.

Based in the arguments above, any HTA institution should be able and ready to explain its concrete application of methodologies to external parties. What may in some cases currently be viewed as strictly methodological policies, guidelines and procedures should be considered for wider discussion between the institutions that define and implement these scientific practices and their relevant clients, e.g. decision makers and stakeholders.

## 1.6 Similarities and discrepancies in methodologies used by HTA institutions

Differences between HTA institutions in terms of their choice of scientific methodology to address specific elements of assessments, such as comparison between technologies and choice of outcome measures in assessments, have drawn the attention of researchers and stakeholders (Akehurst, 2017, Charles River Associates, 2011, Drummond, 2008, Nicod, 2017).

Behind the present study lies the assumption that methodology choices which are made by HTA institutions have consequences for the way concrete assessments are done and with what quality. However, as argued above, not only the *scientific quality* of the assessments but also their *relevance, value and usefulness to be a help in reaching a decision* hinge on methodology choices.

At this stage of the development of network cooperation it seems relevant to map the situation in Europe and consider how to more actively address outstanding differences in the choice of scientific and technical methodologies between HTA institutions. A mapping of current methodologies applied in the Member States has become relevant for several reasons, such as

- intensified scientific and technical cross-border cooperation in HTA
- manufacturers' interactions with HTA institutions in various countries on assessment of their products
- relations between requirements for marketing authorisation and HTA
- research projects in HTA methodology

A mapping of HTA methodologies should aim at revealing discrepancies in choice of methodology to answer frequently asked questions in assessments and contribute to a discussion on possibilities of alignment in Europe. Two examples of a choice of methodology that has implications for work across borders are: "Which outcome measures can be used in the assessment of the clinical effect of a technology?" and "Can indirect comparisons be applied in assessments?" In addition, methodology choices made by HTA institutions may be directly influenced by legislation or by formal agreements between an HTA institution and a decision maker. Thus, it is also relevant to map the extent of formal arrangements that may be in place in the Member States to govern methodology choices in HTA.

The present study (SANTE/2016/B4/026) was undertaken at the request of the European Commission, DG SANTE, with the main objective of mapping HTA methodologies in the EU and the EEA countries. The results of the study will be used, *inter alia*, as input for the Impact Assessment for an EU initiative on HTA.

## 1.7 Aim of the study

This study aims to

- provide a concise and accurate overview of the scientific methodologies implemented by the European Union Member States' HTA bodies;
- inform a better understanding of the current methodological framework in each country;
- identify the potential needs and limitations of the HTA collaboration.

# 2 Methods

## 2.1 Key concepts

*Health technology* is "the application of scientific knowledge in health care and prevention. Examples of health technology: Diagnostic and treatment methods, medical equipment, pharmaceuticals, rehabilitation and prevention methods, organisational and supportive systems within which health care is provided" (EUnetHTA).

*Health technology assessment (HTA)* is "a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Despite its policy goals, HTA must always be firmly rooted in research and the scientific method" (EUnetHTA)[7].

*HTA Core Model®* is a methodological framework for joint production and sharing of HTA information. The Model consists of three components: 1) an ontology containing a set of generic questions that define the contents of an HTA, 2) methodological guidance that assists in answering the questions and 3) a common reporting structure that enables standardised reporting of HTAs[8].

*HTA methodologies* are defined for this study as "scientific and technical methodologies applied by HTA institutions or groups of HTA researchers in the collection, analysis and synthesis of evidence and information on health technologies and their use in healthcare to inform decision making".

*Relative effectiveness* can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice (High Level Pharmaceutical Forum 2005-2008, European Commission DG Enterprise & Industry and DG Health & Consumers)[9].

## 2.2 Desk research

The themes and topics for this study were derived from a combination of published HTA methodology guidance, particularly by EUnetHTA, studies of applied HTA methodology and experience from national, European and global HTA practice.

HTA methodology guidance was reviewed to identify pertinent research questions for this study (Guidelines, procedures and normative papers - in practice meaning EUnetHTA guidelines[10], the HTA Core Model®, EUnetHTA procedures for Relative Effectiveness Assessment (REA) of pharmaceuticals[11] and other technologies[12] and comprehensive HTA[13]).

[7] http://www.eunethta.eu/about-us/faq#t287n73

[8] http://meka.thl.fi/htacore/ViewHandbook.aspx

[9] https://publications.europa.eu/da/publication-detail/-/publication/4fddf639-47cc-4f90-9964-142757d2515a

and http://www.rees-france.com/en/article.php3?id_article=501

[10] http://www.eunethta.eu/eunethta-guidelines

[11] https://meka.thl.fi/htacore/documents/WP5_ProcedureManual_RapidREAofPharmaceuticals.pdf

[12] https://meka.thl.fi/htacore/documents/WP5_ProcedureManual_RapidREAofOtherTechnologies.pdf

[13] https://meka.thl.fi/htacore/documents/WP4_MSP_%20Final.pdf

Published studies of methodologies applied by HTA institutions were searched and reviewed to further refine research questions and identify additional items that should be addressed by this mapping study (Allen, 2013, 2017; Ciani, 2015; Chales River Associates, 2011; CIRS Regulatory and Reimbursement Atlas™, 2014; Fuchs, 2016, 2017; Franken, Kleijnen, 2012; Le Polain, 2010; Mathes, 2013; Nicod, 2016, 2017; Schwartzer, 2009; Stephens, 2012; Tarracone, 2017; Van Wilder, 2015; WHO, 2015).

## 2.3 Rationale for using a survey to obtain data

Information from literature review and from visiting websites of HTA organisations in Europe proved to be insufficient for obtaining comprehensive, representative and detailed data on applied scientific and technical methodologies in HTA institutions. A systematic study of methodology sections of published HTA reports from institutions in many countries with different languages was not an option to pursue. Besides, the study should address the relation between the formal national context in which the HTA institutions do their assessments and the choice of methodologies – i.e. the degree to which there are formal agreements with a decision maker or legislation that influence methodology choices. Consequently, a survey approach involving the relevant target group of institutions was decided.

## 2.4 Selection of HTA institutions

The geography and jurisdictions of this study are European Economic Area (EEA) countries, i.e. all 28 EU Member States and Norway (the remaining two EEA countries Iceland and Lichtenstein having no specific HTA activity)[14].

The institutions of interest in this study are those that play an official role of producing HTA reports and information in the relevant countries, and the nomination in 2015 by ministries of health of EU Member States and Norway to partake in EUnetHTA Joint Action 3 was assumed to be an indicator of such a role. An agreement was made with the Coordinator of Joint Action 3, Zorginstituut Nederland (ZIN) to distribute a study invitation to the partner organisations.

## 2.5 Selection of issues and a tool for data collection

Review of published studies identified during the first phase of the project made clear that a primary data collection at HTA institution level was necessary to meet the objectives. Items for a self-administered survey were developed to collect information on scientific and technical methodologies applied together with background items to facilitate description and analysis of these methodologies at institution and country level.

The items were developed and selected based on methodology topics mentioned in the HTA Core Model's several applications, e.g. REA of pharmaceuticals and REA of other technologies which are considered to reflect broad scoped as well as focused HTA), EUnetHTA methodological guidelines, procedure descriptions and published surveys of applied methodology. A few normative questions stemming from a good HTA practice article were added (Drummond, 2008).

One of the aims of the study was to identify the potential needs and limitations of the HTA collaboration. To contribute to meeting this aim, background questions on types of technologies assessed, the administrative level (national, regional, institutional) and formal background (legislation, formal

[14] Mapping of HTA national organisations, programmes and processes in EU and Norway, Julia Chamova, Stellalliance AB - June 2017

agreement, internal guideline) of certain methodological requirements in the institutions were also included in the survey.

An established survey tool (EUSurvey)[15] was provided by the European Commission to allow data collection by way of a link to a dedicated electronic questionnaire provided inside an invitation to participate. The tool allows a respondent to receive a PDF copy of the response for validation and reference when they provide an e-mail address.

## 2.6 Survey data collection

A total of 78 institutions in 27 EU countries and Norway that had been designated by Ministries of Health to participate in EUnetHTA Joint Action 3 in 2015 were contacted with the help of the Directorate in the coordinating organisation, ZIN, Netherlands. In addition, the Ministry of Health of Luxembourg was contacted directly. Thus, the total sample invited to participate in the survey was 79 institutions from all 28 EU countries and Norway. The first survey invitation e-mail was distributed by ZIN to Joint Action 3 contact persons in the partner institutions on December 2, 2016 with an encouragement by the coordinator to partake. Three reminders were sent by ZIN, the final one on January 18, 2017.

The invitation and reminders explained the survey background and it was explicitly requested that the response be made by one or a group of staff designated by the institution to have the expertise and to answer questions on applied HTA methodologies for the institution. Detailed practical instructions on how to fill out the survey were included as was a letter of support from the European Commission, DG SANTE.

Data were collected between December 2016 and February 2017. The total number of respondents by end of February 2017 was 61 and a total of 48 institutions in 27 EU countries and Norway confirmed having a defined role of directly informing a decision maker by way of HTA reports or structured HTA information. A decision maker was defined in the questionnaire in the following way: A defined decision maker that decides on e.g. reimbursement/payment of pharmaceuticals and medical devices or provision of healthcare services[16]. Thus, the survey study population consists of 48 institutions with a confirmed role of informing a decision maker.

## 2.7 Analysis of the survey results

The survey tool, EUSurvey, provided all individual survey responses as PDF copies as well as unique data records in a MS Excel Workbook.

In a first step, the 48 institutions with a confirmed role of informing a decision maker were selected for analysis. The dataset was validated for completeness of responses by contacting a limited number of respondents for clarification where relevant. In a few cases institutions came back with amendments to their original response. Resulting alterations were entered in a revised dataset that was used for all analyses.

[15] https://ec.europa.eu/eusurvey/home/about

[16] In Slovakia, a consortium was created between the Pharmaceutical faculty of Comenius University in Bratislava (a EUnetHTA Joint Action 3 partner) and the Union Health Insurance Fund, with the objective of collaborating in activities related to assessments of medicinal products and medical devices, and the response to the questionnaire is for the Union Health Insurance Fund.

**Tables and figures**

The results are presented in a combination of text, tables and graphics.

For yes/no responses, the results are presented in *pie charts* with numbers and percentages, e.g. Figure 7.

Most other figures are qualitatively, and not quantitatively descriptive. Generally, the total number of survey responses e.g. on pharmaceuticals, from which the sets of specific responses are derived, is given as N=x in the lower right corner of the figures.

In cases where several responses to multiple-choice questions were allowed each response is depicted with an oval object and the relevant number inside, or outside with an arrow.

Some of the illustrations are inspired by *Set Diagrams,* also called Venn Diagrams, to help elicit overlaps or full inclusion between response options in the survey items, e.g. overlaps in choice of comparator in assessments, or inclusion of a description of evidence synthesis in the pre-specified plan for methodologies to be applied in an assessment. The areas are not quantitatively reflecting the numbers.

The number inside overlaps between objects represents the number of respondents that gave e.g. both or all three responses to the question. It is not the intention to reflect the precise relative or absolute size of the quantity of responses with the size of objects or subsets of object in the illustrations.

Mutually exclusive responses to questions conditional on responses to yes/no questions are illustrated as non-overlapping objects inside an object (with the relevant number inside), e.g. Figure 34 and 48.

The study dataset was used to produce country profiles, a key output agreed with the European Commission to inform the impact assessment. Each country profile includes the institutions in the country that confirmed to have a role of informing a decision maker. The profiles are structured in primary tables that report various issues in scientific and technical methodology applied in the HTA institutions' work. Other tables describe the formal context where HTA methodology is applied. Eight appendix tables provide additional detailed information on each institution relating to the primary tables, e.g. where any background in legislation of a methodology choice of an institution can be found.

The analysis was descriptive in nature and a multitude of illustrations and tables are used to illustrate similarities and discrepancies in the application of methodology across the 48 institutions. Tables within the report text list organisations by their choice in relation to each issue, e.g. methods in synthesis of clinical evidence and pre-specified plans for assessments. Information in the report and in the country profiles point to formal backgrounds that HTA institutions may have for methodology choices.

## 2.8 Limitations of the study

The empirical data in this study were collected with a survey. Designation by the institution of an individual to respond who had expertise in the institution's applied methodologies was requested, and the survey background was explained in the invitation. Detailed practical instructions on how to fill out the survey were included. However, factors such as interpretation of questions, amount of assessment practice in the responding institution to build the response on, transparency of its methodology, and the attention to the matter and the knowledge possessed by the respondent may

all play a role. Survey validity issues appear to be minor as the "Don't know" option was used infrequently in the survey and no respondents used the explicit option of contacting us for assistance. However, some responses might have been different if another individual had responded[17].

[17] Two organisations provided seemingly inconsistent responses to questions about which technologies they assess. The Italian Medicines Agency, AIFA, lists only pharmaceuticals as technologies assessed. The institution also lists non-pharmaceutical technologies as potential comparators in assessments of pharmaceuticals, confirms that the institution assesses non-pharmaceutical technologies for certain sections of the survey and provides information on e.g. scope of assessments of these technologies. Thus, the information provided by AIFA on e.g. scope in non-pharmaceuticals was deemed relevant. Consequently, the total number of institutions that assess non-pharmaceutical technologies varies between 36 and 37 in figures and tables depending on the issue. Likewise, Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) indicated to assess non-pharmaceutical technologies only. However, the institution indicated to assess pharmaceuticals in some section of the survey. In this case the information was also deemed relevant for the study, thus bringing the total number of institutions in pharmaceuticals to vary between 37 and 38.

# 3 RESULTS

## 3.1 Country HTA Profiles

Volume II of this report consists of the mapping of the 28 countries and their 48 HTA institutions that directly inform a decision maker. The survey study results are reported in 28 standardised country profiles consisting of 9 tables and 8 appendix tables per country.

The country tables are organised to first report *issues in research methodology* applied in the HTA institutions moving from the general to the more specific (Country Profile Table 1-6 and Table A1-A6)

- Choice of assessment comparator(s) (Table 1 and Table A1)
- Scope of assessments - clinical domains addressed (Table 2 and Table A2)
- Scope of assessments - non-clinical domains addressed (Table 3 and Table A3)
- Study designs considered relevant as sources of evidence (Table 4 and Table A4)
- Specific methodology issues in assessment and synthesis of evidence (Table 5 and Table A5)
- Evidence search and handling (Table 6 and Table A6)

The profiles start with tables on issues that are essential for a decision maker: Which technology or technologies is the technology (pharmaceutical, medical device, or e.g. diagnostic) in focus going to be compared with in the assessment (Table 1), which kind of questions will be addressed (Table 2). The next tables address issues of methodology choice that also have, perhaps indirectly, influence on the applicability of assessment reports to inform a decision maker's questions, e.g. study design, sources of evidence, and method of synthesis of evidence.

The *formal context* where HTA methodology is applied in the HTA institutions is reported in Country Table 7-9 and Table A7-A8

- Description of the institution in relation to decision making, technologies assessed, legal requirements and guidelines (Table 7 and Table A7)
- Recommendations in reports and their relation to decision-making (Table 8)
- Contribution to HTA from outside the institution (Table 9 and Table A8)

The following pages present results across the 48 institutions in 28 countries in the same sequence as that of the tables in the country HTA profiles in Section II. This means that the focus is first on scientific and technical methodology which is applied by the institutions and then on the context in which the HTA methods are applied (e.g. legal framework, formal agreements, internal guidelines).

## 3.2 Issues in research methodology applied in HTA institutions in EU Member States and Norway (EEA) (Country Profile Table 1-6 and Table A1-A6)

### 3.2.1 Choice of assessment comparators (Country Profile Table 1 and Table A1)

HTA is comparative in nature reflecting that the decisions it informs are about choosing between alternatives. Analysis of clinical effectiveness/efficacy (added therapeutic value) and safety are central elements in HTA and the choice of comparator(s) is a decisive step in each single assessment of a technology. It influences the relevance of the assessment report for the decision maker and stakeholders and must strike a balance between the relevance of the comparator to the actual decision, e.g. is it used in current practice, and the availability of results from comparative studies with a rigorous research design, such as randomised or non-randomised prospective studies.

A survey question on criteria for choice as comparator allowed multiple answers:

1. A technology likely to be replaced by the assessed technology if proven inferior to it
2. A technology supported by evidence on its efficacy and safety profile for the clinical indication/population
3. A Europe-wide agreed reference comparator technology
4. Other criteria
5. Don't know

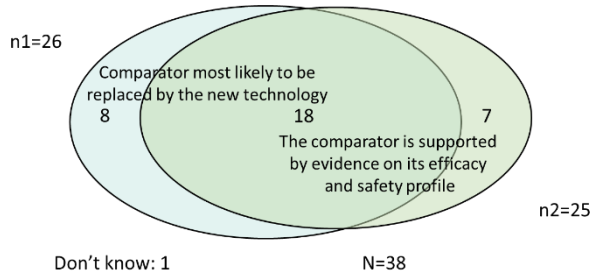
For this report, criterion 1 is an indicator of emphasis on the selection a comparator that reflects the current healthcare practice, called "comparator oriented", while criterion 2 is an indicator of putting weight on selecting a comparator that is supported by evidence, called "evidence oriented".

#### 3.2.1.1 Pharmaceuticals

Country profile Table 1 in Section II of this report shows each institution's multiple-choice responses. Figure 1 shows the distribution of institutions on two important criteria for choice of the comparator(s) in assessments of clinical evidence in pharmaceuticals, a technology likely to be replaced by the assessed technology if proven inferior to it, and a technology supported by evidence on its efficacy and safety profile for the clinical indication/population.

As illustrated in Figure 1 26 (n1) of 38 (N) HTA institutions (68 %) reported that they include the comparator technology or technologies likely to be replaced by the assessed technology if proven inferior to it as *a criterion or among criteria for choice* of comparator(s) in the assessment of pharmaceuticals.

**Figure 1. Comparator oriented and/or evidence oriented choice of comparator – in assessments of pharmaceuticals**




A total of 25 (n2) of 38 institutions (66 %) indicated the comparator(s) supported by evidence of its efficacy and safety profile as *a criterion or among criteria for choice*. More than one answer was possible and of these 25 institutions 18 (47 % of all 38) also pointed to the comparator most likely to be replaced. This is depicted with the overlap zone in Figure 1 and listed in Table 1.

Notably, seven institutions (18 % of all 38) pointed *only* to the comparator technology or technologies that are likely to be replaced by the assessed technology if proven inferior to it as the criterion (Table 2), while 4 institutions (11 % of all 38) only indicated a comparator supported by evidence of its efficacy and safety profile as criterion (Table 3) [18].

[18] To account for difference in the numbers given in Figure 1 and Table 2 and 3 it should be noted that there were 2 other multiple choice options: "A Europe-wide agreed reference comparator technology" and "Other criteria", and that tables 2 and 3 list the institutions that *only* indicated one criterion.

## Other criteria

A total of 9 institutions (24 %) indicated "Other criteria" alone or in combination with other multiple-choice options.

"Other criteria" was indicated as the *only* multiple-choice response by 4 institutions (11 % of all 38): Haute Autorité de Santé (HAS), France, Dental and Pharmaceutical Benefits Agency (TLV), Sweden, National Institute for Health and Care Excellence (NICE), United Kingdom, and All Wales Therapeutics and Toxicology Centre (AWTTC), United Kingdom.

"Other criteria" was indicated together with both criteria in Figure 1 by 2 institutions (5 % of all): State Institute for Drug Control (SUKL), Czech Republic and Zorginstituut Nederland (ZIN), Netherlands.

"Other criteria" was indicated together with the comparator technology or technologies likely to be replaced by the assessed technology by 1 of the 8 institutions in Figure 1 (3 % of all): Directorate for Pharmaceutical Affairs - Ministry for Health, Malta.

"Other criteria" was indicated together with the comparator supported by evidence of its efficacy and safety profile by 2 institutions (5 % of all): Gemeinsamer Bundesausschuss (G-BA), Germany and Institute for Quality and Efficiency in Health Care (IQWiG), Germany.

**Table 1. Institutions which combine comparator oriented and evidence oriented choice of comparator - in assessments of pharmaceuticals (n=18)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Regione Emilia-Romagna | Italy |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| Scottish Medicines Consortium (SMC) | United Kingdom |

**Table 2. Institutions that *only* indicated comparator oriented choice of comparator as criterion in assessments of pharmaceuticals (n=7)**

| Institution | Country |
|---|---|
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |

**Table 3. Institutions that *only* indicated evidence oriented choice of comparator as criterion – in assessments of pharmaceuticals (n=4)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| The National Health Service (NVD) | Latvia |
| Ministry of Health | Slovakia |

One institution indicated "Don't know": Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Spain.

### Formal requirements

The survey study asked where any formal requirements regarding the choice of comparator in pharmaceuticals by the HTA institution could be found with the following options: In internal guidelines or procedure descriptions, legislation, or formal agreement with a decision maker.

A total of 10 institutions (26 % of all 38 institutions) explicitly indicated that for pharmaceuticals such formal requirements can be found in national legislation. These are listed in Table 4.

**Table 4. institutions which explicitly indicated that for pharmaceuticals formal requirements on choice of comparator can be found in national legislation (n=10)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| State Institute for Drug Control (SUKL) | Czech Republic |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| The National Health Service (NVD) | Latvia |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |

Three institutions (8 % of all 38) pointed to a formal agreement with a decision maker, while not indicating legislation, as background for requirements in pharmaceuticals: Health Information and Quality Authority (HIQA), Ireland, Università Cattolica del Sacro Cuore (UCSC), Italy, and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Spain.

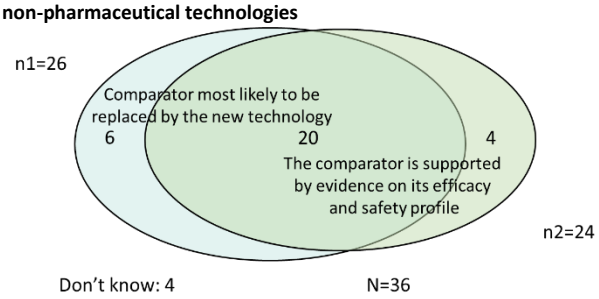
In Section II, Table 7, A1, and A7 in the country profiles show for each country where the respondents indicated that the formal background for choice of comparator can be found.

#### 3.2.1.2 Medical technologies and other non-pharmaceutical technologies

As a criterion or among criteria for choice of comparator(s) in the assessment of medical technologies and other non-pharmaceutical technologies 26 (n1) of 36 (N) HTA institutions (72 % of all 36) that explicitly responded to the question on comparators include the comparator technology or technologies likely to be replaced by the assessed technology if proven inferior to it (Figure 2).

A total of 24 (n2) of 36 institutions (67 %) indicated as a criterion the comparator(s) supported by evidence of its efficacy and safety profile.

**Figure 2. Comparator oriented and/or evidence oriented choice of comparator – in assessments of medical technologies and other non-pharmaceutical technologies**




More than one answer was possible and 20 (56 %) of the 36 institutions indicated both criteria (listed in Table 5). Notably, 6 institutions (17 %) *only* pointed to the comparator technology or technologies that are likely to be replaced by the assessed technology if proven inferior to it (Table 6), while 3 (8 %) *only* indicated a comparator supported by evidence of its efficacy and safety profile as criterion (Table 7)[19].

##### Other criteria

"Other criteria" was indicated as the only multiple-choice response by 2 institutions (6 % of all 36): Cellule d'expertise médicale in the Ministry of Health, Luxembourg, and National Institute for Health and Care Excellence (NICE), United Kingdom.

"Other criteria" was indicated together with the comparator(s) supported by evidence of its efficacy and safety profile by 1 institution (3 %): Haute Autorité de Santé (HAS), France.

"Other criteria" was indicated together with both comparator likely to be replaced and comparator supported by evidence by 1 institution (3 %): Zorginstituut Nederland (ZIN), Netherlands. Four institutions indicated don't know (11 %): Gemeinsamer Bundesausschuss (G-BA), Germany Institute of Hygiene, Lithuania, National Institute of Public Health, Romania, and Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Spain.

##### Formal requirements

[19] To account for difference in the numbers given in Figure 2 and Table 6 and 7 it should be noted that there were 2 other multiple choice options: "A Europe-wide agreed reference comparator technology" and "Other criteria", and that the tables list the institutions that only indicated one criterion.

Three institutions (8 % of all 36) explicitly indicated that for medical technology and other non-pharmaceutical technologies the formal requirements can be found in national legislation: Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ), Croatia, Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland, and Institute for Quality and Efficiency in Health Care (IQWiG), Germany.

Two institutions (6 % of all) pointed to a formal agreement with a decision maker, while not indicating legislation, as background for the requirements: National Agency for Regional Health Services (AGENAS), Italy and Galician Health Knowledge Agency (Avalia-t, ACIS), Spain.

In Section II, Table 7, A1, and A7 in the country profiles show for each country where the respondents indicated that the formal background for choice of comparator can be found.

**Table 5. Institutions that combine a comparator oriented and an evidence oriented choice of comparator – in assessments of non-pharmaceutical technologies (n=20)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Regione Emilia-Romagna | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

**Table 6. Institutions that indicated comparator oriented choice of comparator only - in assessments of non-pharmaceutical technologies (n=6)**

| Institution | Country |
|---|---|
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| Union Health Insurance Fund | Slovakia |

**Table 7. Institutions that indicated evidence oriented choice of comparator only - in assessments of medical technology and other non-pharmaceutical technologies (n=3)**

| Institution | Country |
|---|---|
| Haute Autorité de Santé (HAS) | France |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Ministry of Health | Slovakia |

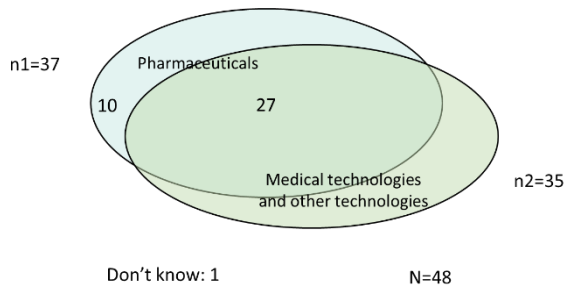
### 3.2.2 Technologies considered eligible as comparators in assessment of pharmaceuticals

Choice of comparator is obviously influenced by which groups of technologies are considered eligible for comparison. For example, a surgical procedure or an implantable medical device may be a relevant alternative to a pharmaceutical and vise versa. However, some institutions may restrict choice of comparator to certain (similar) technologies – for example, comparing pharmaceuticals with pharmaceuticals only. The survey explored this, and the results are reported in the following.

#### 3.2.2.1 Pharmaceuticals

Figure 3 shows that 37 (n1) institutions assess pharmaceuticals (77 % of all 48 (N)) and 36 (n2) institutions (75 % of all) assess non-pharmaceutical technologies including medical devices and e.g. therapeutic and other interventions. Figure 3 also shows technologies considered to be an eligible comparator in assessment of pharmaceuticals distributed on these two main groups of technologies.

**Figure 3. Technologies seen as relevant potential comparators when assessing pharmaceuticals**




As Figure 3 illustrates, 27 of the 37 institutions (73 %) that compare pharmaceuticals with pharmaceuticals consider also non-pharmaceutical interventions as potential comparators (illustrated with the overlap between the ovals). A total of 10 HTA institutions (27 % of all 37) compare pharmaceuticals with other pharmaceuticals only. These 10 institutions are listed in Table 8. One respondent indicated "Don't know".

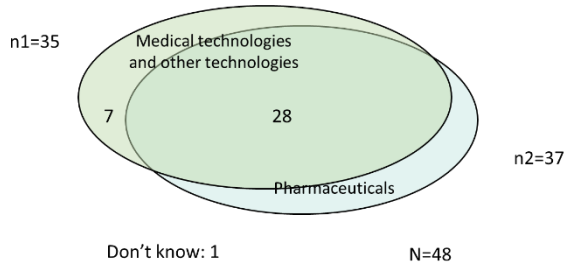
**Table 8. Institutions which use pharmaceuticals only as relevant potential comparators in assessments of pharmaceuticals (n=10)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| University of Tartu | Estonia |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Regione Emilia-Romagna | Italy |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |

### 3.2.2.2 Medical technologies and other non-pharmaceutical technologies

For assessment of medical technology and other non-pharmaceutical technologies Figure 4 shows the technologies considered to be an eligible comparator distributed on the two main groups of technologies: pharmaceuticals and medical technology and non-pharmaceutical technologies.

**Figure 4. Technologies seen as relevant potential comparators in assessments of medical technology and other non-pharmaceutical technologies**




While 28 of the 35 (n1) institutions (74 %) that compare non-pharmaceutical technologies with non-pharmaceutical technologies may select pharmaceuticals as comparator, 7 HTA institutions (19 %) *only* compare non-pharmaceutical technologies with other non-pharmaceutical technologies. The 7 institutions are listed in Table 9. One respondent indicated "Don't know".

**Table 9. Institutions which use non-pharmaceutical technologies only as relevant potential comparators in assessments of non-pharmaceutical technologies (n=7)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Institute of Hygiene | Lithuania |
| National Institute of Public Health | Romania |

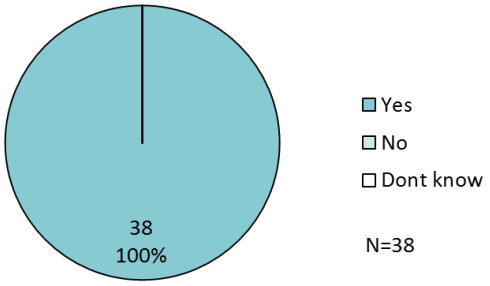
Section II, Table 7, A1, and A7 in the country profiles show for each country where the respondents indicated that the formal background for choice of comparator can be found.

### 3.2.3 Scope of assessments - clinical domains addressed (Country Profile Table 2 and Table A2)

Each Country Profile Table 2 in Section II of this report confirms the observation that all institutions that inform a decision maker in 27 Member States and Norway include the following 4 domains in the scope of their assessments of pharmaceuticals, medical devices and all other technologies – always or depending on what is assessed:

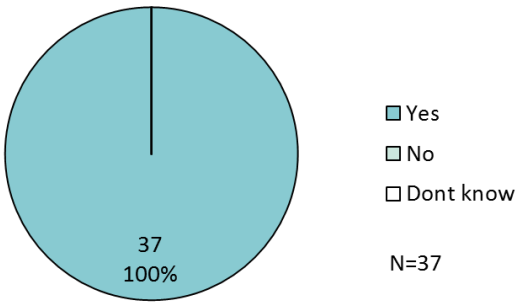
- Description of technical characteristics of the technology
- Health problem and current use of technology
- Clinical effectiveness/efficacy
- Safety

**Figure 5. The four clinical domains of the HTA Core Model included in the scope of the assessments of pharmaceuticals – always or depending on what is assessed**




The graphics in Figure 5 and 6 illustrate that the four "clinical domains" covered in the HTA Core Model® for Relative Effectiveness Assessment (REA) are indeed considered relevant in HTA done by all institutions that inform a decision maker.

**Figure 6. The four clinical domains of the HTA Core Model included in the scope of the assessments of medical technologies and other technologies – always or depending on what is assessed**




Section II, Table 7, A2, and A7 in the Country Profiles show for each country where the respondents indicated that the formal background for including the clinical domains in the scope of their assessments can be found.

### 3.2.4 Scope of assessments - non-clinical domains addressed (Country Profile Table 3 and Table A3)

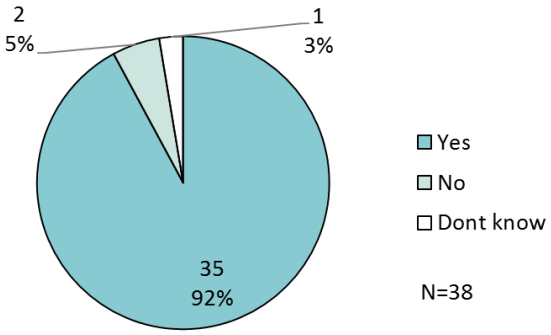
This study has shown that the 4 clinical domains are all covered by the 48 institutions in their assessments. The importance of including economic, patient, organisational, social, ethical and legal aspects in the scope of a specific HTA project and report depends on which concrete technology is being assessed. Which questions that are considered relevant and included in the scope of an assessment vary from technology to technology and decision context to context. For example, in the outset, an implantable medical device as an alternative to major thoracic surgery would call for a broader-scoped assessment than a new pharmaceutical in the same class as one or several well-

known comparator pharmaceuticals. According to shared international perceptions of what could be included in the scope of HTA the survey study systematically asked into a wider scope of assessments beyond the clinical domains following the domain structure of the HTA core Model®. This was done by listing each domain name in a separate survey question, without explicit reference to the Model. I.e., the questionnaire can be considered generic in its mapping of the scope of each institution's assessments.

#### 3.2.4.1 Pharmaceuticals

A very large majority, 35 among the 38 institutions that assess pharmaceuticals (92 %), responded explicitly that they include "non-clinical" domains of the HTA Core Model, such as economic, organisational, or patient aspects, in the scope of their assessments of pharmaceuticals – always or depending on what is assessed (Figure 7).

**Figure 7. Non-clinical domains of the HTA Core Model included in assessments of pharmaceuticals**



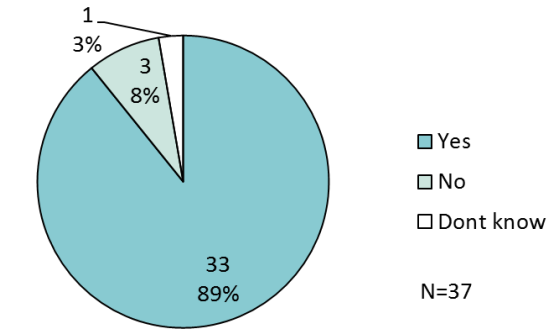

Only two institutions, Gemeinsamer Bundesausschuss (G-BA), Germany, and Ministry of Health, Slovakia indicated that they do not include "non-clinical" domains such as economic, organisational or patient aspects in their assessments of pharmaceuticals.

Section II, Table 7, A3, and A7 in the Country Profiles show for each country where the respondents indicated that the formal background for including non-clinical domains in the scope of their assessments of pharmaceuticals can be found.

#### 3.2.4.2 Medical technologies and other non-pharmaceutical technologies

In non-pharmaceutical technologies a large majority, 33 institutions (89 %), include "non-clinical" domains of the HTA Core Model such as economic, organisational and patient aspects in the scope of their assessments of medical technologies and other non-pharmaceutical technologies (Figure 8).

**Figure 8. Non-clinical domains of the HTA Core Model included in assessments of medical technology and non-pharmaceutical technologies – always or depending on the technology**




Only three institutions, Gemeinsamer Bundesausschuss (G-BA), Germany, State Health Care Accreditation Agency at the Ministry of Health (VASPVT), Lithuania and Ministry of Health, Slovakia indicated that they do not include "non-clinical" domains in their assessments of non-pharmaceutical interventions.

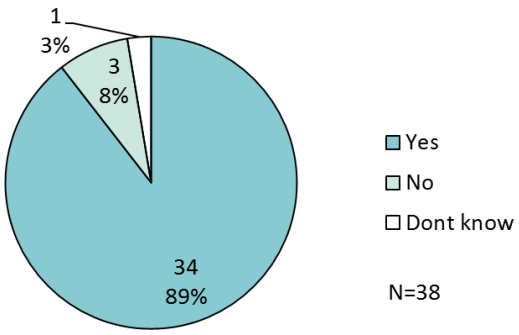
Table 7, A3, and A7 in the Country Profiles in Section II show for each country where the respondents indicated that the formal background for including non-clinical domains in the scope of their assessments of non-pharmaceutical interventions can be found.

## 3.2.5 Cost, budget impact, economic evaluation

### 3.2.5.1 Pharmaceuticals

Economic aspects are included in assessments of pharmaceuticals by 34 of 38 HTA institutions (89 %) – always or depending on the technology being assessed (Figure 9).

**Figure 9. Cost, budget impact, economic evaluation included in assessments of pharmaceuticals – always or depending on the technology**




Three institutions, Gemeinsamer Bundesausschuss (G-BA), Germany, Regione Emilia-Romagna, Italy and Ministry of Health, Slovakia indicated that they do not include cost, budget impact or economic evaluation in their assessments of pharmaceuticals.

The survey study also addressed if the origin of explicit formal requirements to address health economic aspects (and other aspects as shown below) was in legislation or formal agreement with a decision maker.

Table 10 lists the 17 institutions (45 % of all 38 institutions that assess pharmaceuticals) where the respondent indicated that a formal requirement to address cost, budget impact or include economic evaluation in their assessments of pharmaceuticals is found in legislation.

**Table 10. Institutions having a formal requirement found in legislation to address cost, budget impact or include economic evaluation in their assessments of pharmaceuticals (n=17)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| State Institute for Drug Control (SUKL) | Czech Republic |
| Haute Autorité de Santé (HAS) | France |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

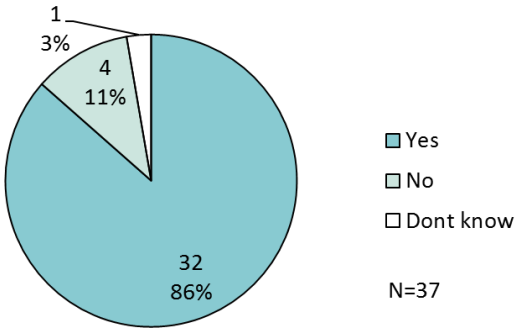
Three institutions (8 %) indicated a formal agreement with a decision maker, while not indicating legislation, as the background for addressing cost, budget impact or include economic evaluation in

their assessments of pharmaceuticals: Zorginstituut Nederland (ZIN), Netherlands, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Spain, and All Wales Therapeutics and Toxicology Centre (AWTTC), United Kingdom.

#### 3.2.5.2 Non-pharmaceutical technologies

Economic aspects are included in assessments of medical technology and other non-pharmaceutical technologies by 32 of 37 institutions (86 %) that assess non-pharmaceutical technologies – always or depending on the technology being assessed (Figure 10).

**Figure 10. Cost, budget impact, economic evaluation included in assessments of non-pharmaceutical technologies – always or depending on the technology**




Four institutions, Gemeinsamer Bundesausschuss (G-BA) and Institute for Quality and Efficiency in Health Care (IQWiG), Germany, State Health Care Accreditation Agency at the Ministry of Health (VASPVT), Lithuania and Ministry of Health, Slovakia indicated that they do not include cost, budget impact or economic evaluation in their assessments of medical technology and other non-pharmaceutical interventions.

Table 11 list the 9 institutions (24 %) that indicated that a formal requirement to address cost, budget impact or include economic evaluation in their assessments of non-pharmaceutical interventions is found in legislation.

**Table 11. Institutions having a formal requirement found in legislation to address cost, budget impact or include economic evaluation in their assessments of non-pharmaceutical technologies (n=9)**

| Institution | Country |
|---|---|
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| The National Health Service (NVD) | Latvia |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |

Three institutions (8 %) indicated a formal agreement with a decision maker, while not indicating legislation, as the background for addressing cost, budget impact or include economic evaluation in their assessments of non-pharmaceutical interventions: National Agency for Regional Health Services (AGENAS), Italy, Università Cattolica del Sacro Cuore (UCSC), Italy, and Galician Health Knowledge Agency (Avalia-t, ACIS), Spain.

### 3.2.6 Quality-adjusted life year (QALY)

The quality-adjusted life year (QALY) is a valuation of health benefit and was originally developed as a measure of health effectiveness for cost-effectiveness analysis, a method intended to aid decision-

makers charged with allocating scarce resources across competing health-care programs (Weinstein, 2009). The survey explored to which extent QALYs are applied in the assessments done by the 48 institutions.

### 3.2.6.1 Pharmaceuticals

In the case of pharmaceuticals, almost 80 % of HTA institutions reported that they use QALYs, always or depending on the technology that is assessed (Figure 11).

**Figure 11. Quality Adjusted Life Years (QALYs) applied in assessments of pharmaceuticals – always or depending on the technology**

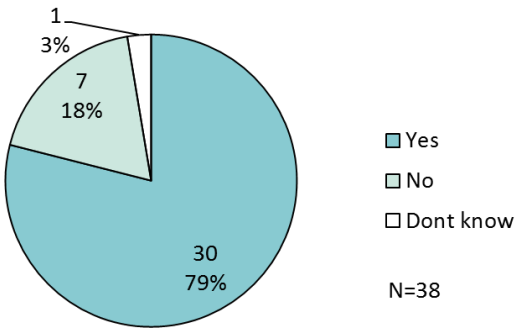


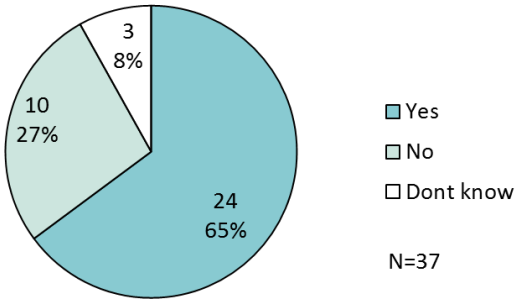

Table 12 lists the 7 institutions that responded that they do not apply QALYs in the assessment of pharmaceuticals.

**Table 12. Institutions that do not apply Quality Adjusted Life Years (QALYs) in assessments of pharmaceuticals (n=7)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Ministry of Health | Slovakia |

### 3.2.6.2 Non-pharmaceutical technologies

**Figure 12. Quality Adjusted Life Years (QALYs) applied in assessments of non-pharmaceutical technologies – always or depending on the technology**




In the case of non-pharmaceutical technologies 24 of 37 institutions (65 %) reported that they use QALYs always or depending on the technology that is assessed (Figure 12). This is not substantially less frequent than is the case with HTA of pharmaceuticals. Table 13 lists the seven

institutions that responded that they do not apply QALYs.

**Table 13. Institutions that do not apply Quality Adjusted Life Years (QALYs) in assessments of medical technology and other non-pharmaceutical technologies (n=10)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Regione Emilia-Romagna | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Institute of Hygiene | Lithuania |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Ministry of Health | Slovakia |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |

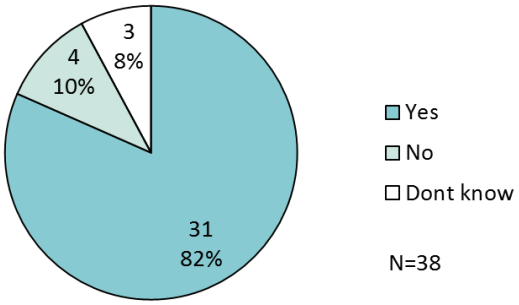
### 3.2.7 Patient aspects

The importance of including patient aspects - beyond what is reflected in the clinical aspects - as a separate area of attention in HTA has grown significantly over the recent two decades. Patient aspects cover issues such as “What are the experiences of living with the condition?”, “What expectations and wishes do patients have about the technology and what do they expect to gain from the technology?” and “How do patients perceive the technology under assessment?”.

#### 3.2.7.1 Pharmaceuticals

In pharmaceuticals, 31 of 38 institutions (82 %) reported that they address patient aspects always or depending on the pharmaceutical being assessed (Figure 13).

**Figure 13. Patient aspects beyond the clinical aspects included in assessments of pharmaceuticals – always or depending on the technology.**




The 4 institutions that do not address patient aspects are listed in Table 13.

**Table 13. Institutions that do not analyse patient aspects beyond the clinical aspects in assessments of pharmaceuticals (n=4)**

| Institution | Country |
|---|---|
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| The National Health Service (NVD) | Latvia |
| Ministry of Health | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |

Four institutions (11 %) indicated that a formal requirement to address patient aspects in their assessments of pharmaceuticals is found in legislation: National Center of Public Health and Analyses (NCPHA), Bulgaria, State Institute for Drug Control (SUKL), Czech Republic Health Information and Quality Authority (HIQA), Ireland, and Norwegian Medicines Agency (NoMA), Norway.

Two institutions (5 %) indicated that addressing patient aspects in their assessments of pharmaceuticals is based on a formal agreement with a decision maker, while not indicating legislation: Università Cattolica del Sacro Cuore (UCSC), Italy, and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Spain.

#### 3.2.7.2 Non-pharmaceutical technologies

For medical technology and other non-pharmaceutical technologies 29 of 37 institutions (78 %) reported that they address patient aspects always or depending on the technology being assessed (Figure 14).

**Figure 14. Patient aspects beyond the clinical aspects included in assessments of medical technology and other non-pharmaceutical technologies – always or depending on the technology**

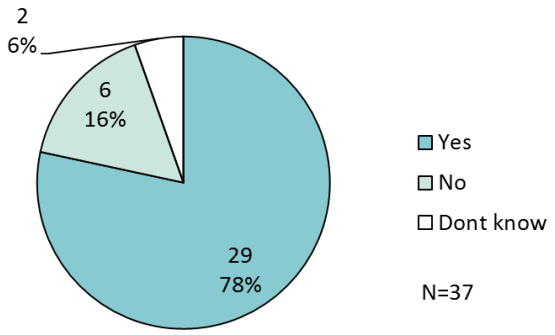



**Table 14. Institutions that do not analyse patient aspects beyond the clinical aspects in assessments of medical technology and other non-pharmaceutical technologies (n=6)**

| Institution | Country |
|---|---|
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute of Hygiene | Lithuania |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Ministry of Health | Slovakia |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

Two institutions (5 %) indicated that a formal requirement to address patient aspects in their assessments of medical technology and other non-pharmaceutical technologies is found in legislation: National Institute of Pharmacy and Nutrition (OGYÉI), Hungary and The National Health Service (NVD), Latvia.

Two institutions (5 %) indicated that addressing patient aspects in their assessments of medical technology and other non-pharmaceutical technologies is based on a formal agreement with a decision maker, while not indicating legislation: Health Information and Quality Authority (HIQA), Ireland, and National Agency for Regional Health Services (AGENAS), Italy.

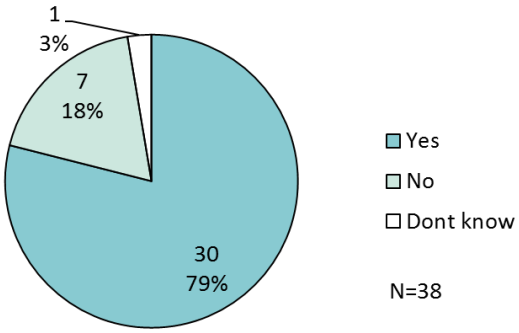
### 3.2.8 Organisational aspects

Organisational aspects cover issues such as "…… How does the technology affect the current work processes? How do de-centralisation or centralisation requirements influence the implementation of the technology? How does the technology modify the need for other technologies and use of resources?

#### 3.2.8.1 Pharmaceuticals

In pharmaceuticals, 30 of the 38 institutions (79 %) explicitly address organisational aspects always or depending on the pharmaceutical being assessed (Figure 15).

**Figure 15. Organisational aspects included in assessments of pharmaceuticals – always or depending on the technology**




The 7 institutions that do not address organisational aspects in pharmaceuticals are listed in Table 16.

**Table 16. Institutions that do not analyse organisational aspects in assessments of pharmaceuticals (n=7)**

| Institution | Country |
|---|---|
| State Institute for Drug Control (SUKL) | Czech Republic |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| The National Health Service (NVD) | Latvia |
| Ministry of Health | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |

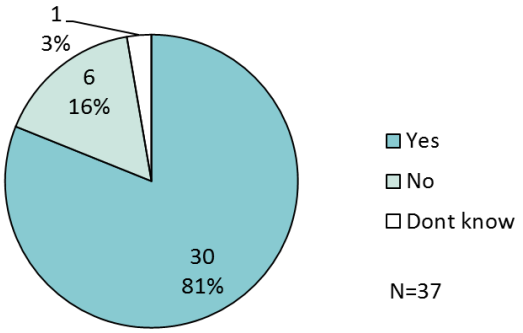
Five institutions (13 %) indicated that a formal requirement to address organisational aspects in their assessments of pharmaceuticals is found in legislation: Hauptverband der Österreichischen Sozialversicherungsträger (HVB), Austria, National Center of Public Health and Analyses (NCPHA), Bulgaria, Haute Autorité de Santé (HAS), France, Directorate for Pharmaceutical Affairs - Ministry for Health, Malta, and Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland.

Three institutions (8 %) indicated that addressing organisational aspects in their assessments of pharmaceuticals is based on a formal agreement with a decision maker, while not indicating legislation: Health Information and Quality Authority (HIQA), Ireland, Università Cattolica del Sacro Cuore (UCSC), Italy, and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Spain.

#### 3.2.8.2 Non-pharmaceutical technologies

In non-pharmaceutical technologies, 30 of the 37 institutions (81 %) explicitly address organisational aspects always or depending on the technology being assessed (Figure 16).

**Figure 16. Organisational aspects included in assessments of medical technology and non-pharmaceutical technologies – always or depending on the technology**




The 6 institutions that do not address organisational aspects of non-pharmaceutical technologies are listed in Table 17.

**Table 17. Institutions that do not analyse organisational aspects in assessments of non-pharmaceutical technologies (n=6)**

| Institution | Country |
|---|---|
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Ministry of Health | Slovakia |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

Five institutions (14 %) indicated that a formal requirement to address organisational aspects in their assessments of medical technology and other non-pharmaceutical technologies is found in legislation: Università Cattolica del Sacro Cuore (UCSC), Italy, The National Health Service (NVD), Latvia, Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland, Galician Health Knowledge Agency (Avalia-t, ACIS), Spain, and Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII), Spain.

Three institutions (8 %) indicated that addressing organisational aspects in their assessments of non-pharmaceutical interventions is based on a formal agreement with a decision maker, while not indicating legislation: Health Information and Quality Authority (HIQA), Ireland, National Agency for Regional Health Services (AGENAS), Italy, and Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA), Spain.

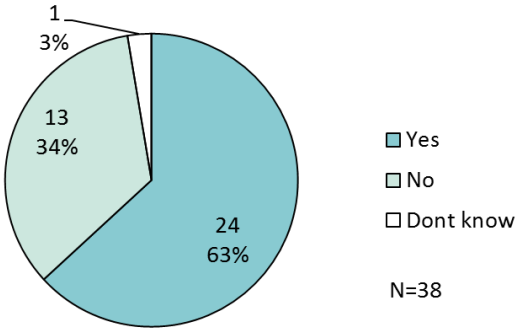
### 3.2.9 Social aspects

Social aspects cover issues such as “Are there groups of patients who currently don’t have good access to available therapies? Are there factors that could prevent a group or person from gaining access to the technology? What is the burden on care-givers?”

#### 3.2.9.1 Pharmaceuticals

In pharmaceuticals, 24 of 38 of the institutions (63 %) explicitly address social aspects always or depending on the pharmaceutical being assessed (Figure 17).

**Figure 17. Social aspects included in assessments of pharmaceuticals – always or depending on the technology**




The 13 institutions that do not address social aspects of pharmaceuticals are listed in Table 18.

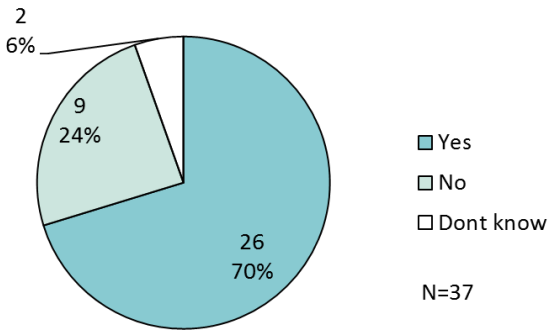
**Table 18. Institutions that do not analyse social aspects in assessments of pharmaceuticals (n=13)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Regione Emilia-Romagna | Italy |
| The National Health Service (NVD) | Latvia |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Ministry of Health | Slovakia |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |

### 3.2.9.2 Non-pharmaceutical technologies

For medical technology and other non-pharmaceutical technologies 70 % of the institutions address social aspects always or depending on the technology being assessed (Figure 18).

**Figure 18. Social aspects included in assessments of medical technology and non-pharmaceutical technologies – always or depending on the technology**



The 9 institutions that do not address social aspects of non-pharmaceutical technologies are listed in Table 19.

**Table 19. Institutions that do not analyse social aspects in assessments of non-pharmaceutical technologies (n=9)**

| Institution | Country |
|---|---|
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| Italian Medicines Agency (AIFA) | Italy |
| The National Health Service (NVD) | Latvia |
| Institute of Hygiene | Lithuania |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Ministry of Health | Slovakia |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

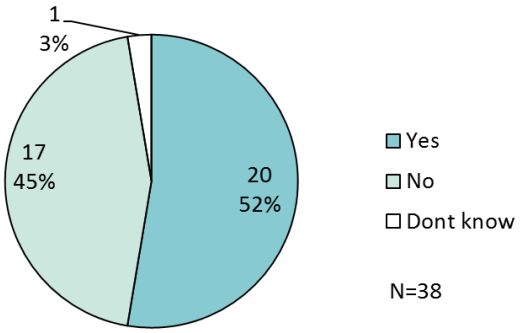
## 3.2.10Ethical aspects

Ethical aspects cover issues such as “Does the implementation or use of the technology affect the patient´s capability and possibility to exercise autonomy?”, “Does the implementation or use of the technology affect the patient’s moral, religious or cultural integrity?”, and “How does implementation or withdrawal of the technology affect the distribution of health care resources?”.

### 3.2.10.1 Pharmaceuticals

In pharmaceuticals, 20 of the 38 institutions (52 %) explicitly indicated that they address ethical aspects always or depending on the pharmaceutical being assessed (Figure 19).

**Figure 19. Ethical aspects included in assessments of pharmaceuticals – always or depending on the technology**




The 17 institutions that do not address ethical aspects of pharmaceuticals are listed in Table 20.

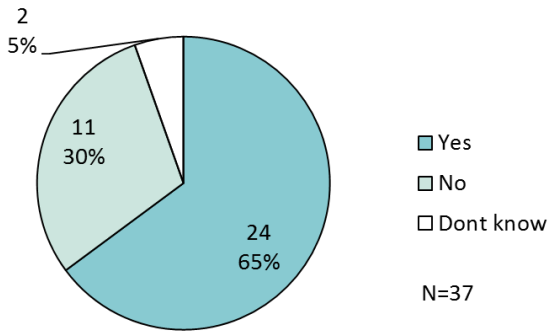
**Table 20. Institutions that do not analyse ethical aspects in assessments of pharmaceuticals (n=17)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Regione Emilia-Romagna | Italy |
| The National Health Service (NVD) | Latvia |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| Ministry of Health | Slovakia |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

### 3.2.10.2 Non-pharmaceutical technologies

In medical technology and other non-pharmaceutical technologies 24 of 37 institutions (65 %) responded that they address ethical aspects always or depending on the technology being assessed (Figure 20).

**Figure 20. Ethical aspects included in assessments of medical technology and non-pharmaceutical technologies – always or depending on the technology**




Assuming no difference in the percentage between the two groups of technologies the difference between pharmaceuticals and non-pharmaceutical technologies is not statistically significant at the 0.05 level (chi-square).

The 11 institutions that do not address social aspects of non-pharmaceutical technologies are listed in Table 21.

**Table 21. Institutions that do not analyse ethical aspects in assessments of non-pharmaceutical technologies (n=11)**

| Institution | Country |
|---|---|
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Italian Medicines Agency (AIFA) | Italy |
| The National Health Service (NVD) | Latvia |
| Institute of Hygiene | Lithuania |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| Ministry of Health | Slovakia |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

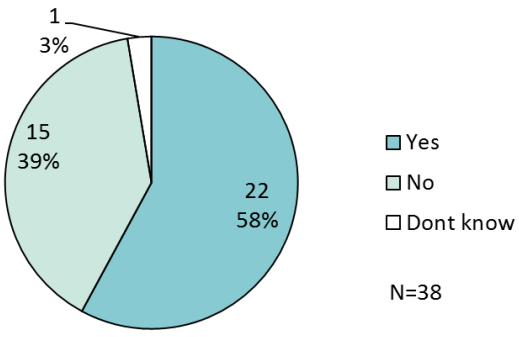
## 3.2.11Legal aspects

Legal aspects cover issues such as “What kind of regulation exists for the acquisition and use of the technology?”, “What do laws/binding rules require about appropriate measures for securing patient data and how should this be addressed when implementing the technology?”, and “What do laws/binding rules require about appropriate processes or resources which would guarantee equal access to the technology?”.

### 3.2.11.1 Pharmaceuticals

In pharmaceuticals, 22 of the 38 institutions (58 %) explicitly indicated that they address legal aspects always or depending on the pharmaceutical being assessed (Figure 21).

**Figure 21. Legal aspects included in assessments of pharmaceuticals – always or depending on the technology**




The 17 institutions that do not address legal aspects of pharmaceuticals are listed in Table 22.

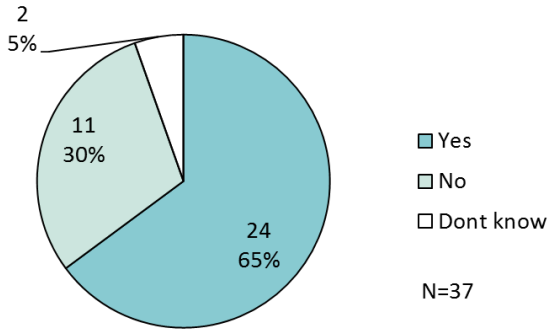
**Table 22. Institutions that do not analyse legal aspects in assessments of pharmaceuticals (n=17)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Regione Emilia-Romagna | Italy |
| The National Health Service (NVD) | Latvia |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Norwegian Medicines Agency (NoMA) | Norway |
| Ministry of Health | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

### 3.2.11.2 Non-pharmaceutical technologies

In medical technology and other non-pharmaceutical technologies 24 of the 37 institutions (65 %) address legal aspects always or depending on the technology being assessed (Figure 22).

**Figure 22. Legal aspects included in assessments of medical technology and non-pharmaceutical technologies – always or depending on the technology**




The 11 institutions that do not address legal aspects of non-pharmaceutical technologies are listed in Table 23.

**Table 23. Institutions that do not analyse legal aspects beyond the clinical aspects in assessments of non-pharmaceutical technologies (n=11)**

| Institution | Country |
|---|---|
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| Italian Medicines Agency (AIFA) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Ministry of Health | Slovakia |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

### 3.2.12 Study designs considered relevant as sources of evidence (Country Profile Table 4 and Table A4)

Balancing methodological rigor in the design of studies to be included in the clinical assessment – particularly of efficacy/effectiveness – with expectations of external validity, generalisability and applicability is an ever-present dilemma for HTA researchers and institutions. Many questions were introduced to map the institutions' choice of methodologies – choices that have consequence for the applicability of their assessments in a real world setting of decision making.

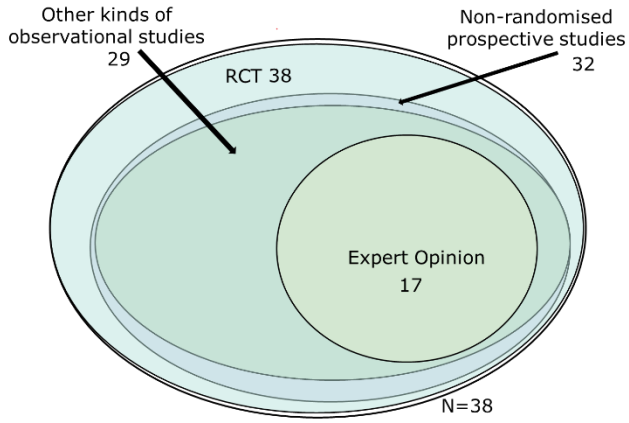
Study designs that are considered by the institutions to be relevant for providing sources of evidence in assessments were addressed in a multiple-choice question that allowed several answers, including the application of expert opinion.

A summary finding on study designs used in assessments across all technologies is that non-randomised prospective studies and other kinds of observational studies are used together with RCTs by 29 of 38 institutions (76 %) in pharmaceuticals and 29 of 36 (81 %) institutions in non-pharmaceutical technologies.

#### 3.2.12.1 Pharmaceuticals

All 38 institutions use randomised controlled trials (RCT) as sources of evidence in pharmaceuticals (Figure 23).

**Figure 23. Study designs for evidence generation included as relevant sources of evidence for the clinical assessment within HTA of pharmaceuticals**




When expert opinion (which tends to be ranked low in strength of evidence hierarchies based on study design) was indicated among the sources (17 responses) this was never as a stand-alone source, in fact in all cases it was indicated together with RCT, non-randomised prospective studies and other kinds of observational studies. The 17 institutions that apply expert opinion together with such an inclusive approach to the evidence base of assessments are listed in Table 24.

**Table 24. Institutions that include randomised controlled studies (RCT), non-randomised prospective studies, other observational studies and expert opinion in the clinical assessment within their HTA of pharmaceuticals (n=17)**

| Institution | Country |
|---|---|
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| State Institute for Drug Control (SUKL) | Czech Republic |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

The 4 institutions that include randomised controlled studies (RCT) only in the clinical assessment of pharmaceuticals are listed in Table 25.

**Table 25. Institutions that include randomised controlled studies (RCT) only in the clinical assessment within their HTA of pharmaceuticals (n=4)**

| Institution | Country |
|---|---|
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Ministry of Health | Slovakia |

#### 3.2.12.2 Formal requirements to include a certain design or designs for evidence generation in the "clinical" assessment of pharmaceuticals

Table 26 lists the 9 institutions (24 % of 38) that indicated that a formal requirement on criteria to be met by data to be included as relevant clinical evidence on pharmaceuticals can be found in legislation.

**Table 26. Institutions that indicated that a formal requirement on criteria to be met by data to be included as relevant clinical evidence on pharmaceuticals can be found in legislation (n=9)**

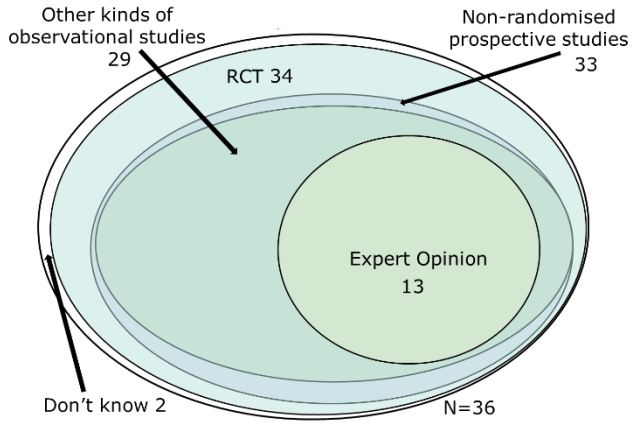
| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| State Institute for Drug Control (SUKL) | Czech Republic |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| The National Health Service (NVD) | Latvia |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |

Two institutions (5 %) indicated a formal agreement with a decision maker, while not indicating legislation, as background for requiring criteria to be met by data to be included as relevant clinical evidence: Università Cattolica del Sacro Cuore (UCSC), Italy and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Spain.

#### 3.2.12.3 Non-pharmaceutical technologies

All 34 institutions that could give an answer on sources of evidence use randomised controlled trials (RCT) (Figure 24).

**Figure 24. Study designs for evidence generation included as relevant sources of evidence for the clinical assessment of non-pharmaceutical technologies**




When Expert Opinion was indicated among the sources (13 responses) in all cases was this indicated together with RCT, non-randomised prospective studies and other kinds of observational studies. The 13 institutions that apply expert opinion together with such an inclusive approach to the evidence base of assessments of non-pharmaceutical technologies are listed in Table 27.

**Table 27. Institutions that include randomised controlled studies (RCT), non-randomised prospective studies, other observational studies and expert opinion in the clinical assessment within their HTA of medical technology and other non-pharmaceutical technologies (n=13)**

| Institution | Country |
|---|---|
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Zorginstituut Nederland (ZIN) | Netherlands |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

The 5 institutions that include randomised controlled studies (RCT) only in the clinical assessment of non-pharmaceutical technologies are listed in Table 28.

**Table 28. Institutions that include randomised controlled studies (RCT) only in the clinical assessment within their HTA of medical technology and other non-pharmaceutical technologies (n=5)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| University of Tartu | Estonia |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Ministry of Health | Slovakia |

#### 3.2.12.4 Formal requirements to include a certain design or designs for evidence generation in the "clinical" assessment of medical technology and other non-pharmaceutical technologies

The following 4 institutions (11 % of all 36) indicated that a formal requirement on criteria to be met by data to be included as relevant clinical evidence on non-pharmaceutical technologies can be found in legislation: Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ), Croatia, Institute for Quality and Efficiency in Health Care (IQWiG), Germany, The National Health Service (NVD), Latvia, and Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland.

One institution indicated a formal agreement with a decision maker, while not indicating legislation, as background for requiring criteria to be met by data to be included as relevant clinical evidence on non-pharmaceutical technologies: National Agency for Regional Health Services (AGENAS), Italy.

### 3.2.13 Overlap between the institutions' methodology requirements and methodology features of the HTA Core Model

EUnetHTA was established to create an effective and sustainable network for HTA across Europe to work together to help developing reliable, timely, transparent and transferable information to contribute to HTAs in European countries[20].

EUnetHTA developed the HTA Core Model to facilitate the production, sharing and reporting of health technology assessments as recently described in an overview article (Kristensen, 2017

The Model intentionally reflects "mainstream" HTA methodology and has continuously been developed, tested, amended, and applied in practice by a large group of HTA institutions. The Model consists of the following three components, each with a specific purpose:

1. A standardised set of HTA questions (the HTA ontology) allows you to define your research questions based on a standard structure
2. Methodological guidance that supports you in answering your research questions
3. A common reporting structure for presenting your findings in a standardised format

Depending on needs and preferences one can according to the HTA Core Model User Guide choose to use either one, two or all three of these components in a HTA project[21].

In the EUnetHTA Joint Actions the HTA Core Model for REA and several other applications of the Model were developed and tested. There are now procedure descriptions and submission templates in place for REA of pharmaceuticals, non-pharmaceutical technologies, and full HTA. These are all publicly available, see "Desk research" in the methodology section for hyperlink references.

There was a high degree of continuity in the participation of HTA institutions in Joint Action 1 and 2 from 2010 to 2016[22] (Kristensen, 2017). Among the 48 government institutions in this study that were nominated to participate in Joint Action 3 and that inform a decision maker, 28 institutions (58 %) have previously participated in both Joint Action 1 and Joint Action 2 as government designated partners and 8 institutions (17 %) have been participating as kind collaborating partners in the previous 2 Joint Actions. Altogether, 36 of the institutions (75 %) have actively participated in the scientific and technical activities on the HTA Core Model and related tools and documents and training – or at least been "exposed" to the Model - for several years due to their official designation to participate in EUnetHTA by their respective Ministry of Health.

Taking the aims and objectives of the scientific and technical activities supported by the EU Health Programme and the Member States since 2006 into account, the penetration of the tools developed by the network into the practices of HTA institutions in Europe after two Joint Actions is an important indicator of the Network's success in contributing to harmonisation and standardisation in scientific methodologies and procedures.

An important indicator of the penetration of EUnetHTA tools in the practice of HTA institutions is the degree to which the methodology requirements for the "clinical" assessment done by HTA institutions (as reflected in the first four domains of the HTA Core Model) compare to the methodology

[20] http://www.eunethta.eu/about-us

[21] https://meka.thl.fi/htacore/documents/HTACoreModel_UserGuide_Version1.1.pdf

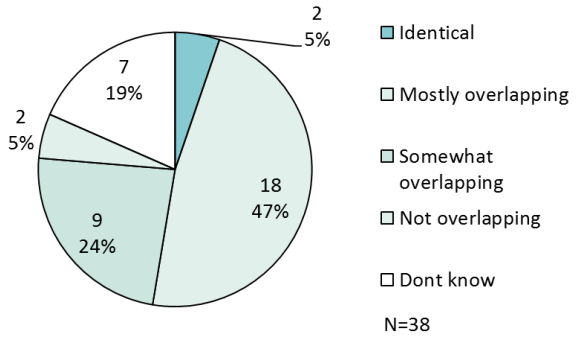
[22] http://www.eunethta.eu/outputs/eunethta-ja1-final-technical-report%20

features of the HTA Core Model for REA of pharmaceuticals and non-pharmaceutical technologies. This was addressed in the survey study (Figure 25 and 26 and Table 29 - 38).

### 3.2.13.1 Pharmaceuticals

Figure 25 shows three degrees of overlap with the HTA Core Model for REA in pharmaceuticals.

**Figure 25. Degree to which the methodology requirements for the institution's "clinical" assessment compare to the HTA Core Model for REA of pharmaceuticals**




The "clinical" assessments in 20 institutions that assess pharmaceuticals (53 %) overlap mostly or completely with the methodology features of the HTA Core Model for REA.

Table 29 - 33 list the institutions according to degree of overlap with the HTA Core Model for REA in pharmaceuticals.

**Table 29. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of pharmaceuticals (identical) (n=2)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Health Information and Quality Authority (HIQA) | Ireland |

**Table 30. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of pharmaceuticals (mostly) (n=18)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| University of Tartu | Estonia |
| Haute Autorité de Santé (HAS) | France |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |

**Table 31. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of pharmaceuticals (somewhat) (n=9)**

| Institution | Country |
|---|---|
| State Institute for Drug Control (SUKL) | Czech Republic |
| Finnish Medicines Agency (FIMEA) | Finland |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Union Health Insurance Fund | Slovakia |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

**Table 32. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of pharmaceuticals (not overlapping) (n=2)**

| Institution | Country |
|---|---|
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |

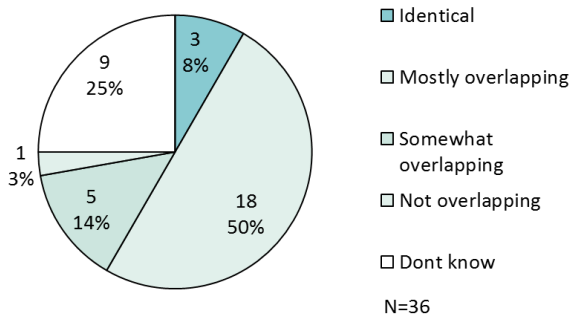
**Table 33. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of pharmaceuticals (Don't known) (n=7)**

| Institution | Country |
|---|---|
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Ministry of Health | Slovakia |
| Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |

### 3.2.13.2 Non-pharmaceutical technologies

Figure 26 shows the degree of overlap with the HTA Core Model for REA in medical devices and other non-pharmaceutical technologies as subsets of institutions that indicated some degree of overlap.

**Figure 26. Degree to which the methodology requirements For the institution's "clinical" assessment compare to the HTA Core Model for REA of non-pharmaceutical technologies**



A total of 21 institutions (58 % of those assessing non-pharmaceutical technologies) indicate that they overlap completely or mostly with the methodology features of the HTA Core Model for REA in their assessments.

Table 34 – 38 list the institutions according to degree of overlap with the HTA Core Model for REA in non-pharmaceutical technologies.

**Table 34. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of non-pharmaceutical technologies (identical) (n=3)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Health Information and Quality Authority (HIQA) | Ireland |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |

**Table 35. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of non-pharmaceutical technologies (mostly) (n=18)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Haute Autorité de Santé (HAS) | France |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

**Table 36. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of non-pharmaceutical technologies (somewhat) (n=5)**

| Institution | Country |
|---|---|
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| The National Health Service (NVD) | Latvia |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Union Health Insurance Fund | Slovakia |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

**Table 37. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of non-pharmaceutical technologies (not overlapping) (n=1)**

| Institution | Country |
|---|---|
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |

**Table 38. Degree to which the methodology requirements for the institution's clinical assessment compare to the methodology features of the HTA Core Model for REA of non-pharmaceutical technologies (Don't know) (n=9)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute of Hygiene | Lithuania |
| National Institute of Public Health | Romania |
| Ministry of Health | Slovakia |
| Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |

Very few institutions could explicitly indicate that there was no overlap with the HTA Core Model. The relative frequent "don't know" responses to this question is not a positive finding (18 % in pharmaceuticals, 25 % in other technologies) and it will be taken up in the discussion. In first instance, it reflects the individual respondent's degree of knowledge about details of the HTA Core Model and the methodology of the institution. However, it was explicitly requested that the response to the questionnaire be made by one or a group of staff designated by the institution to have the expertise and to be able to answer questions on applied HTA methodologies for the institution. Thus, it is reasonable to assume that the "don't know" response reflects the institution's insufficient knowledge of the HTA Core Model as an organisation.

### 3.2.14 Specific methodology issues in assessment and synthesis of evidence (Country Profile Table 5 and Table A5)

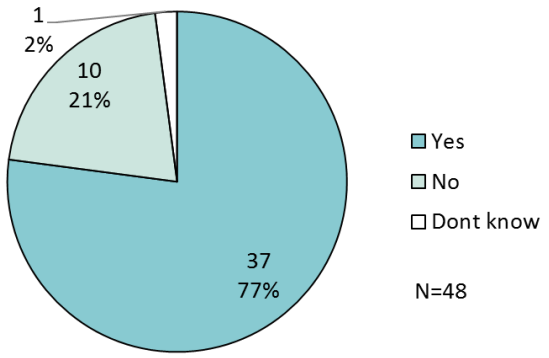
HTA is based on science and the scientific method and the research in HTA tends to be organised as projects (objective, methods, data collection and analysis, reporting) rather than as e.g. administrative work. Many questions in the survey study addressed issues related to the existence of a pre-specified plan for the scientific and technical methodologies to be applied by institutions in their assessments. The rationale behind including questions on plans for assessments is that they allow the study to map the individual institution's approach in the choice of methodology. For example, the HTA Core Model for rapid REA as well as the full Model assumes a predefined plan for methodologies to be used in the assessment, and a written project plan. This can be seen in the practical guidance for project groups working on rapid REA and full assessments [23]. The expectation that there is a pre-defined plan for an assessment also reflects and underlines HTA's basis in research.

[23] http://meka.thl.fi/htacore/ViewHandbook.aspx

### 3.2.14.1 Pre-specified plans for assessment and synthesis

As shown in Figure 27, 37 of the 48 institutions (77 %) reported that they include a pre-specified plan on methodology to be applied in their assessments, and thus are in harmony with the practical guidance developed by EUnetHTA.

**Figure 27. Institutions that include a pre-specified PLAN for methodologies to be applied in their own production of assessments and in externally produced assessments/submissions**




The following tables list the institutions according to the existence of pre-specified plans for assessment and synthesis.

**Table 39. Institutions that do not include a pre-specified PLAN for methodologies to be applied in their own production of assessments and in externally produced assessments/submissions (n=10)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| Finnish Medicines Agency (FIMEA) | Finland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Ministry of Health | Slovakia |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

**Table 40. Institutions that include a pre-specified PLAN for methodologies to be applied in their own production of assessments and in externally produced assessments/submissions (n=37)**

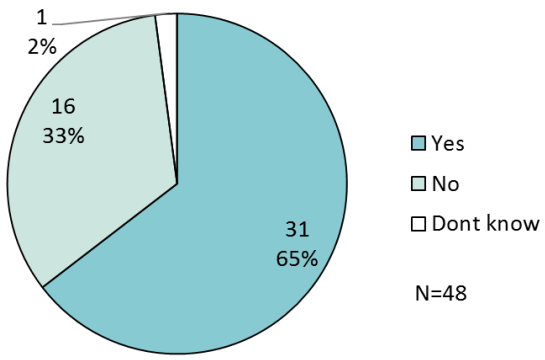
| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Institute of Hygiene | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Ministry of Health | Slovakia |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |

For one institution, the respondent indicated “Don’t know”: Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Spain.

The institutions that include a pre-specified plan for methodologies in their assessments were asked to provide more details in the survey while those answering “no” could jump the next group of questions.

### 3.2.14.2 Pre-defined methodologies for information retrieval

**Figure 28. Institutions that include a description of methodologies of Information retrieval to be applied in their assessment plans**




Pre-defining methodologies for information retrieval for assessments is considered standard practice in scientific information retrieval, and is included in EUnetHTA guidance such as guidelines, procedures and submission tables. They are particularly expected in searches of published scientific literature, primarily indexed scientific journals. Plans for information retrieval are included in 31 of the 48 institutions (65 %) (Figure 28). These 31 institutions are listed in Table 41.

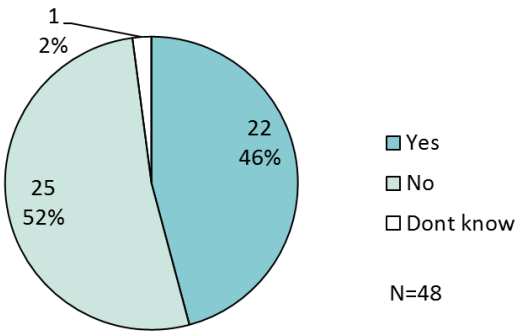
**Table 41. Institutions that include a pre-specified plan for methodologies to be applied in their assessments which also includes a plan for information retrieval (n=31)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Regione Emilia-Romagna | Italy |
| Institute of Hygiene | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

### 3.2.14.3 Plans for finding information when there are no published data

Retrieving published scientific literature, primarily from indexed scientific journals only, may leave out important scientific evidence.

**Figure 29. Institutions that include a plan for finding information when there is no published data in their pre-specified plan for methodologies to be applied in their assessments**




Among the 37 institutions that have prespecified methodology plans 22 institutions (58 %) include plans for finding information when there are no published data. Figure 29 shows that these 22 institutions represent 46 % of the total 48.

**Figure 30. Institutions that include a plan for finding information when there is no published data shown as a subset of institutions that have pre-specified plans for methodologies to be applied in their assessments**

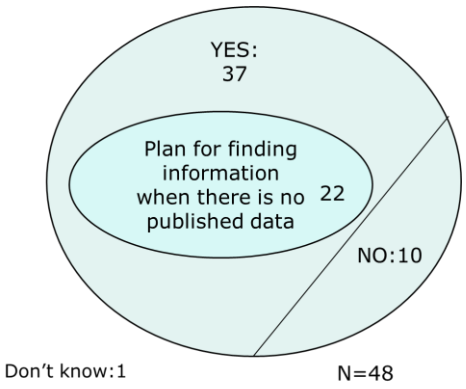



Figure 30 shows the 22 institutions as a subset of institutions that have prespecified assessment plans. They are listed in Table 42, while Table 43 lists the 15 institutions that do not include a plan for finding information when there is no published data in their information retrieval plans.

**Table 42. Institutions that include a plan for finding information when there is no published data in their pre-specified plan for methodologies to be applied (n=22)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Norwegian Medicines Agency (NoMA) | Norway |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

**Table 43. Institutions that do not include a plan for finding information when there is no published data in their pre-specified plan for methodologies to be applied (n=15)**

| Institution | Country |
|---|---|
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| DEFACTUM | Denmark |
| Haute Autorité de Santé (HAS) | France |
| Italian Medicines Agency (AIFA) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Regione Emilia-Romagna | Italy |
| Institute of Hygiene | Lithuania |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Institute of Public Health | Romania |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| Scottish Medicines Consortium (SMC) | United Kingdom |

Later in this report, Table 62 and Country Profile Table 6 in Section II provide more information on which type of evidence is retrieved with a systematic search strategy by the HTA institutions.

#### 3.2.14.4 Assessment of available evidence

Shifting topic from plans for *evidence retrieval* to plans for the *assessment of available evidence* Figure 31 shows that 27 of the 37 institutions (73 % or 56 % of all institutions) include descriptions of how assessment of the evidence will be done in their pre-specified plans for methodologies to be applied.

**Figure 31. Institutions that include a description of how the assessment of the available evidence will be done in their pre-specified plan for methodologies to be applied in their assessments**

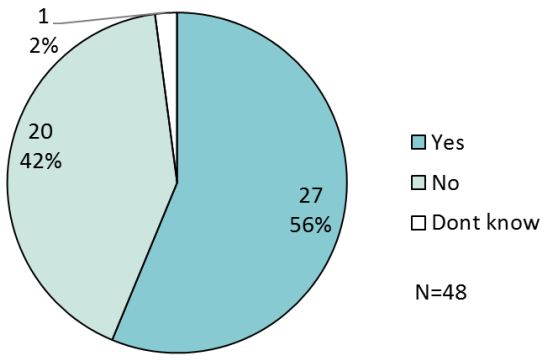



Table 44 lists the institutions that include a description of how the assessment of the available evidence will be done.

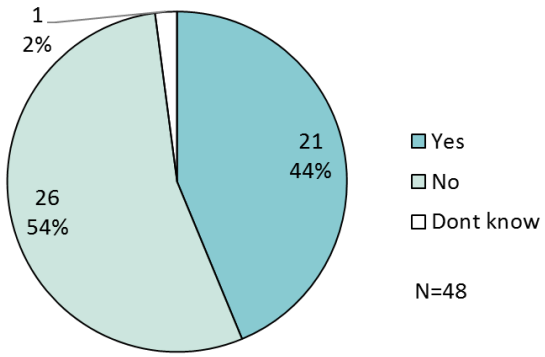
**Table 44. Institutions that include a description of how the assessment of the available evidence will be done in their pre-specified plan for methodologies to be applied (n=27)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Regione Emilia-Romagna | Italy |
| Institute of Hygiene | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Norwegian Medicines Agency (NoMA) | Norway |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

#### 3.2.14.5 Requirements to use formal tools or algorithms for evidence grading

An important part of the assessment of available evidence is the scientific examination (called “critical appraisal”) of each available literature review, meta-analysis and primary research report. A total of 21 institutions include a requirement to use formal tools or algorithms for evidence grading in their pre-specified assessment plan (Figure 32 and Table 45, which lists the institutions).

**Figure 32. Institutions that include a requirement to use formal tools or algorithms for evidence grading in their pre-specified plan for methodologies to be applied**




The 21 institutions represent 78 % of the 27 institutions that have pre-specified plans for assessment of the available evidence, 57 % of the 37 institutions that have pre-specified plans for evidence assessment methodologies to be applied and 44 % of all 48 institutions.

**Table 45. Institutions that include a requirement to use formal tools or algorithms for evidence grading in their description of how the assessment of the available evidence will be done (n=21)**

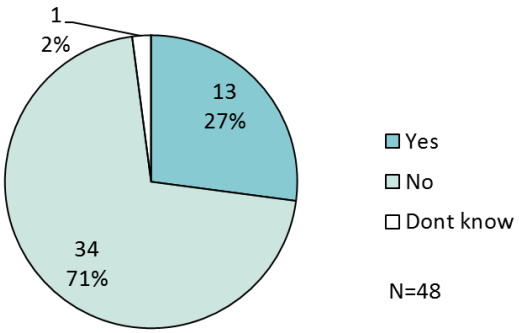
| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Regione Emilia-Romagna | Italy |
| Institute of Hygiene | Lithuania |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

### 3.2.14.6 Application of the GRADE approach to the assessment of the available evidence

GRADE was developed by the "Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group" as an effective method of linking evidence-quality evaluations to clinical recommendations[24].

[24] gradeworkinggroup.org

**Figure 33. Institutions that include a requirement to use formal tools or algorithms for evidence grading and routinely use GRADE in their description of how the assessment of the available evidence will be done**




Though not developed specifically for HTA but rather for informing clinical recommendations GRADE has been taken up by some HTA institutions in their scientific critical examination of available evidence. Among the 21 institutions that include a requirement to use formal tools or algorithms for evidence grading in their pre-specified plan 13 institutions routinely use GRADE (just over 60 % of these 21 institutions) – see Figure 33 and Table 46, which lists the institutions.

**Figure 34. Institutions that routinely use GRADE as a subset of institutions that include a requirement to use formal tools or algorithms for evidence grading in their description of how the assessment will be done**

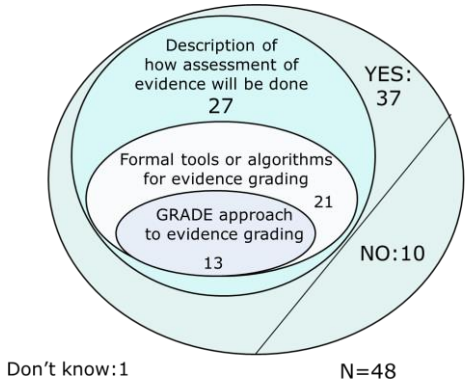



Figure 34 shows the institutions that routinely use GRADE as a formal tool for evidence grading as a subset of the 37 institutions that have prespecified assessment plans. The relative size of the ovals does not quantitatively reflect the size of the groups.

**Table 46. Institutions that include a requirement to use formal tools or algorithms for evidence grading and routinely use the GRADE approach in their description of how the assessment of the available evidence will be done (n=13)**

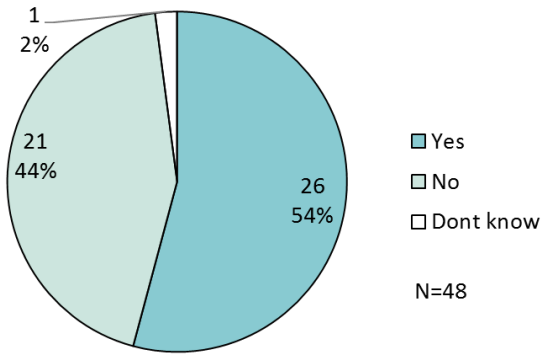
| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |

| | |
|---|---|
| DEFACTUM | Denmark |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Regione Emilia-Romagna | Italy |
| Norwegian Institute of Public Health (NIPH) | Norway |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |

### 3.2.14.7 Evidence synthesis

In mainstream general HTA methodology the critical *examination* of several or many available study reports/publications of evidence is expected to lead into a process of bringing the methodologically appraised evidence together. This next phase is called "*synthesis*" in the HTA literature, and may comprise the use of e.g. "evidence tables" and statistical modelling.

**Figure 35. Institutions that include a description of how the evidence will be synthesised in their pre-specified PLAN for methodologies to be applied in their assessments**




As shown in figure 35 and listed in Table 47 a total of 26 institutions (70 %) of the 37 institutions that have pre-specified plans for the assessment include a description of how the evidence will be synthesised (54 % of all 48).

**Table 47. Institutions that include a description of how the evidence will be synthesised in their pre-specified plan for methodologies to be applied in their own production of assessments or in externally produced assessments / submissions (n=26)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Institute of Hygiene | Lithuania |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

The 10 institutions that have plans for how assessments will be done but do not include a description of evidence synthesis are listed in Table 48.

For two institutions, the respondent indicated “Don’t know”: National Institute of Public Health, Romania and Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Spain.

**Table 48. Institutions that do not include a description of how the evidence will be synthesised in a pre-specified plan for methodologies to be applied in their production of your own assessments or in externally produced assessments / submissions (n=10)**

| Institution | Country |
|---|---|
| University of Tartu | Estonia |
| Haute Autorité de Santé (HAS) | France |
| Italian Medicines Agency (AIFA) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Scottish Medicines Consortium (SMC) | United Kingdom |

Three institutions among the 26 institutions which indicated that their production of HTA includes a plan for how evidence will be synthesised also indicated that they do not have standard forms or tables to fill out: DEFACTUM, Denmark, Norwegian Medicines Agency (NoMA) Norway, and Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland.

#### 3.2.14.8 Methodological issues in HTA where discrepancies in the application in assessments may be expected

The Methodological Guidelines that were developed by EUnetHTA address issues such as surrogate endpoints, composite endpoints, direct and indirect comparisons, network meta-analysis, health related quality of life (HQoL) and utility measures, patient-reported outcomes (PROs), and analysis of subgroups[25]. The first set of guidelines was developed in JA1 to assist REA of pharmaceuticals. In JA2 the guidelines were made universal to cover "all technologies". The issues covered by the guidelines are pertinent methodological issues in HTA where discrepancies in application in assessment practice could be expected based on experience and published studies. The survey study mapped these issues to elicit to which extents there is overlap between the HTA institutions in their proneness to apply the methodologies. The survey results are found in illustrations and tables in the following pages.

##### 3.2.14.8.1 SURROGATE ENDPOINTS

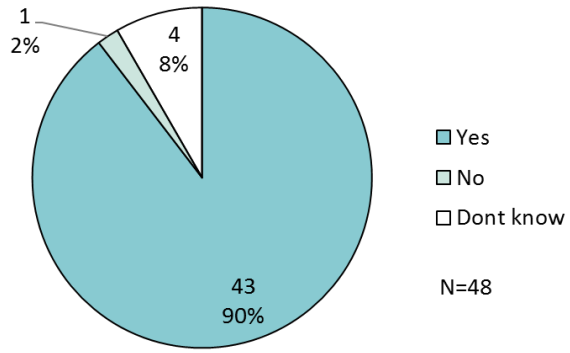
First, the use of surrogate endpoints is addressed. A surrogate endpoint is an endpoint that is intended to replace clinical endpoint of interest that cannot be observed in a trial - it is a variable that provides an indirect measurement of an effect in situations where direct measurement of clinical effect is not feasible in a reasonable timeframe[26].

Figure 36 shows that 43 Institutions (90 % of all) use surrogate endpoints when estimating effectiveness or safety in their assessments.

[25] http://www.eunethta.eu/eunethta-guidelines

[26] http://www.eunethta.eu/outputs/endpoints-used-relative-effectiveness-assessment-surrogate-endpoints-amended-ja1-guideline-f

**Figure 36. Institutions that use surrogate endpoints when estimating effectiveness or safety in their assessments**



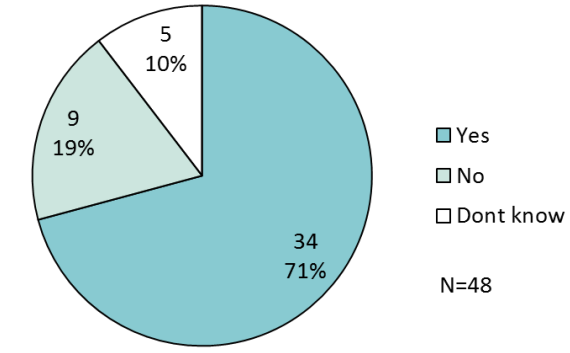

Only one institution Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA), Austria, explicitly does not use surrogate endpoints when estimating effectiveness or safety. "Don't know" was indicated by University of Tartu, Estonia, Institute of Hygiene, Lithuania, and National Institute of Public Health, Romania.

### 3.2.14.8.2 COMPOSITE ENDPOINTS

Composite endpoints combine multiple single endpoints into one endpoint showing the overall treatment effect[27] (EUnetHTA guidelines on clinical endpoints). By treating multiple event types as one endpoint the statistical sensitivity to pick up differences in outcomes in comparative studies is increased. For example, in clinical studies cardiovascular death may be defined as a composite of death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure and stroke, which are all causally associated with cardiovascular disease.

Figure 367 shows that 34 Institutions (71 % of all) use composite endpoints when estimating effectiveness or safety in their assessments.

**Figure 37. Institutions that use composite endpoints when Estimating effectiveness or safety in their assessments**




[27] http://www.eunethta.eu/outputs/endpoints-used-relative-effectiveness-assessment-composite-endpoints-amended-ja1-guideline-f

Table 49 and Table 50 list the institutions that do and do not use composite endpoints when estimating effectiveness or safety in their assessments.

**Table 49. Institutions that use composite endpoints when estimating effectiveness or safety in their assessments (n=34)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Regione Emilia-Romagna | Italy |
| The National Health Service (NVD) | Latvia |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

**Table 50. Institutions that do not use composite endpoints when estimating effectiveness or safety in their assessments (n=9)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| State Institute for Drug Control (SUKL) | Czech Republic |
| DEFACTUM | Denmark |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| National Agency for Regional Health Services (AGENAS) | Italy |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Ministry of Health | Slovakia |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |

### 3.2.14.8.3 PATIENT REPORTED OUTCOMES (PRO)

The term patient reported outcomes (PRO) covers a whole range of measurement types, encompassing simple symptom measures, more complex measures (such as activities of daily living or function) and multidimensional measures, such as health-related quality of life (HRQoL).

**Figure 38. Institutions that use Patient Reported Outcomes (PROs) when estimating effectiveness or safety in their assessments**

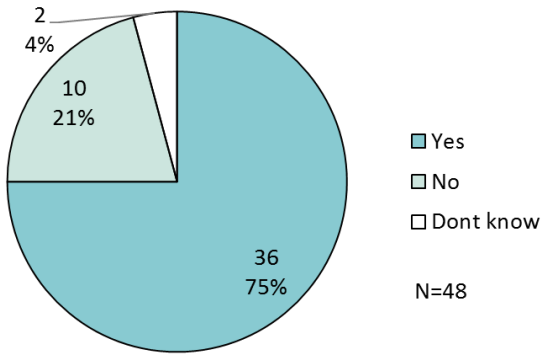



Figure 38 shows that 36 institutions (75 % of all) use Patient Reported Outcomes (PROs) when estimating effectiveness or safety in their assessments.

Table 51 and Table 52 list the institutions that use or do not use Patient Reported Outcomes (PROs) when estimating effectiveness or safety in their assessments.

**Table 51. Institutions that use Patient Reported Outcomes (PROs) when estimating effectiveness or safety in their assessments (n=36)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| State Institute for Drug Control (SUKL) | Czech Republic |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Regione Emilia-Romagna | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Norwegian Institute of Public Health (NIPH) | Norway |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

**Table 52. Institutions that do not use Patient Reported Outcomes (PROs) when estimating effectiveness or safety in their assessments (n=10)**

| Institution | Country |
|---|---|
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| Institute of Hygiene | Lithuania |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Institute of Public Health | Romania |
| Ministry of Health | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

"Don't know" was indicated by two institutions, Directorate for Pharmaceutical Affairs - Ministry for Health, Malta, and Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Spain.

#### 3.2.14.8.4 HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Health-Related Quality of Life (HRQoL) is a broad concept which can be defined as a patient's general subjective perception of the effect of illness and intervention on physical, psychological and social aspects of daily life. They may be generic (not linked to a certain disease) or specific to a disease. There is a EUnetHTA guideline on HRQoL[28]. The survey mapped the use of HRQoL measures by the HTA institutions, but did not distinguish between disease specific and generic measures.

**Figure 39. Institutions that use Health-Related Quality of Life measures (HRQoL) In their assessments**

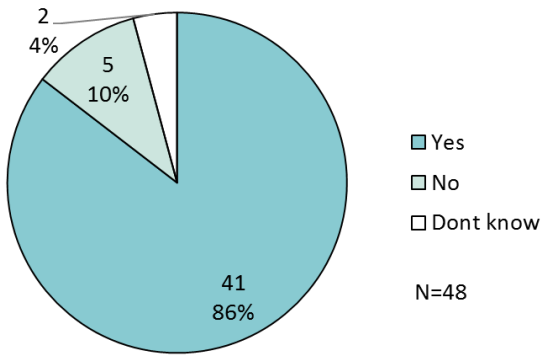



Figure 39 shows that 41 institutions (86 % of all) use HRQoL in their assessments.

Table 53 and Table 54 list institutions that use or do not use HRQoL in their assessments.

[28] http://www.eunethta.eu/outputs/endpoints-used-relative-effectiveness-assessment-health-related-quality-life-and-utility-mea

**Table 53. Institutions that use HRQoL when estimating effectiveness or safety in their assessments (n=41)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| State Institute for Drug Control (SUKL) | Czech Republic |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Regione Emilia-Romagna | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Ministry of Health | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

**Table 54. Institutions that do not use Health-Related Quality of Life measures (HRQoL) when estimating effectiveness or safety in their assessments (n=5)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| The National Health Service (NVD) | Latvia |
| Institute of Hygiene | Lithuania |
| National Institute of Public Health | Romania |

"Don't know" was indicated by two institutions Directorate for Pharmaceutical Affairs - Ministry for Health, Malta, and Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Spain.

#### 3.2.14.8.5 INDIRECT COMPARISON

In HTA the absence of any head-to-head trials (direct comparisons) of interventions is relatively frequent in situations where a decision maker needs to decide on, say, reimbursement of a new drug or procurement of a new implantable medical device. Indirect comparison of interventions is the estimation of the relative effectiveness of two or more treatments based on indirect evidence that can be derived from available direct comparisons[29].

**Figure 40. Institutions that use indirect comparison of technologies when estimating effectiveness or safety in their assessments**

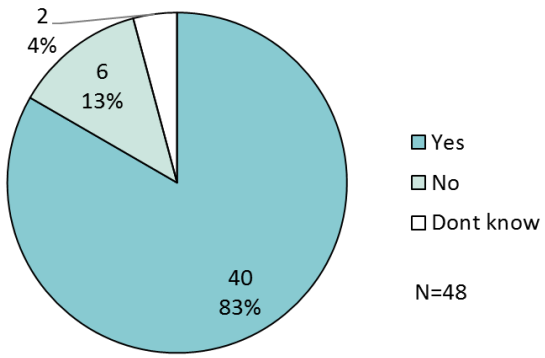



Figure 40 shows that 40 institutions (83 % of all) use indirect comparison of technologies when estimating effectiveness or safety in their assessments.

Table 55 and Table 56 list the institutions that use or do not use indirect comparison of technologies when estimating effectiveness or safety in their assessments.

[29] http://www.eunethta.eu/outputs/comparators-comparisons-direct-and-indirect-comparisons-amended-ja1-guideline-final-nov-2015

**Table 55. Institutions that use indirect comparison of technologies when estimating effectiveness or safety in their assessments (n=40)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

**Table 56. Institutions that do not use indirect comparison of technologies when estimating effectiveness or safety in their assessments (n=6)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| DEFACTUM | Denmark |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Institute of Hygiene | Lithuania |
| Ministry of Health | Slovakia |

In the case of AGENAS, Italy and University of Tartu, Estonia, while not indicating legislation, the background for the exclusion of the use of indirect comparisons is found in a formal agreement with a decision maker. In the case of LBI-HTA, Austria and Ministry of Health, Slovakia the background is in an internal guideline or procedure description.

#### 3.2.14.8.6 NETWORK META-ANALYSIS

The method of network meta-analysis allows the combination of evidence from both direct and indirect comparison and is particularly relevant for the synthesis of evidence that involves indirect comparison[30].

**Figure 41. Institutions that use network meta-analysis when estimating effectiveness or safety in their assessments**

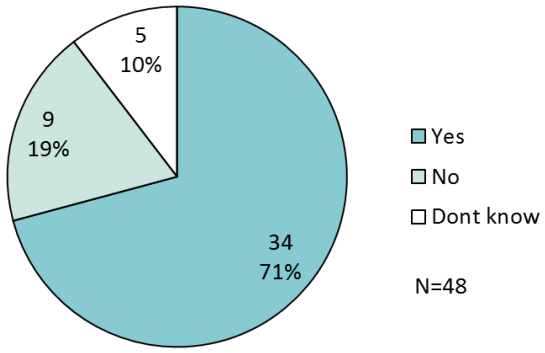



Figure 41 shows that 34 institutions (71 % of all) use network meta-analysis when estimating effectiveness or safety in their assessments. Network meta-analysis is specifically applied when indirect comparisons are included in synthesis of comparative studies.

Table 57 lists the institutions that use network meta-analysis when estimating effectiveness or safety in their assessments.

[30] http://www.eunethta.eu/outputs/comparators-comparisons-direct-and-indirect-comparisons-amended-ja1-guideline-final-nov-2015

**Table 57. Institutions that use indirect comparisons and apply network meta-analysis when estimating effectiveness or safety in their assessments (n=34)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Regione Emilia-Romagna | Italy |
| The National Health Service (NVD) | Latvia |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

Three of the 40 institutions that do indirect comparisons (Figure 40) explicitly do not apply network meta-analysis:

Gemeinsamer Bundesausschuss (G-BA), Germany, State Health Care Accreditation Agency at the Ministry of Health (VASPVT), Lithuania and Cellule d'expertise médicale in the Ministry of Health, Luxembourg.

#### 3.2.14.8.7 SUBGROUP ANALYSIS

Subgroup analysis may be essential where there are potentially large differences in patient characteristics or treatment benefit observed between groups. Subgroups should be defined *a priori* with plausible reasons for expecting different treatment effects across subgroups. Subgroup analysis can, however, pose problems by generating false-positive results and is often at risk of Type II error whereby a genuine treatment effect is not detected because the study was underpowered for that analysis[31].

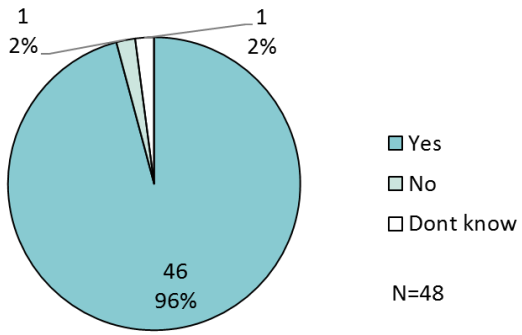



**Figure 42. Institutions that consider relevant patient or population sub-groups in their assessments**

The survey study mapped the institutions that are prone to consider subgroups in their assessments as shown in Figure 42 and we found that a total of 46 institutions (96 %) consider relevant patient or population sub-groups in their assessments. One institution, Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA), Austria, does not consider relevant patient or population sub-groups in its assessments. A background in e.g. internal guideline or agreement with decision maker for not considering sub-groups was not given by the respondent.

#### 3.2.14.8.8 TRANSFERABILITY ISSUES

When discussing HTA cooperation across borders transferability of information is high on the agenda. HTA institutions need to pay attention to the degree to which evidence and information from studies and assessments is valid in the national, regional or institutional context where they are providing their reports. EUnetHTA was established to create an effective and sustainable network for HTA across Europe and to develop *reliable, timely, transparent and transferable* information to contribute to HTAs in European countries. For these reasons, the HTA institutions' proneness to consider issues of transferability was addressed by the survey study.

[31] http://www.eunethta.eu/outputs/endpoints-used-relative-effectiveness-assessment-clinical-endpoints-amended-ja1-guideline-fi

**Figure 43. Institutions that consider issues of transferability in their assessments - e.g. to/from populations studied or to/from other clinical, organisational, economic, social contexts**

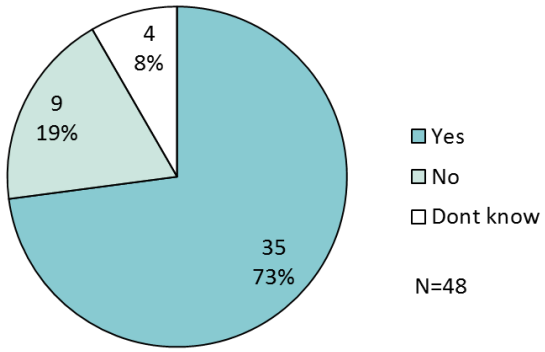



Figure 43 shows that 35 institutions (73 % of all) consider issues of transferability in their assessments - e.g. to/from populations studied or to/from other clinical, organisational, economic, social contexts.

Table 58 lists the institutions that consider issues of transferability in their assessments.

**Table 58. Institutions that consider issues of transferability in their assessments (n=35)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| State Institute for Drug Control (SUKL) | Czech Republic |
| DEFACTUM | Denmark |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Institute of Hygiene | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

Table 59 lists the institutions that do not consider issues of transferability in their assessments.

**Table 59. Institutions that do not consider issues of transferability in their assessments (n=9)**

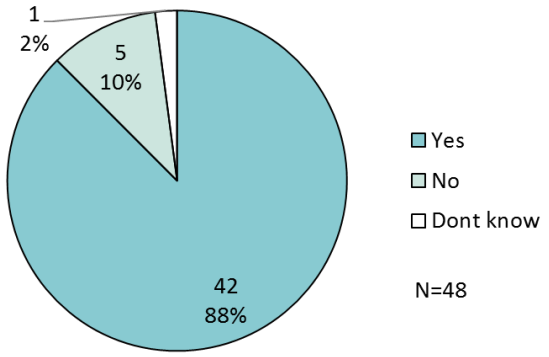
| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| University of Tartu | Estonia |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| Italian Medicines Agency (AIFA) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Ministry of Health | Slovakia |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |

The response from four institutions indicated “don’t know” on the issue of transferability: National Institute for Health and Disability Insurance (INAMI-RIZIV), Belgium, Norwegian Institute of Public Health (NIPH), Norway, National Institute of Public Health, Romania, and Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Spain.

### 3.2.14.8.9 SUMMARY OF FINDINGS INCLUDED IN REPORTS

Summaries may help the readers of a report to rapidly have an idea of the relevance of the report, they can be posted separately on websites, and they can be uploaded to databases of HTA reports. The survey study mapped if HTA institutions include a section with a summary of findings in their reports.

**Figure 44. Institutions that include a section with a summary of findings in their reports (n=42)**




A total 42 of the 48 institutions (88 %) include a summary section in their reports (Figure 44).

Table 60 lists the institutions that include a summary of findings in their reports.

**Table 60. Institutions that include a section with a summary of findings in their reports (n=42)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Institute of Hygiene | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| National Institute of Public Health | Romania |
| Ministry of Health | Slovakia |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

Table 61 lists the institutions that do not include a summary of findings in their reports.

**Table 61. Institutions that do not include a section with a summary of findings in their reports (n=5)**

| Institution | Country |
|---|---|
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |

The respondent for one institution, Zorginstituut Nederland (ZIN), Netherlands indicated "don't know".

### 3.2.15 Evidence search and handling (Country Profile Table 6 and Table A6)

A guideline on the process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness was published in EUnetHTA JA2 in July 2015 and it was updated in JA3 in December 2016. The guidance document reflects the current international state of the art in information retrieval science. Although focused on information retrieval regarding the effectiveness of a health technology, most of the recommended procedures and methods are generally applicable to information retrieval and literature searching in HTA. The survey study mapped the institutions according to the type of evidence that was retrieved with a systematic search strategy (Table 62). Evidence on efficacy/effectiveness (90 %) and safety (83 %) was most often retrieved with a systematic search strategy.

**Table 62. Institutions that apply systematic search strategies by type of evidence (percentages in parentheses)**

| Systematic evidence search strategy applied | Number of institutions | Number of countries |
|---|---|---|
| **Evidence search strategy applied** | **44 (92 %)** | **24 (86 %)** |
| Type of evidence | | |
| Technical characteristics of technology | 13 (27 %) | |
| Efficacy/effectiveness | 43 (90 %) | |
| Safety | 40 (83 %) | |
| Health Problem | 21 (44 %) | |
| Current technology use | 15 (31 %) | |
| Other types of evidence | 17 (35 %) | |
| Respondent does not know | **3 (6 %)** | **3 (11 %)** |
| No answer | **1 (2 %)** | **1 (4 %)** |

The fraction of HTA institutions that have pre-defined methodologies for information retrieval was 65 % as reported in Figure 28 – 30. The higher percentages of institutions with systematic search strategies for efficacy/effectiveness and safety evidence in Table 62 may reflect that some institutions consider this a routine activity that may not need to be put in a pre-specified description of methodologies for an assessment.

#### 3.2.15.1 Data from manufacturers

As shown in Figure 45, a total of 31 of the 48 HTA institutions (65 %) require (or accept) data from the manufacturer of pharmaceuticals or medical technologies while 17 institutions (35 %) do not.

**Figure 45. Institutions that require or accept information from the manufacturer of pharmaceuticals or medical devices**

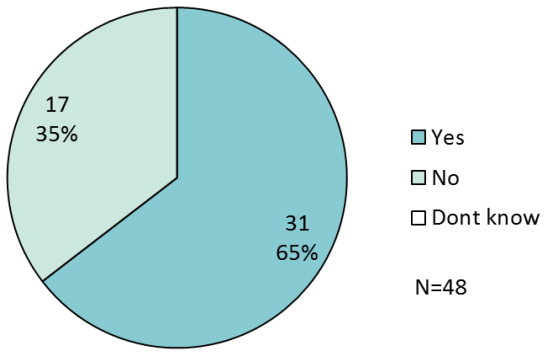
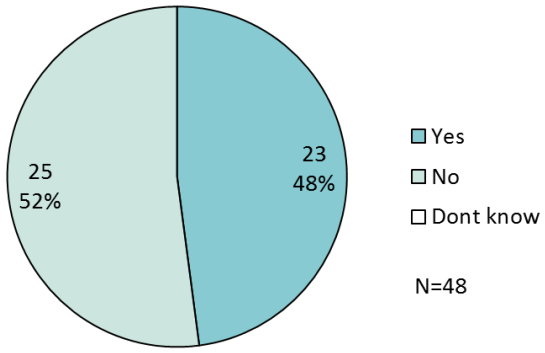



**Figure 46. Institutions that accept and use confidential data from manufacturers**




A total of 23 of the 31 institutions accept *confidential* information from the manufacturer (75 % of those who receive information and 48 % of all institutions) (Figure 46 and 47). The 23 institutions are listed in Table 63 below.

**Figure 47 Institutions that accept and use confidential data from manufacturers shown as a subset of institutions that require (or accept) data from the manufacturer of pharmaceuticals or medical technologies**

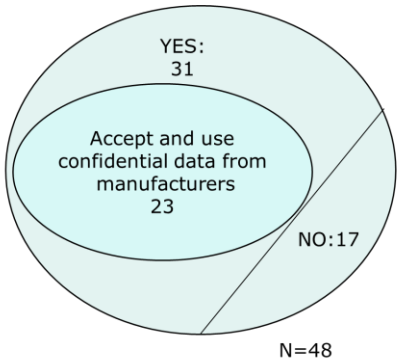


**Table 63. Institutions that require or accept information from the manufacturer of pharmaceuticals or medical devices and also accept and use confidential data from the manufacturer (n=23)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| State Institute for Drug Control (SUKL) | Czech Republic |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| National Institute of Public Health | Romania |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

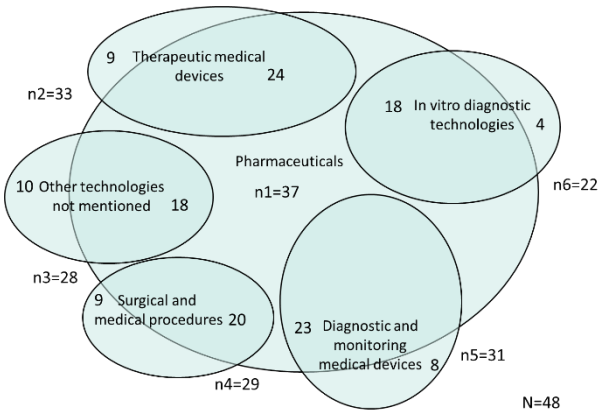
## 3.3 Formal context where HTA methodology is applied in HTA institutions in EU Member States and Norway (EEA) (Country Profile Table 7-9 and Table A7-A8)

### 3.3.1 Description of the institution in relation to decision making, technologies assessed, legal requirements and guidelines (Country Profile Table 7 and Table A7)

#### 3.3.1.1 Health technologies assessed by the HTA institutions

Figure 48 shows that 37 (n1) of the 48 (N) institutions (77%) explicitly confirmed that they assess pharmaceuticals and inform a decision maker[32]. Likewise, a total of 36 institutions (75 %) assess non-pharmaceutical technologies[33]. The figure is inspired by set or Venn diagrams to illustrate the number of institutions that assess various types of technologies and pharmaceuticals and show overlaps between the types of technologies assessed and pharmaceuticals by the institutions. The information on each institution can be found in Table 7 of each Country Profile.

**Figure 48. Health technologies assessed by the 48 institutions**




The responses show that 24 of the 48 institutions (50 %) assess both pharmaceuticals and therapeutic medical technologies. Of the 36 institutions that assess non-pharmaceutical technologies, 33 (92 % of these 36 institution and 69 % of all 48 institutions) assess therapeutic medical devices, 28 (78 % of 36 and 58 % of all) assess other technologies such as IT, e-health and m-health technologies, population level interventions and service delivery systems 29 (81 % and 60 % of all) assess surgical and medical procedures, 31 (86 % and 65 % of all) assess diagnostic and monitoring devices, and 22 (61 % and 46 % of all) assess in vitro diagnostic technologies. The figure does not attempt to depict quantitatively correct areas of the ovals that represent subgroups.

For the 37 institutions that assess pharmaceuticals Figure 48 also shows the overlaps with other kinds of technologies that are assessed by the institution. A total of 24 institutions (65 % of 37) also assess therapeutic medical devices, 20 institutions (54 %) assess surgical and medical procedures, 18 institutions (49 %) also assess "other technologies not mentioned" such as other therapeutic technologies (e.g. physiotherapy) and population level health interventions, while 23 institutions (62 %)

[32] In previous pages of the report the number of institutions that assess pharmaceuticals is reported as 38 in total. One institution, AQUAS, declared to not assess pharmaceuticals, yet, did answer questions related to assessment of pharmaceuticals. A rationale for this may be that an institution which is not tasked to assess pharmaceuticals may sometimes compare non-pharmaceutical technologies with pharmaceuticals.

[33] The Italian Medicines Agency, AIFA, lists only pharmaceuticals as technologies assessed. However, the institution also lists non-pharmaceutical technologies as potential comparators in assessments of pharmaceuticals which accounts for the variation between a total of 36 and 37 in non-pharmaceutical technologies across chapters in this report depending on the topic.

also assess diagnostic and monitoring devices and 18 institutions (49 % of 37) assess in vitro diagnostics. Assessing in vitro diagnostics in e.g. genetic markers is increasingly linked to the assessment of e.g. biological pharmaceuticals, and a large fraction, 18 of the 22 institutions (82 %) that explicitly indicated that they assess in vitro diagnostics also assess pharmaceuticals. This is the largest overlap with assessment of pharmaceuticals among the groups of technologies.

In pharmaceuticals, clinical decision makers in primary care and hospital clinics and hospital managements will often be presented with non-pharmaceutical alternatives, such as surgery, procedures and other interventions and vice versa. Choice of comparator was reported in Figure 3 and 4 and in Table 1 in the Country Profiles, and Figure 48 provides additional information on the potentials for choice of comparator in the 37 institutions that assess pharmaceuticals. In these institutions, non-pharmaceutical therapeutic interventions cannot systematically be addressed as comparators to pharmaceuticals in 13 institutions (35 %) in the case of therapeutic medical devices, 17 (46 %) in the case of medical and surgical procedures and 19 (51 %) in the case of "other non-pharmaceutical technologies".

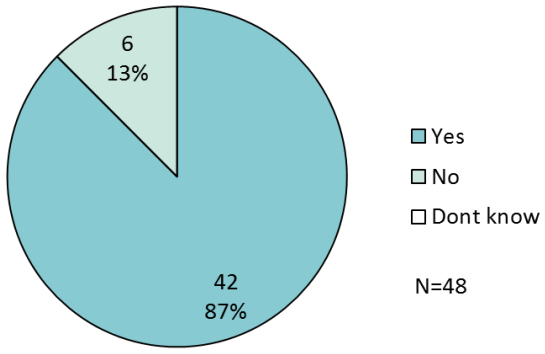
#### 3.3.1.2 Legal requirements from the scientific and technical content of HTA reports

In pharmaceuticals, 20 institutions (42 % of all 48) indicated that there are legal requirements defining how the scientific and technical content of HTA reports should be produced. In medical technologies including in vitro diagnostics, the equivalent number is 16 (33 %).

#### 3.3.1.3 Guidelines for producing HTA reports

Figure 49 shows the distribution of institutions according to the existence of guidelines for HTA production. A large majority, 87 %, indicated that they have written guidelines.

**Figure 49. Institutions that have written guidelines for the production of HTA reports**




The institutions that have and do not have guidelines for HTA production are listed in Table 64 and 65.

**Table 64. Institutions with guidelines for the production of HTA reports (n=42)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| The National Health Service (NVD) | Latvia |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| National Institute of Public Health | Romania |
| Union Health Insurance Fund | Slovakia |
| Ministry of Health | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| HTA Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | UK |
| Scottish Medicines Consortium (SMC) | UK |
| National Institute for Health and Care Excellence (NICE) | UK |
| Healthcare Improvement Scotland (SHTG) | UK |

**Table 65. Institutions that do not have guidelines for the production of HTA reports (n=6)**

| Institution | Country |
|---|---|
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| Regione Emilia-Romagna | Italy |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Institute of Hygiene | Lithuania |

### 3.3.2 Recommendations in reports and their relation to decision-making (Country Profile Table 8)

Most (36 of the HTA institutions or 75 % of all) include recommendations in their reports (Figure 50).

**Figure 50. Institutions that include recommendations on the adoption of the technology in their reports**

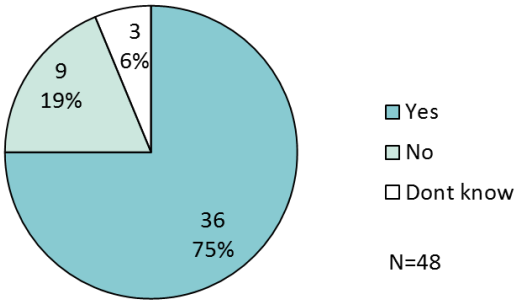



Table 66 and 67 list the institutions that do or do not include recommendations on the adoption of the technology in their HTA reports.

**Table 66. Institutions that include recommendations on the adoption of the technology in their HTA reports (n=36)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Gesundheit Österreich GmbH (GÖG) | Austria |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| DEFACTUM | Denmark |
| University of Tartu | Estonia |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| The National Health Service (NVD) | Latvia |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Medicines Agency (NoMA) | Norway |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| National Institute of Public Health | Romania |
| Union Health Insurance Fund | Slovakia |
| Ministry of Health | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| HTA Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

**Table 67. Institutions that do not include recommendations on the adoption of the technology in their HTA reports (n=9)**

| Institution | Country |
|---|---|
| Pharmaceutical Services, Ministry of Health | Cyprus |
| DEFACTUM | Denmark |
| Finnish Medicines Agency (FIMEA) | Finland |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

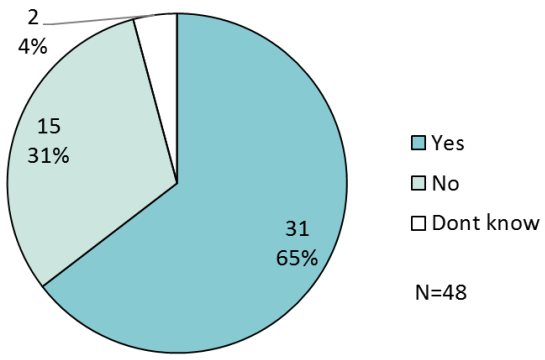
Two of the 36 institutions indicated that they include recommendations in their reports, however do not directly formally inform / support one defined decision maker that has the authority to decide on reimbursement/payment of specific pharmaceuticals and medical devices: National Agency for Regional Health Services (AGENAS), Italy, and Norwegian Institute of Public Health (NIPH), Norway.

## 3.3.3 Contribution to HTA from outside the institution (Country Profile Table 9 and Table A8)

### 3.3.3.1 Submissions dossiers from companies or others

Figure 51 shows that a total of 31 of the 48 institutions (65 %) - from 23 of the 28 countries - responded that they receive submissions dossiers from companies or others, e.g. medical specialty societies. A total of 15 institutions (31 %) do not receive submissions.

**Figure 51. Institutions that receive submissions / dossiers from companies or others**




The 31 institutions and 23 countries that receive submissions are listed in Table 68.

**Figure 52. Institutions that accept submissions / dossiers on pharmaceuticals from companies or others**

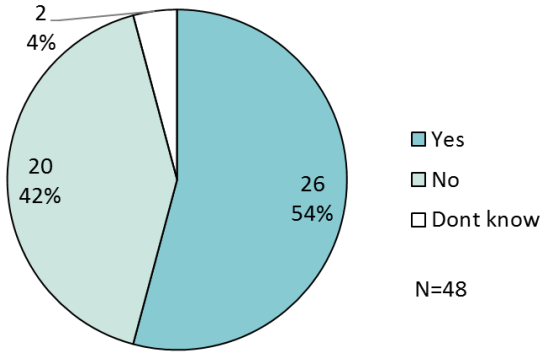



Figure 52 shows that in pharmaceuticals, 26 of all 48 institutions receive submissions / dossiers from companies or others which is 54 % of all and 70 % of the 37 institutions that assess pharmaceuticals.

**Figure 53. Institutions that accept submissions / dossiers on medical technology from companies or others**

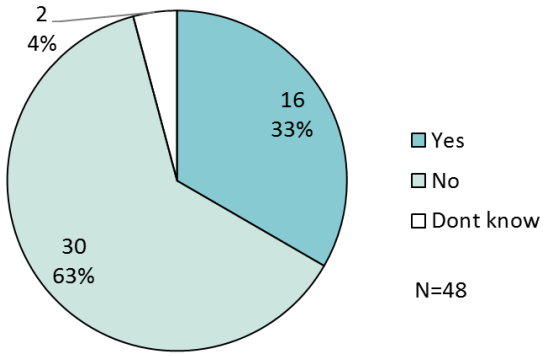



Figure 53 shows that in medical technologies, 16 of all 48 institutions receive submissions / dossiers from companies or others which is 33 % of all and 44 % of the 36 institutions that assess non-pharmaceutical technologies.

**Figure 54. Institutions that accept submissions / dossiers from companies or others distributed on types of technologies**

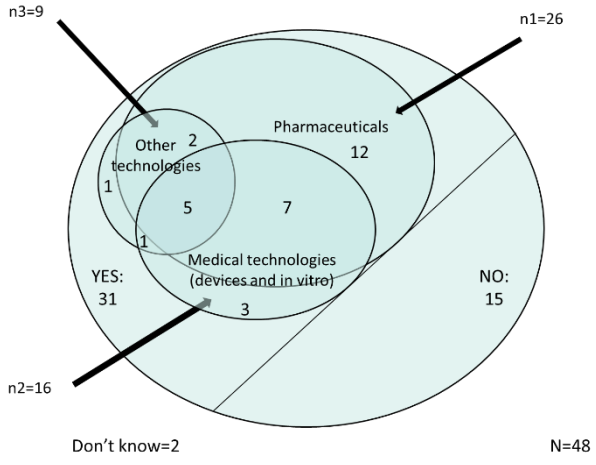



Figure 54 shows the subsets of institutions that receive submissions on various categories of technologies depicted with ovals inside the group of 31 institutions that receive submissions. The numbers in the subsets and their overlaps are put inside the various areas in the figure. For example, 7 institutions accept submissions in both pharmaceuticals and medical technologies, while 5 of these institutions receive submissions in all three categories: pharmaceuticals, medical technologies and other technologies. The figure does not attempt to depict quantitatively correct areas of the ovals that represent subsets.

**Table 68. Institutions that receive submission dossiers from companies or others (n=31)**

| Institution | Country |
|---|---|
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| State Institute for Drug Control (SUKL) | Czech Republic |
| Finnish Medicines Agency (FIMEA) | Finland |
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| Health Information and Quality Authority (HIQA) | Ireland |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Norwegian Medicines Agency (NoMA) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| National Institute of Public Health | Romania |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |

Table 69 lists the institutions that receive submission dossiers on a wide range of technologies.

**Table 69. Institution that receive submissions on both pharmaceuticals, medical technologies including in vitro diagnostics and other technologies (n=4)**

| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
|---|---|
| Haute Autorité de Santé (HAS) | France |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |

It is noteworthy that at least one institution in 23 of the 28 countries responded that they receive submission dossiers on products for assessment. The widespread use of product dossiers across Europe was taken up in EUnetHTA JA2 and lead to the development of submission templates for pharmaceuticals and for medical devices[34].

#### 3.3.3.2 Use of content of assessment reports from HTA bodies in other countries

Figure 55 shows institutions that use of content of assessment reports from HTA bodies in other countries.

**Figure 55. Institutions that use of content of assessment reports from HTA bodies in other countries**

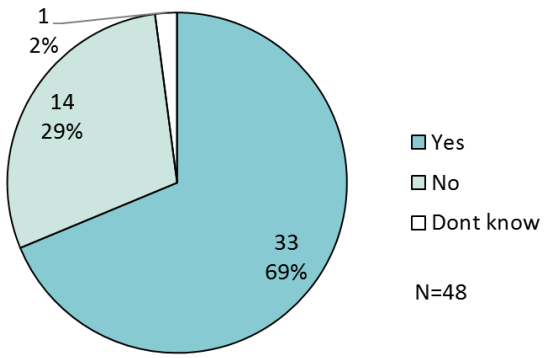



Table 70 lists the Institutions that use of content of assessment reports from HTA bodies in other countries.

[34] http://eunethta.eu/outputs/submission-template-pharmaceuticals-and-submission-template-medical-devices

**Table 70. Institutions that use content of assessment reports from HTA bodies in other countries when producing reports (n=33)**

| Institution | Country |
|---|---|
| Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA) | Austria |
| Hauptverband der Österreichischen Sozialversicherungsträger (HVB) | Austria |
| National Institute for Health and Disability Insurance (INAMI-RIZIV) | Belgium |
| Belgian Health Care Knowledge Centre (KCE) | Belgium |
| Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) | Croatia |
| University of Tartu | Estonia |
| Haute Autorité de Santé (HAS) | France |
| National Institute of Pharmacy and Nutrition (OGYÉI) | Hungary |
| National Centre for Pharmacoeconomics (NCPE) | Ireland |
| Health Information and Quality Authority (HIQA) | Ireland |
| Italian Medicines Agency (AIFA) | Italy |
| Regione Emilia-Romagna | Italy |
| Università Cattolica del Sacro Cuore (UCSC) | Italy |
| National Agency for Regional Health Services (AGENAS) | Italy |
| The National Health Service (NVD) | Latvia |
| State Health Care Accreditation Agency at the Ministry of Health (VASPVT) | Lithuania |
| Institute of Hygiene | Lithuania |
| Cellule d'expertise médicale in the Ministry of Health | Luxembourg |
| Directorate for Pharmaceutical Affairs - Ministry for Health | Malta |
| Zorginstituut Nederland (ZIN) | Netherlands |
| Norwegian Institute of Public Health (NIPH) | Norway |
| Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT) | Poland |
| National Authority of Medicines and Health Products (INFARMED) | Portugal |
| National Institute of Public Health | Romania |
| Union Health Insurance Fund | Slovakia |
| Agency for Medicinal Products and Medical Devices (JAZMP) | Slovenia |
| Servicio de Evaluación del Servicio Canario de Salud (SESCS) | Spain |
| Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) | Spain |
| Health Technology Assessment Agency - Institute of health Carlos III (AETS-ISCIII) | Spain |
| Galician Health Knowledge Agency (Avalia-t, ACIS) | Spain |
| Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | Sweden |
| All Wales Therapeutics and Toxicology Centre (AWTTC) | United Kingdom |
| Healthcare Improvement Scotland (SHTG) | United Kingdom |

Table 71 lists the Institutions that do not use content of assessment reports from HTA bodies in other countries.

**Table 71. Institutions that do not use content of assessment reports from HTA bodies in other countries when producing reports (n=10)**

| Institution | Country |
|---|---|
| Gesundheit Österreich GmbH (GÖG) | Austria |
| National Center of Public Health and Analyses (NCPHA) | Bulgaria |
| Pharmaceutical Services, Ministry of Health | Cyprus |
| State Institute for Drug Control (SUKL) | Czech Republic |
| DEFACTUM | Denmark |
| Finnish Medicines Agency (FIMEA) | Finland |
| Gemeinsamer Bundesausschuss (G-BA) | Germany |
| Institute for Quality and Efficiency in Health Care (IQWiG) | Germany |
| Ministry of Health | Slovakia |
| Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) | Spain |
| Dental and Pharmaceutical Benefits Agency (TLV) | Sweden |
| National Institute for Health and Care Excellence (NICE) | United Kingdom |
| Scottish Medicines Consortium (SMC) | United Kingdom |
| Norwegian Medicines Agency (NoMA) | Norway |

Table 72 shows the distribution of the 48 institutions and 28 countries on types of content used from assessment reports from HTA bodies in other countries.

**Table 72. The 48 institutions' use of content of assessment reports from HTA bodies in other countries by type of content used (percentages in parentheses)**

| Content of assessment reports used | Number of institutions | Number of countries |
|---|---|---|
| Some content of assessment reports from HTA bodies in other countries used | **33 (69 %)** | **22 (79 %)** |
| Type of content used | | |
| Clinical Effectiveness | 28 (58 %) | |
| Safety | 26 (54 %) | |
| Technical characteristics | 23 (48 %) | |
| Health Problem and Current Use | 21 (44 %) | |
| Cost and economic evaluation | 17 (35 %) | |
| Patient and Social aspects | 14 (29 %) | |
| Organisational aspects | 12 (25 %) | |
| Legal aspects | 9 (19 %) | |
| Other kind of information | 8 (17 %) | |
| Conclusions | 19 (40 %) | |
| Recommendations | 18 (38 %) | |
| | | |
| Do not use content of assessment reports from HTA bodies in other countries | **14 (29 %)** | **6 (21 %)** |
| Respondent does not know | **1 (2 %)** | |

Two thirds of the institutions use content of reports from other countries, and they represent 21 Member States and Norway (Table 72). The most frequently used information from HTA bodies in other countries is the clinical information typically covered by REA which about half of the institutions use. Conclusions and recommendations in reports from other institutions are used by 19 and 18 institutions of the HTA institutions respectively (just under 40 % of all 48). It is beyond the scope of this study to provide information on how conclusions and recommendations are used, except from one aspect: The use of "scorecards".

In a World Bank pharmaceutical sector analysis (2007), which is available on the official websites of World Bank[35] and the World Health Organisation's (WHO) Essential Medicines and Health Products Information Portal[36] it was recommended to consider using "scorecards" as a means of fast-tracking assessment of new medicines in the absence of the capacity to undertake a pharmaco-economic assessment: "Select five countries that are using some sort of pharmaco-economic assessment as a means to decide on reimbursement, and give two points for each of them that provides highest national reimbursement level, one point of each that provides some form of limited reimbursement, and zero points for those that do not reimburse a drug… The scorecard can then be completed with some parameters that can be assessed by consensus specifically….." (Seiter, 2007). This was further recommended in "implementing de facto HTA" in 2012 as a "useful for prioritizing consideration, in the absence of more robust and locally relevant processes, even though it may be limited as a basis for decision-making" by NICE International, a group of global care experts that moved from National Institute for Health and Clinical Excellence (NICE), UK to Imperial College London in 2016 (Lopert, 2013).

Because recommendations for consideration of more elaborated scorecard approaches building on these original recommendations are still circulating in (Central and Eastern) European countries, a specific question was introduced in the survey. None of the institutions that inform a decision maker in 28 countries confirmed that they apply weights or scores to include conclusions and/or recommendations by bodies in other countries in their assessments.

[35] http://documents.worldbank.org/curated/en/763671468294308875/Romania-Pharmaceutical-sector-analysis

[36] http://apps.who.int/medicinedocs/en/d/Js16762e/

# 4 Discussion

## 4.1 Keeping focus on informing decisions and being firmly rooted in research and the scientific method

For more than 10 years, since 2006, the emphasis in European HTA cooperation has been on developing and implementing practical solutions. The *aim* was to *inform decisions* while stressing the associated *requirements* from the HTA *process*: "Health technology assessment (HTA) is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Despite its policy goals, HTA must always be firmly rooted in research and the scientific method"[37].

This report focuses on the 48 institutions in 27 EU Member States and Norway which confirm that they inform a decision maker. The decision maker may be e.g. regional or national government, statutory health insurance, or a public procurer. The institutions originate from a total of 61 responding institutions among the 78 EUnetHTA Joint Action 3 partners that were designated by national ministries of health in 2015 and invited to the survey in December 2016.

## 4.2 Observations - similarities and differences in methodology choices between HTA institutions

The results chapter and the Country Profiles in Section II describe the methodology choices in HTA institutions in Europe. In the following, some of the results will be highlighted and discussed with a view to identifying the potential needs and limitations of the HTA cooperation and to encouraging thoughts on how cooperation at the scientific and technical level could be further facilitated while building on what has already been achieved.

Each Country Profile shows all the results in standardised tables per institution. In 18 of the 28 countries there was 1 institution only. For the 10 countries with 2 or more institutions the institutions are shown side by side in the tables.

- It is a relevant observation from the tables in the results chapter and the Country Profiles in Section II that in the 10 countries with 2 or more HTA institutions there often are important discrepancies in technologies assessed and choice of methodology between institutions in the same country

This makes meaningful quantitative reporting of statistics by country difficult to produce and difficult to use. Consequently, the number of institutions across Europe is both "nominator" and "denominator" in the quantitative reporting of distributions on methodology choices and background information.

### 4.2.1 Overlap with Relative Effectiveness Assessment and transferability

The topics and issues in Relative Effectiveness Assessment (REA) address the most central topics in HTA which are also considered to contain the least context specific information under headlines such as "description and technical characteristics" and "effectiveness". Assessment reports coming out of REA can provide the most sharable and transferable HTA information. REA is also called "clini-

[37] http://www.eunethta.eu/about-us/faq#t287n73

cal assessment" and is largely overlapping with the concept "added therapeutic value" (Van Wilder, 2015).

- *All 48 institutions in 27 Member States and Norway that inform a decision maker do indeed address the 4 REA domains* (Health problem and current use of technology, Technical characteristics, Clinical effectiveness, and Safety) that are included in the HTA Core Model for REA

The finding that all institutions address the 4 REA domains suggests that going ahead with production of REA (at both national and EU level) based on the HTA core Model is feasible. There is a sufficient number of institutions with a high degree of overlap between their clinical assessment and REA to go ahead with joint assessments to be then used at national level (generally known as "national uptake"). However, *transferability* of evidence not only hinge on the information being least depending on the context where it was collected, analysed and translated into evidence. Transferability also depends on the scientific and technical methodology that was applied in the process.

- This study shows that *3 in 4 institutions consider issues of transferability* in their assessments - e.g. to/from populations studied or to/from other clinical, organisational, economic, social contexts

The choice and the application of appropriate methodology in an assessment influence the ability to use the HTA results in other settings, different from where they were produced. So, the consideration of transferability in a large majority of institutions is a positive finding because it reflects an important step in maturity in the critical handling of information and assessment results from other settings among the European HTA institutions. In close combination with this, a high degree of *transparency* in methodology choice by an institution or a network cooperation is important for others to be able to ascertain the transferability of results to their own setting.

- More than half of the institutions explicitly indicated that their *"clinical" assessment mostly or completely overlaps with the methodology features of the HTA Core Model for REA* in all technologies (53 % in pharmaceuticals and 58 % in medical technologies and other non-pharmaceutical technologies). Only 3 institutions indicated that there was no overlapping.

This is one of the strengths to build further on for the European cooperation on HTA. There is a sufficient number of institutions with a high degree of overlap between their clinical assessment and REA to go ahead with joint assessments and national uptake. Because all institutions assess topics covered by the HTA Core Model for REA they and their decision makers and stakeholders can get direct value from joint assessments – and from sharing REAs done by a single or a group of institutions.

- About 1 in 5 institutions could not respond on the degree to which their methodology overlaps with the features of REA, and about 1 in 5 found only methodologies in the clinical assessment "somewhat" overlapping

The HTA Core Model has existed since the EUnetHTA Project and was scientifically published first time in 2009 (Lampe, 2009). As described in the results chapter there is a high degree of continuity in the participation of HTA institutions in EUnetHTA. A total of 36 of the 48 institutions in Joint Action 3 that inform a decision maker (75 %) also participated in Joint Action 1 and 2 from 2010 to 2016. The Model, not least the Model application for REA, reflects mainstream scientific scope and methodology in international HTA. Therefore, this result indicates a surprising lack of knowledge in 1 in 5 respondents. In addition, the lack of or minor overlaps between national HTA methodology and the HTA Core Model in 1 in 5 respondents could present a serious challenge to the scientific and

technical HTA cooperation in Europe. From the 2006-8 Project throughout the Joint Actions, EUnetHTA addressed capacity building to do HTA and developed training in the HTA Core Model (such as Handbook on HTA Capacity Building (2008)[38], Report of HTA training and capacity building (2011)[39] and Training material on the HTA Core Model (2016)[40]). The HTA Core Model is a key pivot in practical, result-oriented cross-border HTA cooperation and the need to implement and use the Model in HTA production should have the attention of all stakeholders.

If real, the lack of knowledge of REA and lack of sufficient overlap in methodology with The HTA Core Model for REA in a large fraction of HTA institutions could be a serious limitation in the current HTA cooperation. This should be systematically addressed by the HTA Network and Joint Action to increase the value of working together.

- In addition to showing complete overlap in the priority given to the content of REA, this study makes clear that applying the *wider scope of HTA (economic, patient, organisational, ethical, social, legal aspects*) - which is reflected in the domains of the full HTA Core Model - is indeed practiced by *a large majority* of countries/institutions when it is relevant for the technology assessed. Besides, the study shows that there is a *declining slope in frequency of inclusion of domains in pharmaceuticals and in non-pharmaceutical technologies from clinical (100 %) to economic (more than 85 %), patient (about 80 %), organisational (about 80 %) and further to social, legal and ethical aspects (52 % in pharmaceuticals and 65 % in other technologies).*

The study shows that the institutions go beyond the four domains included in REA which fits with a generally shared view on what an assessment could comprise in its scope to meet the needs of the decision makers – depending on the topic of the assessment. This fits with the HTA Core Model that was developed to serve this purpose. The full Model offers a set of questions that tend to be considered in assessments that involve these domains, and even though information may need to be analysed at the national level, there is still an argument for cross-border cooperation in identifying issues that would generally be relevant to address nationally.

The degree of *transferability* of assessment results between countries and contexts is a real issue to keep in mind for the non-clinical domains. However, assessment approaches, methodology, modelling algorithms, and in some cases data, may be shared - potentially leading to gains in efficiency and quality. This is in the interest of all those involved in HTA, including stakeholders, such as manufacturers and health professionals who provide e.g. submission documents to national or regional institutions and payer organisations across Europe.

The most frequently used information from HTA bodies in other countries is the clinical information typically covered by REA. Interestingly, conclusions and recommendations in reports from other institutions are used by about 40 % of all the 48 institutions – most likely as a kind of “validation” although the context and decision maker differ

[38] http://www.eunethta.eu/outputs/eunethta-handbook-hta-capacity-building

[39] http://www.eunethta.eu/outputs/ja1-outputreport-hta-training-and-capacity-building-line-activities

[40] http://www.eunethta.eu/outputs/training-material-hta-core-model

### 4.2.2 Scientific and technical methodology choices

In the *scientific and technical methodology choices* related to the content of REA, differences across Europe were found, however with clear identifiable "majorities" of institutions that provided identical answers regarding methodology choices on e.g. comparator, methodology of comparison, endpoints, and methods of evidence search and synthesis. In relation to the comparator, the following points highlight a few examples of choice of methodology from the results.

- In pharmaceuticals 26 of 38 HTA institutions (68 %) reported that they include the *comparator technology or technologies most likely to be replaced* by the assessed technology if proven inferior to it as *a criterion or among criteria* for choice of comparator(s) in their assessments.
- Contrary to this, 4 institutions (11 % of all 38) indicated a *comparator supported by evidence of its efficacy and safety* profile as the *only criterion* for choice of comparator.
- However, 18 (47 %) pointed to *both* the comparator *most likely to be replaced and a comparator supported by evidence* of its efficacy and safety profile.
- "Other criteria" was a multiple-choice option and in pharmaceuticals it was chosen by a quarter of the institutions (24 %) among which were leading organisations such as G-BA, IQWIG, HAS, NICE and ZIN. In the case of HAS and NICE that both indicated "Other" only as response it is not possible to get closer to mapping how these two institutions balance the two criteria.

There is a deep-rooted challenge associated with balancing these two criteria, and the analogue problem in the care for individual patients or groups of patients in clinical practice is well known. With Evidence-based Medicine (EBM), "best available evidence" was introduced in the 1990'ies as a key concept which grew out of working at the interface between clinical practice and its scientific basis[41] (Sackett, 1996). While it is useful to go back to the definition of EBM by David Sackett's group, it is important to underline that there is no single place to go and find *the* "international standards of EBM". The concept is continuously discussed in the interface between every-day real-world decision-making and the "conscientious, explicit, and judicious use of current best evidence". In an international discussion of how to move forward in HTA cooperation the concept of "best available evidence" should be a focal point. It would be appropriate to remind those who quote "expert approved international standards of EBM" as a normative argument for a certain practice in evidence requirements that the original definition of EBM is indeed about "best available evidence".

Finding the balance on best available evidence should be practiced according to the decision-makers' request to have evidence-based input that meet good methodology standards and that can be a direct help when the decision is made. After more than 10 years of finding practical solutions the European HTA cooperation is mature, and it should take upon itself to find the balance in this ever-present challenge through joint work. For example, the version of the HTA Core Model for Rapid REAs developed by Work Package 5 in Joint Action 2[42] and the Procedure Manuals for rapid REA of pharmaceuticals and for other health technologies such as medical devices, surgical interventions or

[41] "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research." "….. Evidence based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions. …."

[42] http://meka.thl.fi/htacore/model/HTACoreModel_ForRapidREAs4.2.pdf

diagnostics developed in Joint Action 2[43] [44] have paved the way for finding a balance (see 4.2.3 below).

HTA is by nature comparative, and methodologies in scientific comparison need to be clearly stated.

- A total of 40 (83 %) of the 48 institutions explicitly apply *indirect comparison* when estimating effectiveness or safety in their assessments. Among these 40 institutions that use indirect comparisons 34 institutions explicitly also apply the methodology of *network meta-analysis* in their estimations (83 % of these institutions or 71 % of all institutions). Three institutions explicitly do not apply this methodology.

Network meta-analysis is quite developed and widely applied as a methodology that brings quantitative estimation, probability and reproducibility into indirect comparison. Therefore, for many readers it may be a surprising finding that three institutions that apply indirect comparison do not use network meta-analysis.

Design in underlying primary studies that generated the evidence for assessment is part of the clarification of "best available evidence".

- All institutions use RCTs as sources of evidence for all technologies when they are available. A small minority of institutions *only* include RCTs in the clinical assessment (11 % in pharmaceuticals and 14 % in non-pharmaceutical technologies)

RCT design is the standard in regulatory requirements of clinical studies in pharmaceuticals, and often, but not always, these studies are available among the sources of evidence in HTA. For example, in orphan drugs and targeted therapies in stratified medicine for various reasons the RCT design is currently infrequently applied which is a challenge shared with regulators (Eichler, 2015). This situation is well-known in medical technologies. The evidence available for the clinical assessment in institutions that only accept RCTs as evidence will be limited or missing, particularly in medical technology and other non-pharmaceutical technologies.

There was no noteworthy difference in the frequency of use of non-randomised prospective studies and other kinds of observational studies in assessment of pharmaceuticals and assessment of medical technology and other non-pharmaceutical technologies. In both cases it was relatively high, about 80 %.Two observations from the results on outcome measures or "endpoints" are highlighted in the following.

- In the case of using *surrogate endpoints*, 43 Institutions (90 %) explicitly indicated that they use this measure when estimating effectiveness or safety in their assessments.
- Only 1 of the 48 institutions explicitly does not use surrogate endpoints

Not accepting surrogate endpoints (e.g. biochemical assay results, biomarkers, results of imaging) instead of clinical indicators (e.g. morbidity, mortality) when such are not available has consequences for an institution's ability to provide assessment results to a decision maker. For example, progression free survival in cancer studies, sustained RNA virologic assay response (SVR) in hepatitis C studies, and precancerous cervical intraepithelial neoplasia (CIN) grade 2/3 in human papilloma virus

[43] http://eunethta.eu/outputs/procedure-manual-strand-rapid-relative-effectiveness-assessment-pharmaceuticals

[44] http://eunethta.eu/outputs/procedure-manual-strand-b-rapid-assessments-other-health-technologies-such-medical-devices-s

(HPV) vaccination studies are all surrogate endpoint. It may be difficult for an institution to uphold the position not to use surrogate endpoints in a situation where a decision maker would request assessments to inform decisions on an ongoing basis for a given health system and could not wait for, say, long-term prospective follow-up or late results from trials.

- In the case of using Health-Related Quality of Life measures (HRQoL) 41 institutions (86 %) use these measures in their assessments depending on what is assessed. *Only a handful of institutions indicated that they do not use HRQoL* measures in their assessments

This kind of measure is growing in numbers within a range of clinical disciplines and reflect the increased role of the patients' voice in healthcare and health policy.

### 4.2.3 Pre-specified plans for methodology to be applied (project descriptions) and internal guidelines

Project descriptions facilitate consistency in the application of methodologies to fit with the purpose of each specific assessment and with internal guidelines, procedure descriptions and various templates for entering data. This does not need to be very work intensive – and it clearly facilitates transparency for stakeholders and later helps the user of the report to have trust in the quality of the product. Pre-specified plans for methodology to be applied are ubiquitously recommended in EUnetHTA guidance and used in assessments by EUnetHTA.

- A total of 37 of the 48 institutions (77 %) include *a pre-specified plan on methodology to be applied* in their assessments, and thus are in harmony with the practical guidance developed by EUnetHTA
- A large *majority of the institutions (87 %) indicated that they have written guidelines* for the production of HTA reports.

An obvious starting point for more alignment would be to check the 14 methodological guidelines that were developed in EUnetHTA Joint Action 1 and 2 with a focus on methodological challenges that are encountered by HTA assessors while performing a rapid REA. A note of caution is warranted when it comes to the 9 Joint Action 2 Guidelines for REA that are identical to the original guidelines for REA of pharmaceuticals issued with minor, however important, text amendments. The amendments make the guidelines universal to cover "all technologies" with no specifications or exceptions[45].

Fortunately, the HTA Core Model for Rapid REAs version 4.2 developed by Work package 5 in Joint Action 2 makes clear distinctions between therapeutic technologies and diagnostic or screening technologies and points to well-known issues of test accuracy, sensitivity and specificity, likelihood ratios etc[46]. So does the Procedure Manual for rapid REA of other health technologies such as medical devices, surgical interventions or diagnostics developed by the same Work package 5[47]. Besides, EUnetHTA developed and tested the full HTA Core Model in several applications, such as the HTA

[45] The colophon of the amended guidelines reads: "During Joint Action 2 the wording in this document has been revised by WP7 in order to extend the scope of the text and recommendations from pharmaceuticals only to the assessment of all health technologies. Content and recommendations remained unchanged." (http://eunethta.eu/sites/default/files/WP7-SG3-GL-clin_endpoints_amend2015.pdf)

[46] http://meka.thl.fi/htacore/model/HTACoreModel_ForRapidREAs4.2.pdf

[47] http://eunethta.eu/outputs/procedure-manual-strand-b-rapid-assessments-other-health-technologies-such-medical-devices-s

Core Model Application for Diagnostic Technologies (3.0) and the HTA Core Model Application for Screening Technologies (3.0)[48] – and Evidence Submission Templates (see below). All this documentation can help a coordinated process of alignment between HTA institutions in the HTA cooperation.

### 4.2.4 Receiving or requesting submission dossiers on products from manufacturers

- At least one institution in *23 of the 28 countries responded that they receive submission dossiers*

This means that manufacturers that typically bring their drugs, devices, and other technologies to market in many or all countries in Europe may be met with a request to provide information in a certain structured way in submission dossiers. These may vary slightly or substantially between institutions and country, yet may basically ask for the same information from an assessment point of view. It can be very work intensive to tailor information into documents that meet national requirements which are similar or even identical content-wise, but have to be structured in a different way from one organisation/country to another. Since 2016 there are non-country specific Evidence Submission Templates for pharmaceuticals and for medical devices developed by EUnetHTA[49].

### 4.2.5 General requirements from legislation on how HTA reports should be produced

- Some degree of *explicit general requirements on how assessments should be produced exists in 42 % of institutions for pharmaceuticals and 33 % for medical technologies* (including all types of medical devices and in vitro diagnostics) according to the survey responses.

### 4.2.6 Specific requirements from legislation or agreements with a decision maker on choice of methodology

- Generally, across this study the choice of specific assessment methodology is influenced by legislation or a formal agreement with a decision maker in a relatively small fraction of institutions (about 10 %). However, there are exceptions.
- *Choice of comparator* in assessment of pharmaceuticals is one exception where a *third of the institutions have legislation or a formal agreement* with a decision maker as a background for their choice
- Another exception is the *inclusion of cost, budget impact or economic evaluation in the assessment of pharmaceuticals where half of the institutions have legislation or a formal agreement* with a decision maker included as a background in their responses.
- Interestingly*, aspects related to the research designs to be included in the assessment of pharmaceuticals are formally governed by either legislation or a formal agreement with a decision maker in nearly a third (29 %) of the institutions.* Formal requirements in these areas are less frequent in non-pharmaceutical technologies

In general, for European cooperation to be successful in spearheading national involvement and uptake it seems important that the relation between HTA and decision making in each country is clear for all those involved and that the relation is transparent to stakeholders.

[48] http://meka.thl.fi/htacore/BrowseModel.aspx

[49] http://eunethta.eu/outputs/submission-template-pharmaceuticals-and-submission-template-medical-devices

### 4.2.7 Range of technologies undergoing assessment and the need of national coordination

- This study confirms that European HTA institutions *assess a wide range of health technologies*. A limited number of the HTA institutions focus only on e.g. pharmaceuticals or medical technologies

Often a focus on e.g. pharmaceuticals only is due to an agreed division of work between institutions in a country. For example, there is such a division of work in Italy, Scotland, Spain and Sweden. However, this study may indicate that countries should consider if their current national framework for assessment sufficiently covers the technology alternatives that decision makers are presented with in the real world of healthcare practice, and whether assessment bodies in their jurisdiction are well-coordinated and the country has sufficient capacity to cover the range of technology choices presented in healthcare.

An institution having focus on one type of technology only, may meet challenges associated with cross-technology comparisons, e.g. pharmaceuticals with medical technology and vice versa – which is often precisely the choice the decision maker may be presented with. It may be appropriate to develop national strategies for covering relevant technologies according to health policy goals and to avoid "silos" by establishing a national framework of institutions that together can cover all the relevant types of technologies if indeed the decision is not to have a single national institution to cover all technologies. For example, this network approach is practiced by the Spanish Network of Agencies for Assessing National Health System Technologies and Performance[50]. Such a model which includes agencies "specialised" in certain areas would fit well into European cooperation on HTA.

### 4.2.8 Systematic evidence retrieval

- The survey study mapped the institutions according to the type of evidence that was retrieved with a systematic search strategy, and *evidence on efficacy/effectiveness (90 %) and safety (83 %) was most often retrieved with a systematic search strategy*

There may be large efficiency gains in jointly coordinated literature searches. This is practiced in the Joint Assessments done by EUnetHTA. The core literature that would tend to emerge from the many searches done by the individual institutions would be covered and more languages could be covered due to less exclusion of potential evidence due to language barriers among the searchers and assessors. Besides searches and assessment of literature on, say, patient, organisational and ethical aspects could be done by specialised assessors within the network cooperation.

It may increase the value of the European HTA cooperation in national decision making involving information from HTA if observations like these in 4.2.1 – 4.2.8 are taken up in discussions about priorities for further steps in European HTA cooperation.

## 4.3 Previous study of methodology in clinical assessments in 29 countries

Only one published study is sufficiently close to explore possibilities of comparison with this study (Kleijnen, 2012, EUnetHTA JA Work Package 5: Relative Effectiveness Assessment (REA) of Pharmaceuticals Background review July 2011 (version 5B))[51]. The study aimed to "provide an overview of

[50] http://www.redets.msssi.gob.es/en/

[51] http://www.eunethta.eu/outputs/final-version-background-review-relative-effectiveness-assessment

the processes, the scope and the scientific methods used for relative effectiveness assessment in current national practice, as a starting point for the development of models and guidelines that have the best chance of acceptance/usage across the Member States". It addressed similarities and differences in *REA of pharmaceuticals* in 29 jurisdictions (countries) in- and outside Europe. Data were captured with an extraction form with 38 multiple-choice questions to gather data from publicly available information combined with eliciting information from representatives of institutions. The results were reported at the country level. A total of 23 countries overlap with countries in this survey study. Because this study has EUnetHTA guidelines and other guidance documents as a key determinant of what the study should address some of the questions address identical issues, such as choice of comparator, if indirect comparison, surrogate, composite, quality of life measures and utilities (QALYs) are used, and if there are guidelines. However, the scope of the two studies differs. This study addressed all technologies, not only pharmaceuticals. The scope is covering economic, patient, organisational, social, ethical, and legal aspects, thus is broader than REA, and this study reports at both institution and country level. There are also substantial differences between the studies in the design and phrasing of questions. In conclusion, it is not possible to determine if there is e.g. a time trend in degree of alignment between institutions and countries by direct comparison of the two studies.

## 4.4 Shared scientific and technical methodology in Europe

### 4.4.1 Balancing requirements to be met by methods to ensure quality with usefulness in decisions

For an assessment report to be trustworthy as a product coming out of HTA it needs to meet some *scientific* quality criteria in planning, design, methodology, available data and analysis. Trustworthiness is also associated with meeting some criteria of quality in *applicability*, i.e. being useful to inform a concrete decision that must be made by a payer, a minister of health or a hospital administration.

One of the aims of this study was to provide a mapping that can facilitate alignment in methodology where this is appropriate for those who have a stake in decision making on heath technology. Hopefully, the figures with percentage distributions of HTA institutions in Europe on methodology choice and the many tables that list institutions by their choice in the result chapter can contribute to a process of defining good practice in HTA methodology.

As discussed in 4.2 above, the survey results show that approaches to many specific research methodology issues are shared by a large majority of institutions and aligned with the HTA Core Model, EUnetHTA guidelines and procedures. This fact should lead to constructive discussion on best practices with a view to even more alignment between institutions of methodologies that will fit to cross-border cooperation. The discussion should not only be between researchers. It seems important for further alignment that a discussion of applied methodologies be stimulated by, and involve institution managements, decision makers, and stakeholders as well.

The information in the report and in the Country Profiles on underlying requirements in the form of legislation or formal agreement with a decision maker can contribute to clarification of any formal backgrounds for methodology choices in the institutions. In addition, the mapping of formal requirements from methodology can facilitate discussion of how legal texts translate into methodology guidance in institutions, and how helpful it is to set the framework for scientific and technical methodology by way of legislation.

### 4.4.2 The wide spectre of technologies in healthcare raises specific assessment methodology needs

Cooperation in HTA should pay attention to the specific needs arising from assessment of such varied technologies as pharmaceuticals, medical devices, in-vitro diagnostics, public health interventions, surgical procedures and e-health support systems. In practical terms, this means that cooperation should aim at meeting two requirements on methodology. EUnetHTA paid attention to this by developing the HTA Core Model and its applications (rapid and full) for several types of technologies.

1) There should be one shared general methodological approach spanning across different types of technologies. Today, this is represented by the HTA Core Model which was developed as a generic tool for this purpose. The generic approach should consistently be applied in concrete practical assessments by way of "translations" into specific fit for purpose documents for types of technologies, e.g. pharmaceuticals, therapeutic medical technologies, diagnostic medical technologies, and in vitro diagnostics. To the level of detail that was possible with the survey study one is left with the impression that there is little difference in how methodology is applied to pharmaceuticals and to other technologies. Thus, there indeed seems to be a general methodological approach spanning across different types of technologies today that is shared by majorities of institutions.

2) There should be several written procedures for the implementation of HTA methodology that are tailored to type of technology considering the specific characteristics of the technology. Such already exist for REA of pharmaceutical and non-pharmaceutical interventions and for several applications of the full HTA Core Model. As the group "non-pharmaceutical technologies" covers a wide range of technologies additional fit for purpose procedures should be developed, e.g. for in vitro diagnostics, imaging and information and communication technologies. Involvement of relevant stakeholders and testing for usefulness of assessments to inform concrete decisions should be considered.

### 4.4.3 Focus on developing good assessment practices by pragmatically translating standards developed within the sciences that contribute to HTA

To the largest extent possible, the scientific and technical cooperation in HTA should build on consensus standards of good research practices from contributing sciences such as clinical epidemiology and health economics. Scientific practices tend to be stable but may change with demands resulting from e.g. new challenges to health (such as epidemics), the identification of multiple strata within cancer diagnoses based on genetic markers, or scientific innovations such as improved computer technology in diagnostics and therapy.

Several international scientific communities of methodologists and academia, international collaborations, consortia and societies develop and publish consensus standards of good research practices which may undergo revisions over time as science and practice evolve. Such documents are publicly available including to HTA institutions for their consideration. Three examples are 1) Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011), 2) Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices—Part 2 (Hoaglin, 2011) and 3) Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ (Tong, 2012).

By the nature of the assessment work, after years of producing assessment reports diligent researchers in HTA institutions can become specialists in translating and applying various research methodologies from contributing sciences into assessment practice. Further cross-border harmonisation and standardisation of the scientific and technical work in assessments should focus on translation of methodologies from e.g. health economics, clinical epidemiology and biostatistics into good

technology assessment practices. This should fit with the practical work of informing decisions and should be combined with developing and updating shared assessment methodology guidance that is already used in an increasing number of joint assessments. This is in fact where the work on guidelines in EUnetHTA started in Joint Action 1.

### 4.4.4 Political priority to using the tools and output of EUnetHTA in national and European settings

There is an urgent need that the Ministries of Health and HTA Network and the European Commission facilitates that the Member States and their HTA institutions start using the tools, guidance and output that EUnetHTA has made available in the work of the HTA institution. These resources developed over a decade with the support of the EU Health Programme are publicly available, including for stakeholders and research institutions.

At least one institution in 21 of the 28 EU Member States formally uses the content of HTA reports from other countries in the assessments. These foreign reports are tailor-made for a specific jurisdiction to be useful for a specific decision maker. The development of the HTA Core Model by EUnetHTA started precisely when it was realised by HTA institutions and Ministries of Health that European HTA cooperation should start much earlier in the assessment process than with sharing final reports.

Advice provided to governments over the last decade to use ad hoc developed "pragmatic value assessment frameworks", "de facto HTA" and "scorecards", and other "here and now" solutions do not seem to have any real impact. This survey could not confirm that any of the 48 ministry designated HTA institutions use weights or scores to include conclusions and/or recommendations by bodies in other countries in their assessments.

From the 2006-8 Project throughout the Joint Actions, EUnetHTA addressed capacity building and training to do HTA and training material on the HTA Core Model. With an increased number of EUnetHTA Joint Action 3 rapid assessments (and collaborative assessments by smaller groups partners) expected from 2017 onwards there is an opportunity to kick-start national HTA on pharmaceuticals and medical technology in countries, particularly in Central and Eastern Europe, that do not have de facto HTA processes to inform procurement and reimbursement.

Capacity to do HTA grows out of participation in the Network collaboration, currently Joint Action 3, and it should be a priority for the cooperation to facilitate scientific and technical capacity building with relevant partners. This would be a contemporary and forward-looking European solution.

Synergies with regulators. EUnetHTA's cooperation with the EMA which was started in 2010 has proven very helpful and is intensified in Joint Action 3[52][53] (Berntgen, 2014). In the coming years, it will be important to pay similar attention to the clarification of cooperation – and division of work - in the field of medical technologies during the implementation of the new legislation on medical devices and in vitro medical devices.

[52] http://www.eunethta.eu/outputs/ema-eunethta-cooperation-implementation-report-2012-2015

[53] http://www.eunethta.eu/news/all-minutes-eunethtaema-meetings-are-now-available (2013)

# 5 CONCLUSIONS

The objective of this study was to map HTA methodologies implemented by the HTA bodies in the EU and the EEA countries and to contribute to a better understanding of how the current methodological frameworks in each country are similar to and differ from each other and to explore possibilities of further cross-border harmonisation and standardisation of the scientific and technical work in assessments.

## 5.1 Highlighted findings on scientific methodologies that are implemented by the European Union Member States' HTA bodies

Four findings are highlighted below:

- All 48 institutions in 27 Member States and Norway that inform a decision maker address the 4 domains addressed in HTA Core Model for REA and more than half of the institutions explicitly indicate that in all technologies their ”clinical” assessment mostly or completely overlaps with the methodology features of the Model. Besides, applying the wider scope of HTA (economic, patient, organisational, ethical, social, legal aspects) - which is reflected in the domains of the full HTA Core Model - is practiced by a large majority of countries/institutions when it is relevant for the technology assessed. There are differences across Europe in the scientific and technical methodology choices related to the content of Relative Effectiveness Assessment (REA) but there are clear identifiable “majorities” of institutions regarding methodology choices on e.g. comparator, methodology of comparison, endpoints, and methods of evidence search and synthesis.

There is a sufficient number of institutions and countries with a high degree of overlap between their clinical assessment and REA to stride ahead with joint assessments and national uptake to get direct value from the production of REA based on the HTA core Model. For the non-clinical domains, assessment approaches, methodology, modelling algorithms, and in some cases data, may be shared with critical caution - potentially leading to gains in efficiency and quality.

- A large majority of institutions include a pre-specified plan on methodology to be applied in their assessments and a large majority of the institutions have written guidelines for the production of HTA reports

The HTA Core Model for Rapid REAs and the Procedure Manuals for rapid REA of pharmaceuticals and for other health technologies such as medical devices, surgical interventions or diagnostics is publicly available to be used. Besides, EUnetHTA developed and tested the full HTA Core Model in several applications, such as the HTA Core Model Application for Diagnostic Technologies and the HTA Core Model Application for Screening Technologies. All this documentation can help a coordinated process of alignment between HTA institutions in the HTA cooperation.

- Some degree of general legal requirements, defining how the scientific and technical content of HTA reports should be produced, exist in nearly half of the institutions for pharmaceuticals and a third for medical technologies. The choice of specific assessment methodologies is influenced by legislation or a formal agreement with a decision maker in small fraction of institutions (about 10 %). However, a third of the institutions have legislation or a formal agreement with a decision maker as a background for their choice of comparator in assessment of pharmaceuticals. The inclusion of cost, budget impact or economic evaluation in the assessment of pharmaceuticals has a background in legislation or a formal agreement with a decision maker in half of the institutions. Which research designs to include in the as-

sessment of pharmaceuticals is formally governed by either legislation or a formal agreement with a decision maker in nearly a third of the institutions. Formal requirements in these areas are less frequent in non-pharmaceutical technologies

If barriers to cooperation lie in real or perceived restraints in choice of methodology arising from legislation or formal agreement, it is important for progress in the HTA collaboration that the relation between HTA and decision making in each country is clear for all those involved and that the relation is transparent to external stakeholders.

A potential serious limitation to the HTA collaboration was identified.

- About 1 in 5 institutions could not respond on the degree to which their methodology overlaps with the features of the HTA Core Model for REA, and another 1 in 5 only find methodologies in the clinical assessment "somewhat" overlapping

The need to implement and use the HTA Core Model in practical, result-oriented HTA production should have the attention of all stakeholders. The lack of knowledge of REA and lack of sufficient overlap in methodology with The HTA Core Model for REA in a large fraction of HTA institutions is a serious limitation in the current HTA cooperation. This should be systematically addressed by the HTA Network and Joint Action to increase the value of working together.

## 5.2 The HTA Core Model should continue as the basic assessment framework behind tailored applications for assessments across the spectre of technologies

When it is relevant, a large majority of institutions and countries apply a wider scope than what is covered with the clinical domains of the HTA Core Model for REA. Often, assessment of these other domains, including economic assessment, will to a varying degree need to build on national data when reported to a national context and decision makers. However, cooperation on which questions would be relevant to address on e.g. patient and organisational aspects, which methodology to apply, including economic models, and which procedures to follow in the assessment work can still contribute to efficiency and quality at the national level. Therefore, to cover the scope of assessment of a range of different technologies the full HTA Core Model should be continued as the basic framework from which tailored fit for purpose applications can be drawn.

To the level of detail that it was possible to reach with the survey study there is little difference in how methodology is applied to pharmaceuticals and to other technologies. Thus, there seems in practice to be a general methodological approach spanning across different types of technologies today which is shared by the majority of institutions.

Several written procedures for the implementation of HTA methodology that are tailored to type of technology and address the specific characteristics of the technology already exist for REA of pharmaceutical and non-pharmaceutical interventions and for several applications of the full HTA Core Model. As the group "non-pharmaceutical technologies" covers a wide range of technologies additional fit for purpose procedure documents should be developed, e.g. for in vitro diagnostics, imaging and information and communication technologies. Involvement of relevant stakeholders and testing for usefulness of assessments to inform concrete decisions should be applied.

## 5.3 Further alignment can grow out of joint assessment work that is linked better with national HTA

Further alignment of methodologies can grow out of joint practical assessment work within a committed scientific and technical cooperation. This must go hand in hand with national processes facilitated by the country partners in Joint Action 3 which was given a remarkable priority in the EU Health Programme. With a sizable four-year grant Joint Action 3 should create the results that will bring about methodology alignment.

The type of decisions that HTA informs and the interface where the results are handed over to policy and decision making varies from country to country and may even vary from context to context within a country, e.g. between HTA institutions that inform health insurance and institutions that inform government, or between regional and state institutions. For European cooperation to be successful in national involvement and uptake it seems important that the nature and properties of the relation between HTA and decision making in each country is clear for all parties involved and that it is transparent to stakeholders.

## 5.4 Internal institution guidelines to be aligned with EUnetHTA guidance

If there is a wish to align the scientific and technical practices with other HTA institutions to increase the quality, quantity and efficiency in the production of assessments, the first step could be to encourage the institution to review, revise or to develop their internal guidelines or procedure descriptions. Such encouragement could originate from various sides: managements, staffs, management and/or advisory boards, clients/decision makers, stakeholders, academia and scientific societies - and the HTA Network/EUnetHTA. All these groups have a legitimate stake in the use of the assessment results and many of them in the assessment process as well.

Guidance to assist HTA “doers” from EUnetHTA includes the procedure manuals for applying the HTA Core Model for Rapid REAs of pharmaceuticals and for medical technology and other technologies, the full HTA Core Model in several applications, such as diagnostic and screening Technologies, the Submission Templates – and 15 guidelines. These documents can help a coordinated process of alignment between the HTA institutions in the HTA cooperation and bring other institution closer.

Having good guidance for assessments of best available evidence on health technologies to inform decision making should be at the core of EU cooperation on HTA - also beyond 2020. The distance is not far to having good scientific and technical solutions in using best available evidence for valid and reliable comparative assessments of technology options. Aiming at having shared guidance that is used at both national and EU level is getting closer than ever to becoming a reality.

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