AdvanceHTA

Rethinking the future of Health Technology Assessment

Health Technology Assessment Toolbox for Emerging Settings

Best Practices and Recommendations

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ADVANCE_HTA Toolbox Coordinators

Overview

A fundamental challenge for all health systems is to manage allocation of finite resources to unlimited demand for health services. In some countries of Central, Eastern and South Eastern Europe (CESEE) and the Region of the Americas, a greater proportion of gross domestic product devoted to health, also accompanies economic growth. This has led to a significant increase in health spending, often because of costly technologies, while most of the population remains without access to basic and highly cost-effective care.

Decision making in health is a complex process that involves diverse elements such as assessment of needs, effectiveness evaluation, economic and budgetary impact assessment, estimating operational capacity of a system, ethical and social implications of incorporating health technology, among others.

This toolbox is focused on the use of health technology assessment (HTA) in emerging settings. Its primary audience is decision- and policy- makers, and professionals directly or indirectly, involved in the allocation or prioritization of health resources and technologies, with a particular interest in learning the advantages and potential use of HTA as a process, its main instruments and results.

Purpose

The aim of this practical HTA Toolbox is to outline best practices and include recommendations for emerging countries. Countries more experienced in this area will be the source of examples.

This toolbox intends to support countries wishing to implement HTA as a tool for decision-making processes. The Toolbox addresses methodological issues, but its main value is the provision of examples and good practices developed by CESEE and the Region of the Americas countries. Practices obtained from the literature or information provided by countries through previously developed alternative methods will also be presented.

Specifically, the toolbox aims to:

- Improve understanding of the complete HTA process, from topic selection to the final HTA product, considering other key elements such as social values and participation of different social actors.
- Increase the skills of decision makers contributing to the HTA process.
- Provide guidance, resources and tools at each stage of the HTA process.
- Provide recommendations based on successful experiences using HTA
- This Toolbox has five chapters. Each chapter discusses the conceptual background to its topic, evidence in which real life applications of HTA are presented, tools to facilitate the HTA application and, finally, main recommendations.

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List of Abbreviations

AAZ	Agency for Quality and Accreditation in Health Care and Social Welfare (Croatia)
AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali (Italy)
AHTAPol	Agency for Health Technology Assessment (Poland)
AIFA	Italian Medicines Agency
ALIMS	Medicines and Medical Devices Agency (Serbia)
ANMAT	Administración nacional de medicamentos, Alimentos y Tecnología Médica (Argentina)
ANO NC HTA	National Center for Health Technology Assessment (Russian Federation)
ANS	National Regulatory Agency for Private Health Insurance Plans (Brazil)
ANVISA	Agência Nacional de Vigilância Sanitária (Brazil)
AOTMiT	Agency for Health Technology Assessment (Poland)
ARCSA	Agencia Nacional de Regulación, Control y Vigilancia Sanitaria (Ecuador)
ASSR	Regione Emilia Romagna, Regional Agency for Health and Social Care (Italy)
AUGE	Acceso Universal con Garantías Explícitas (Chile)
BIA	Budget impact analysis
BIQG	Bundesinstitut für Qualität im Gesundheitswesen (Austria)
CADTH	Canadian Agency for Drug and Technologies in Health
Catsalut	Catalonian health institute (Spain)
CC	Consultative Council
CCSS	Caja Costarricense de Seguro Social (Costa Rica)
CECMED	Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (Cuba)
CENABAST	Central de Abastecimiento del Sistema Nacional de Servicios de Salud (Chile)
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud (Mexico)
CESEE	Central, Eastern and South Eastern Europe
CHE	Centre of Health Economics within the National Health System (Latvia)
CIHI	Croatian Institute for Health Insurance (Croatia)
CMED	Câmara de Regulação do Mercado de Medicamentos (Brazil)
CNSS	Consejo Nacional de Seguridad Social (Dominican Republic)
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios (Mexico)
CONETS	Comisión Nacional de Evaluación de Tecnología en Salud (Venezuela)
CONITEC	Comissão Nacional de Incorporação de Tecnologias (Brazil)
DHMA	Danish Centre for Health Technology Assessment
DIGEMID	Dirección General de Medicamentos, Insumos y Drogas (Peru)
DNM	Dirección Nacional de Medicamentos (El Salvador)
EASP	Escuela Andaluza de Salud Pública, Andalusian School of Public Health (Spain)
ECRI	Emergency Care Research Institute (Panama)
EE	Economic Evaluation
EHIF	Estonian Health Insurance Fund (Estonia)
EOF	National Drug Organization (Greece)
EOPYY	National Organisation for the Provision of Healthcare Service (Greece)
ETESA	Evaluación de Tecnologías Sanitarias (Chile)
FNR	Fondo Nacional de Recursos (Uruguay)
FONASA	Fondo Nacional de Salud (Chile)
GYEMZI	National Institute for Quality and Organizational Development in Healthcare and Medicines (Hungary)
HAS	Haute Autorité de Santé (France)
HII	Health Insurance Institute (Albania)
HIIS	Health Insurance Institute (Slovenia)

HIQA	Health Information and Quality Authority (Ireland)
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
IECS	Instituto de Efectividad Clínica y Sanitaria (Argentina)
IER	Institute of Economic Research (Slovenia)
IETS	Instituto de Evaluación Tecnológica en Salud (Colombia)
INAHTA	International Network of Agencies for Health Technology Assessment
INESSS	Institut National d'excellence en santé et en services socieux (Canada)
INFARMED	National Authority of Medicines and Health Products (Portugal)
INVIMA	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (Colombia)
IQWiG	German national institute for quality and efficiency in health care
ISP	Instituto de Salud Pública (MoH) (Chile)
JAZMP	Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (Slovenia)
KCE	Belgian Health Care Knowledge Centre
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment (Austria)
LSE	London School of Economics
LYG	Life years gained
MAH	Market Authorisation Holder
MCDA	Multiple Criteria Decision Analysis
MEEC	Medical and Economic Evaluation Committee (Turkey)
MEF	Ministerio de Economía y Finanzas (Peru) (Uruguay)
MINSA	Ministerio de Salud (Nicaragua)
MINSAL	Ministerio de Salud (Chile)
MOEH	Ministry of Health and Environment
MoH	Ministry of Health
MSP	Ministerio de Salud Pública (Peru) (Uruguay)
MSPS	Ministerio de Salud y Protección Social (Colombia)
MSSS	Ministére de la Santé et des Services Socieux (MoH) (Canada)
MZ	Ministerstwo Zdrowia (Ministry of health) (Poland)
NCPR	National Council on prices and reimbursement of medicinal products (Bulgaria)
NCQSA	National Centre of Quality, Safety and Accreditation of Health Institutions (Albania)
NHIF	National Health Insurance Fund (Russian Federation) (Lithuania)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence (England and Wales)
NOKC	Norwegian Knowledge Center for the Health Services
NPRC	National Council on Prices and Reimbursement of Medicinal Products (Bulgaria)
OEP	National Health Insurance Fund (Hungary)
OGYI	Gyógyszernek nem minősülő gyógyhatású termékek (National Institute of Pharmacy and Nutrition) (Hungary)
PAHO	Panamerican Health Organization
QALY	Quality-adjusted life year or quality-adjusted life-year
RC	Reimbursement Commission
RF	Revolving Fund
RSPC MT	Republican Scientific and Practical Centre for Medical Technologies, Information, Administration and Management of Health (Belarus)
RZZO	National Health Insurance Fund (SBU Swedish Council on Health Technology Assessment (Serbia)
SCTIE	Secretaria de Ciência, Tecnologia e Insumos Estratégicos (Brazil)
SF	Strategic Fund
SLOVAHTA	Working Group for Pharmacoeconomics Clinical Outcomes and HTA of the MoH (Slovakia)
SMC	Scottish Medicines Consortium
SSI	Social Security Institution
SUKL	State Institute for Drug Control (Czech Republic)
TAHD	Technology Appraisal Head Department in the National Institute for Quality and Organisational Development in Healthcare and medicines (Hungary)
THL	FinOHTA, National Institute for Health and Welfare (Finland)

UCEETS	Unidad Coordinadora de Evaluación y Ejecución de Tecnologías en Salud (Argentina)
UNIMED	Unidad de medicamentos y dispositivos médicos (Bolivia)
UTA	University of Tartu (Estonia)
VASPVT	State Health Care Accreditation Agency (Lithuania)
WHO	World Health Organization
ZIN	National Health Care Institute (The Netherlands)
ZZZS	Slovenia Health Insurance Institute (Slovenia)

I. Healthcare System and HTA

1. Health Service & Universal Health Coverage

What are Health Services?

Health services are a set of visible functions from the combination of different inputs such as staff, equipment, money or drugs, to allow for the delivery of health interventions. Health services include disease treatment and diagnosis as well as health promotion, maintenance and restoration (1).

It is important to mention that in defining health services or benefits, we are not referring to essential basic baskets or minimum benefit packages as advocated by health sector reform policies of the 90s. We mean sets of services or universal benefits that are guaranteed, comprehensive, progressive and inclusive, applied to the search for better coverage and access of effective healthcare as a human right (1).

Definition of Universal Health Coverage

The Universal Coverage set must meet certain conditions that make it a tool for progress towards universal access to health and universal health coverage. These features are listed and explained below (1):

Table 1. Definition of features in Universal Health Coverage

Features	Definition
Universal access	Health Services defined to be covered should be directed to the total population of the country.
Progressiveness/ Adaptiveness	The coverage set should be an ongoing and dynamic activity and must adapt and be varied according to the needs of the health system and the population.
Comprehensiveness	Health Services defined should include the promotion of health, prevention, care for health problems, rehabilitation and palliative care.
Feasibility	The coverage should be feasible within the funding capabilities of the system
Scientific basis	The use of evidence-based medicine, HTA and other scientific tools provide the technical support for prioritization and definition of health services in a rational and outcomes-maximising manner for population health.
Social validation	To ensure transparency and accountability via stakeholder inclusion to discuss proposals and define services.

Source: PAHO Internal Document 2014

Defining needs of the population

According to unpublished data (2) from a study led by EASP and PAHO, prioritization is HTA-based in some countries in the Americas. Brazil and Uruguay have a national law stating that the decision making process ought to be based on HTA. Colombia and Chile's law recommends the decision-making process to be based on HTA. Although Argentina, Mexico, Costa Rica and Cuba do not have any legislation establishing HTA-based prioritization, they still use HTA reports for their decision-making and priorities.

Priority setting

Priority setting is a challenge for every health care system in the world because demand for health care outweighs the supply of resources allocated to finance it (3).

Priority setting for new technologies is, for example, frequently conducted under varying degrees of evidence for safety, effectiveness, and appropriateness of particular interventions. Other values important to priority setting include equity, the health of individuals versus the community's, the "rule of rescue," and democratic decision-making (3).

Examples of priority setting

WHO List of Essential Medicines

> *Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness* (4).

A model list is published online by the World Health Organization (WHO), updated every two years and often adopted by governments in developing countries. Lists of Essential Medicines are believed to guide the acquisition and supply of medicines in the public sector worldwide (4,5).

Strategic Fund

It is a PAHO's cooperation mechanism to improve access and supply management to strategic public health supplies. This is a restricted initiative to support PAHO Member States, which have an agreement with the Strategic Fund (SF) to promote access to effective, safe and quality medicines, medical devices and insecticides (6).

The SF covers medicines for communicable diseases (HIV, tuberculosis, malaria, neglected diseases) and non-communicable diseases (cardiovascular diseases, diabetes, cancer). For a medicine to be eligible for inclusion in the fund, it must satisfy at least one criterion from Clinical Evidence Group and one from pharmaceutical market factors, as follows:

(extracted from PAHO internal procedure for reviewing the SF medicine list) (7).

Clinical Evidence Group:

a. It has been included in the WHO List of Essential Medicines (and therefore have supporting evidence for safety, efficacy, and clinical effectiveness).
b. It has been recommended by the Expert Committee, reviewing the SF Medicine List, based on evidence of efficacy, safety, convenience and cost-effectiveness.

Pharmaceutical market factors:

a. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
b. Increasing the volume of medicines procured can result in lower costs.

The inclusion request of medicines to the SF Medicine List has to be done by a Member State or PAHO technical unit. The List is reviewed every two years and is available online at PAHO's website.

Not only Member States are able to buy these medicines at low cost. However, this strategy has increased access to products that difficult to procure, avoided stock outs and assured quality of commodities and technical assistance in supply chain management.

Revolving Fund

Since 1977, the Revolving Fund (RF) improves access to good quality vaccines, immuno-suppressants and related commodities at the lowest possible price for Member States.

This strategy has facilitated the rapid and equitable introduction of new vaccines in the Region of Americas, which helps elucidate why the Americas were the first of the six WHO Regions to eliminate diseases such as polio, measles and rubella. Through the Revolving Fund, financial sustainability of the National Immunization Programs is assured.

Vaccination Program Strategies

WHO publishes vaccine position papers providing global vaccine and immunization recommendations for diseases that have an international public health impact. Policy makers must define vaccination strategies to reach the population for whom specific immunization is required (8).

According to their needs, policy makers, governments and ministries of health can also provide access to new vaccines by adding them to the list. However, when introducing new vaccines and/or additional doses, it is

important to bear in mind the significant investments required to ensure a sufficient chain capacity to accommodate the additional intervention (9).

Health Benefit Plan (health insurance schemes/tax-funded systems)

Some countries have established an explicit positive and/or negative package, plan or list of health technologies to be financed by public resources, insurance or social security contributions (5).

> *Benefit plans can be mechanisms to reform budgeting in the health sector and align funding with priority technologies and populations.*
>
> *(A. Glassman)*

2. What do we mean by HTA?

Health technology is a term widely used to refer to different areas of health around prevention, diagnosis or therapy. The definition of health technology encompasses all products used in health services delivery, procedures, and systems[I].

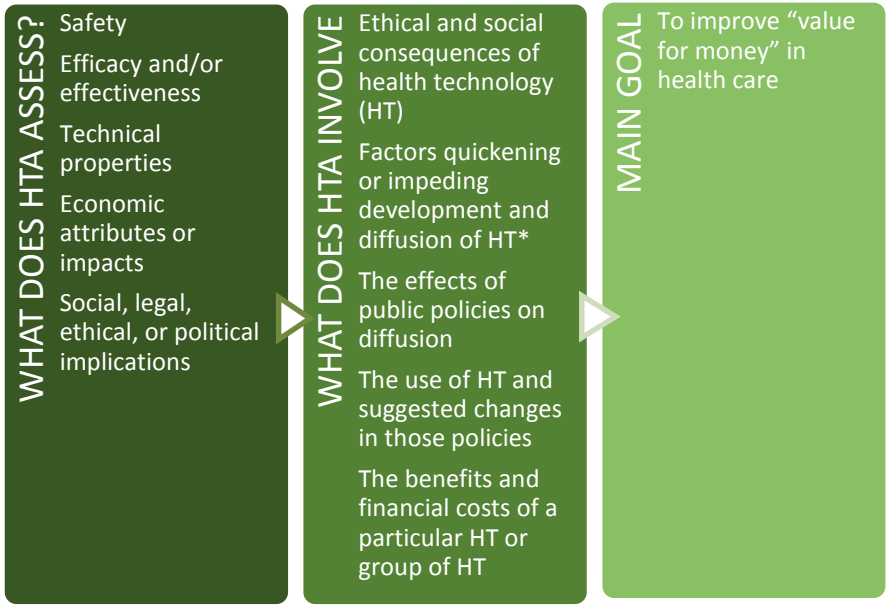
Health technology assessment (HTA) is a tool to help policy makers and/or health managers in the decision making process. It can inform allocation of resources, guidance in the development of health policies, and directly contribute to evidence-based medicine. HTA is the systematic evaluation of properties, effects, and/or impacts of health care technology. It should include medical, social, ethical, and economic dimensions, and its main purpose is to inform decision-making in the health sector[II]. HTA also provides clinical guidance on the use of medical technologies across the world and is commonly viewed as a tool to assist evidence-informed healthcare decisions (10). HTA has the potential to observe the impact of technology on an individual patient, in a group of similar patients, in the health system as a whole, or in all of the above through evidence from a variety sources.

The *scope of HTA is broad*. Not only does HTA include drugs, medical and surgical procedures, biologics, or the organizational and supportive systems (including prevention, screening, diagnosis, treatment and rehabilitation). It also includes a wide range of interventions, from the perspective of health systems and health services, including the most relevant aspects of the interventions in policy, organization and financing (11).

[I] Concept adopted in Health technologies, Resolution WHA60.29 Available from http://www.who.int/healthsystems/WHA60_29.pdf

[II] Definition adapted from the glossary of the International Network of Agencies for Health Technology Assessment [INAHTA] and Health Technology Assessment international [HTAi]. Available from www.paho.org

Figure 1. Key questions of health technology assessment



Source: Adapted from Velasco-Garrido el at 2015 (11)

HTA involves a multidisciplinary process, which bridges the gap between science and politics. In the face of health budget restrictions, HTA has garnered success by providing political decision-makers with timely, evidence-based, and comprehensive information on health technologies[III]. It examines the short- and long-term consequences of the health technology and summarizes information about its medical, social and economic issues in a systematic, transparent, unbiased, robust manner. The application of evidence to a specific and real context facilitates impact assessment of technology incorporation and, in turn, identification of the best value for the money spent for health outcomes. HTA is not discipline-specific but an interdisciplinary process based on evidence, scientific or not (12).

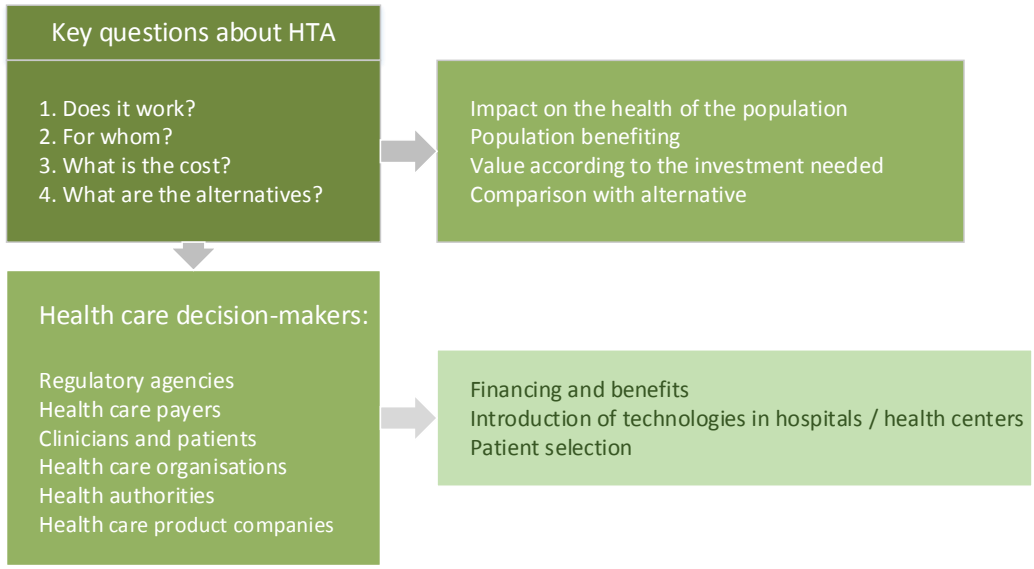
HTA cannot be the only aspect taken into account in the decision-making process. Besides financial considerations, many pressures from patients, industry and media contribute to the decision-making process. Nevertheless, appropriate use of HTA is useful to incorporate in tackling complex decisions along the life cycle of a health technology. HTA can provide better efficiency in public decision-making that usually has limited information or uncertainties about efficacy, security and efficiency (13).

HTA can be used (14):

- As an input into the pricing process, by determining the price of the medicine (see examples from Brazil in Chapter I.2. What do we mean by HTA?).
- As an input into market access decision, by determining the degree to which payers fund a medicine once it has a price and reimbursement decision.
- As a determinant of medicine use, by affecting guidance for physicians or the patients (see examples of Evidence Informed Practice Guidelines in Chapter V.1).

[III] Swiss Network for Health Technology Assessment. Available from: http://www.snhta.ch/ [cited 29 April 2015].

Figure 2. Features of health technology assessment

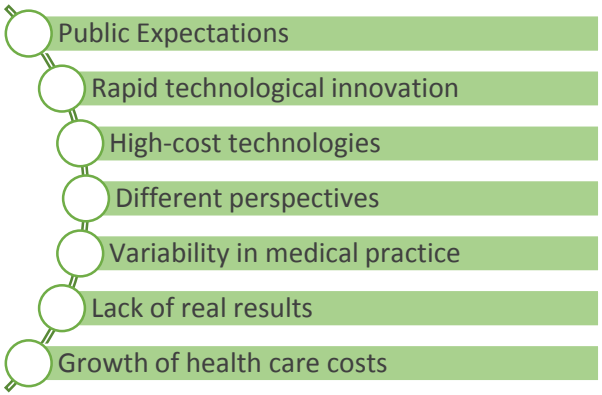


Source: Elaborated by the authors

Role of HTA in the Decision Making Process

In the US, the Congressional Budget Office concluded that *"roughly half of the increase in health care spending during the past several decades was associated with the expanded capabilities of medicine brought about by technological advances"* (2008) (15). The pressure on health expenditure due to an ageing population and a growing number of new and expensive technologies, involves a number of cost-containment measures with direct restriction effects on price or use of the health technology. This explains the increasing number of countries that have implemented HTAs to inform the decision process (16).

Figure 3. Causes of increasing health expenditure



Source: Elaborated by the authors

The main questions that HTA should address are:

- Is it worth spending public money on a health technology?
- If yes, to what extent and for which patients? (17)

In August 2013, an international workshop concluded that HTA is a critical component of evidence-informed policy decision making. HTA should always be part of the priority setting process, and is an essential foundation to secure Universal Health Coverage through the efficient and equitable allocation of health care, along with financial protection and better health outcomes (18). The purpose of HTA is to support the process of decision-making in health care at policy level by providing reliable information through the transfer of the knowledge produced in scientific research.

Therefore, governments and other payers in many jurisdictions have introduced HTA programs to address the dilemma of providing universal access to high-cost and innovative technologies. HTA plays a pivotal role in many countries' health insurance coverage decision, including Netherlands, France, Switzerland, Spain, the United Kingdom, and some non-European countries such as Brazil, Argentina and Uruguay in Latin America, and Taiwan in Asia (19).

In fact, HTA can:

- Strengthen health policy for national public health policy (e.g. vaccines), in regulation of pharmaceuticals and equipment, in payment decisions and in the coverage of health services (4). HTA, or a combination of tools including HTA, can have a substantial

effect on pharmaceutical prices in negotiations and national pharmaceutical budget expenditure (20).

- Help policy-makers decide which technologies are effective and which are not, and define the most appropriate indications for their use. Assessments of the costs and benefits of new treatments compared with existing care, have become ''hardwired'' into the decision on whether to reimburse the new technology (21).
- Reduce or eliminate interventions that are unsafe and ineffective, or whose cost is too high compared with its benefits.
- Improve patient access to appropriate interventions.
- Improve the efficiency of new product development.
- Improve the evidence base for coverage decisions.
- Improve the transparency of those decisions and their rationale to the public.
- HTA is directly and indirectly related to certain patient-oriented concepts, including patient-centered care, patient-centered outcomes, patient-reported outcomes, and patient-centered outcomes research (22).

In recent years, HTA has gained momentum as a tool for assessing value for money in CESEE countries, while its uptake as a formal decision-making mechanism has increased considerably. One of the principles proposed by Drummond states, the *"link between HTA findings and decision making processes needs to be transparent and clearly defined. Criteria for decision makers can legitimately differ across payers or jurisdictions, ideally they should be transparent"* (23). In addition, establishing centralized systems for determining the reimbursement of new health technologies improves the legitimacy of such decisions (24).

Developing appropriate methods for conducting HTA has received significant attention, however equal importance has not been given to the need for proximity between those conducting HTA and the decision makers(4). Thus, Drummond emphasizes the importance of an early dialogue between the agencies of HTA, regulators and those conducting HTA to improve data collection during the development of technology. Drummond explores how those conducting HTA can interface better with the key decision makers, in particular three stakeholder groups: regulators, policy makers and health service managers (4).

However, there is a set of identified barriers to the implementation of HTA, and at different levels. Drummond and Weatherly, in 2000, published a bibliographic review addressing the problems of HTA dissemination and implementation; they categorized the barriers on several levels: public policy, healthcare professional and general public (25). Other difficulties identified by authors were:

Table 2. Main barriers and difficulties to HTA

Barriers and difficulties to HTA
Undefined structures or bodies that assumes the HTA.
Misalignment of HTA with decision making needs.
Political actions often prompted by “lobbying” or “pressure groups”.
Policy makers have a different time horizon, and shorter than that required by the investigation. Their decisions are conditioned by budget limits and based on political bodies who, at times, exclusively focus their decision on budget impact.
Financial barriers in public and private systems. There are limited resources for HTA, particularly limited compared with national healthcare spending. Furthermore, there are rigidities in the health system that impede the reallocation of financial resources.
Lack of capacity and available resources for HTA activities in both the numbers of trained persons and budget to generate HTA reports.
The conflict between professional autonomy and clinical guidelines or externally imposed recommendations.
Marketing and promotion of health technologies, in use of products and direct-to-consumer advertising even against HTA findings.
Financial incentives in health care systems to use these technologies across hospitals, physician groups, patients etc.
Timeliness and accessibility of the results of the HTA – Assessment must be performed early in the technology life cycle and updated when new data becomes available.
Relevant local databases (epidemiology and cost data) and clinical guidelines are often incomplete or unavailable.
Lack of access to HTA reports, complex and technical report formats, questionable data quality, absence of real-world applications, and narrow focus.
Absence of consensus: uncertainty in medical practice and difficulties for the transferability of results.

Sources: Mapping report 2015 (2), Drummond M et al 2000 (25), Goodman CS et al (26), Hoffmann C et al 2000 (27), Deyo RA 2002 (28)

On the other hand, some of the main elements of a successful HTA production and implementation, which will enable societies to expand their ability to conduct and use HTAs were:

Table 3. Successful HTA production and implementation

Successful HTA production and implementation
Defining a clear policy question
Administrative independence and a governance and organizational structure conferring legitimacy to the process and the results.
Clarifying the roles and responsibilities of the various parties.
Adequate and cooperative relationship between HTA agencies and decision-makers, from the beginning to the end - clarifying objectives, requirements and scope.
Involving processes to avoid conflicts of interest (to ensure active participation of experts, clinicians, patients and the industry. Selection criteria must be defined and based on a number of factors, or preferably, amongst other things, HTA should be conducted from a social viewpoint).
Preliminary declaration of interest should be required in order to safeguard the product against bias associated with conflicts of interest.
Financial resources and specific funding.
Availability of trained staff; increasing the cadre of researchers and officials able to do and interpret HTA.
Deadlines need to be explicitly defined. They should have sufficient time to publish responses to a question, be appropriate to influence decision-making, or permit revocation in order to consider the consequences of the evaluation.
Established processes for making systematic and transparent decisions.

Successful HTA production and implementation
The participation of different stakeholders during the HTA process. This increases the acceptance and legitimacy of the decisions (regulators, health policy makers, clinicians, patients and health service managers).
Making recommendations commensurate with the evidence.
Transparency during the entire process of evaluation, dissemination and implementation of decisions based on the evaluation.
A robust implementation methodology (and methods to deal with uncertainty).
Focus on value and economic efficiency.
Incorporating real-world data, scientific evidence and a production of objective and timely research.
Defining the methodology used in the evaluation to selection and review of scientific evidence. The selection of alternatives should be based on established standards or clinical practice. The introduction of a threshold should also be considered.
Good process matters.
Paying attention to incentives and disincentives.
The existence of international collaboration initiatives to reduce duplication of effort, develop and promote best practices, share and facilitate the adaptation of information.
Widespread dissemination.
A framework of action that facilitates and gives incentives to the diffusion of reports and clinical guidelines. The key point is to improve the effectiveness of recommendations and conclusions published by the agencies- An important part of HTA is to ensure the use of HTA in decision-making.

Sources: Del Llano-Señarís JE et al 2014 (13), Dankó D 2014 (17), Emanuel EJ et al 2007 (30), O'Donnell JC et al 2009 (31), Newman PJ 2009 (32), Case studies CEE & LAC 2015 (33)

The published literature on the prerequisites for successful implementation of effective HTA in a health system is vast. However, the local needs of each country must be taken into consideration with regard to these prerequisites. Finally, each *"country will have its own reasons for adopting an individual approach to the themes discussed and the role of HTA will vary with local circumstances"* (36).

3. Examples of the use of HTA in the decision-making process

HTA has been a relatively recent development and its use by health care providers is growing worldwide. It plays an increasingly important role to inform reimbursement decisions and price setting (34).

In some countries, HTA provides information to support decisions about priorities in healthcare or specific decisions based on a judgment of whether they provide value for money. In other countries, the focus may be less on value for money and more on evidence of effectiveness and cost-effectiveness. Countries like the UK, Poland and Slovakia have an explicit threshold (see Chapter III.2) above which the technology will not usually be approved for reimbursement (2).

Some CESEE and Americas countries have created formal structures of decision in which HTA is used. Many of them have entities under government mandates with advisory functions and different responsibilities for the decision-making. However, those entities are mainly in charge of reimbursement and pricing of health technologies. There is a significant degree of heterogeneity in the development of such structures (2).

HTA bodies and/or organizations can be found in Argentina, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Mexico, Paraguay, Peru, Uruguay and Venezuela. From all those countries, only Venezuela does not take part in RedETSA, which is the Health Technology Assessment Network of the Americas (Red de Evaluación de Tecnologías en Salud de las Américas). No HTA organizations were found in the Caribbean Countries (2). – For more information about HTA bodies /organizations identified in in the region of CESEE and the Americas (see Chapter II.1).

Overall, HTA is in different stages of development in the Region of the Americas, which includes the Caribbean. Many healthcare systems remain highly fragmented and inadequately funded, while countries such as Brazil and Colombia have well-established HTA systems in place, with HTA legislation and HTA included in the National Plan (2,26).

In most countries, HTA focuses on pharmaceuticals and medical devices because those are standardized technologies, whose ownership is unclear. They represent a significant financial burden on health systems and have major social impact and visibility (17). In both regions, CESEE and the Americas, pharmaceuticals and medical devices are the technologies most commonly assessed: 85% and 54% respectively for the CESEE countries participating in the mapping study, and 85% and 72% respectively for the Americas.

Variability is also present in the way countries have established public HTA organizations to inform health policy decisions. It has been a more natural fit with the more centralized, government-funded, and administered health-care systems of Europe (32). The receptivity to HTA varies across the continent as practices differ across HTA organizations. Some agencies

are more transparent than others about their deliberations. There are also differences in how HTA organizations set priorities, the degree to which stakeholders are permitted to provide input, how results are communicated to society, how HTA organizations interact with national reimbursement authorities, or how explicitly entities use decision analytic models and cost-effectiveness analysis (35).

Successful HTA production and implementation rely on availability of trained staff, financial resources, established process for making systematic and transparent decisions, and a robust implementation methodology. In contrast, the main limitations CESEE and the Americas' countries are currently facing, are undefined structures of HTA, insufficient local data availability, and lack of capacity and available resources for HTA activities. In fact, the most important limitations faced by those who perform HTA in these countries are described below:

Table 4. Key limitations faced by institutions that perform HTA in CESEE and the Americas

	Countries	
	Central, Eastern and South Eastern Europe	Region of the Americas
Main limitations	1st Lack of funding	1st Skills training 1st Lack of institutional support
	2nd Insufficient human resource allocation	2nd Lack of funding

Source: Mapping report 2015 (2)

Government is the main source of requests for conducting HTA in both regions (2).

HTA decision-making process in the region of Central - Eastern and South Eastern Europe and the Americas

The governance and organization of HTA bodies, decision-makers and involvement of other stakeholders in HTA processes are important factors that can affect the impact of HTA on the health system. The HTA process is not homogenous among settings as the operative processes and the organizations work differently across Americas and European countries. There are countries where the HTA system is more developed, such as Brazil, England and Canada than others (e.g., Czech Republic, Greece, El Salvador).

Some countries in the Americas and CESEE have created formal decision making processes for which HTA is used, mostly for medicines. However, there is much heterogeneity in the degree of development of such structures.

The table below identifies the role of each institution within the decision-making process in each country.

Table 5. Key stakeholder in the HTA decision-making process in CESEE and Americas countries

Country	Marketing authorization	HTA	Reimbursement Decision	Pricing Decision
Albania	National Centre for Drugs Control	NCQSA MoH/ Health Insurance Institute	MoH/ Health Insurance Institute	MoH
Argentina	ANMAT	UCEETS	MoH & Superintendencia de Seguros de Salud	None
Barbados	MoH	None		MoH
Belize	MoH	MoH	MoH	MoH
Bermuda	MOHE and Bermuda Health Council	MOHE and Bermuda Health Council	MOHE and Bermuda Health Council	MOHE and Bermuda Health Council
Bolivia	Unidad de Medicamentos y Tecnología en Salud	Unidad de Medicamentos y Tecnología en Salud	Dirección de Seguros Públicos Ministerio de Salud	Unidad de Medicamentos y Tecnología en Salud
Bosnia-Herzegovina	Agency for Medicines and Medical Devices	Health Insurance Fund	Health Insurance Fund	Federation of Bosnia and Herzegovina Republic of Srpska
Brazil	ANVISA	CONITEC	ANVISA, CONITEC, ANS	CMED
Bulgaria	Drug Act	NPRC	NPRC	NPRC
Canada	Health Canada	CADTH INESSS, in the province of Quebec	MSSS	MSSS
Chile	ISP	MoH, ISP, FONASA and ETESA	MoH and FONASA	CENABAST
Colombia	INVIMA	IETS	MSPS	Comisión Nacional de Precios de Medicamentos y Dispositivos Médicos
Costa Rica	MoH	CCSS	CCSS and MoH	Department of the Treasury
Croatia	HALMED	Agency for Quality and Accreditation in Health Care and Social Welfare (assessment)	CIHI Board (medicines) MoH (health policy, public health program) Hospital Management (medical device)	CIHI Board
Cuba	CECMED	MoH	MoH	MoH and Ministerio de Finanzas y Precios
Cyprus	Drug Council	Drug Committee (MoH)	MoH	MoH

Country	Marketing authorization	HTA	Reimbursement Decision	Pricing Decision
Czech Republic	SUKL	SUKL	SUKL	SUKL
Dominican Republic	MoH	MoH	CNSS	Prices are not regulated
Ecuador	ARCSA	Dirección Nacional de Inteligencia de Salud	Dirección Nacional de Medicamentos y Dispositivos Médicos	Secretaria Técnica del Consejo Nacional de Fijación y Revisión de Precios de Medicamentos
El Salvador	DNM	DNM	MoH and DNM	DNM
Estonia	State Agency of Medicines Medical Devices	Health Insurance Fund	Ministry of Social Affairs	Health Insurance Fund, Ministry of Social Affairs
Former Yugoslav Republic of Macedonia	Drugs Bureau	MoH	MoH	MoH
Greece	EOF	EOF in collaboration with EOPYY	EOF in collaboration with EOPYY	MoH
Guatemala	MoH	None	MoH	Department of the Treasury
Guyana	MoH	None	MoH	MoH
Haiti	Ministère de la Sante Publique et de la Population	Ministère de la Sante Publique et de la Population	Ministère de la Sante Publique et de la Population	
Honduras	MoH	None	Unidad Planificación de la Gestión (under Department of Treasury)	Prices are not regulated
Hungary	OGYI	GYEMSZI TEI	Ministry of Human Resources/OEP/Registered Dispense Committee	MoH
Jamaica	MoH	None	MoH	MoH
Latvia	State Agency of Medicines	CHE	NHS	NHS
Lithuania	VASPVT	VASPVT	MoH /NHIF	MoH / NHIF
Mexico	COFEPRIS	CENETEC	MoH, Consejo de Salubridad General, Seguro Popular (Sistema de Protección Social en Salud) & Social Security Institutions	Seguro Popular, Social Security Institutions & Comisión Negociadora de Precios de Medicamentos
Moldova	Medicines Agency	Medicines Agency	MoH	Medicines Agency / MoH
Nicaragua	MINSA	MINSA	MINSA	MIFIC
Panama	MoH	Instituto ECRI	MoH & Caja de Seguro Social	Caja de Seguro Social

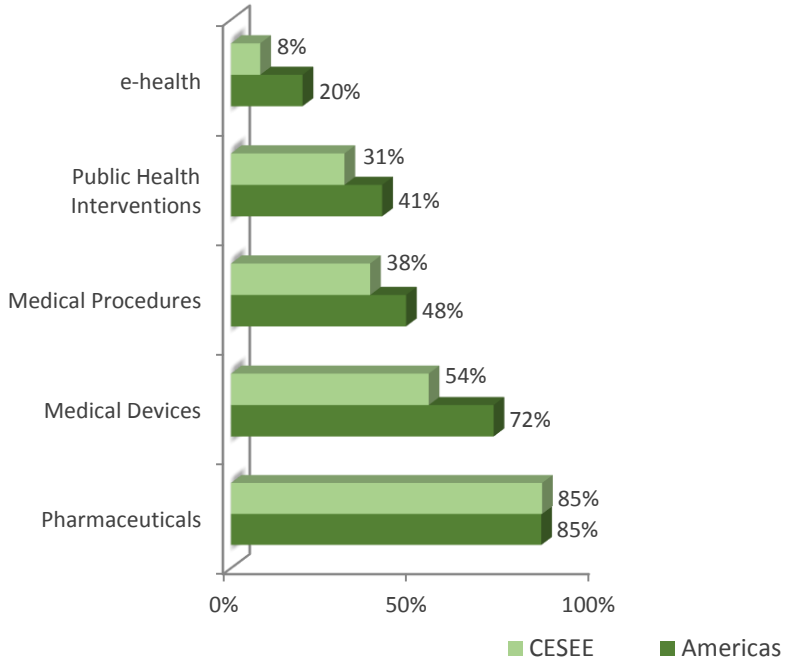
Country	Marketing authorization	HTA	Reimbursement Decision	Pricing Decision
Paraguay	Dirección Nacional de Vigilancia Sanitaria	None	Ministerio de Salud Pública y Bienestar Social & Servicio Nacional de Salud	Ministerio de Salud Pública y Bienestar Social/ Dirección Nacional de Vigilancia Sanitaria
Peru	DIGEMID	Instituto Nacional de Salud	MoH	None
Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	AOTM	MZ (MoH)	MZ (MoH)
Romania	Romanian Medicines Agency	MoH	MoH	MoH
Russia	MoH	Center for HTA at the Russian Presidential Academy of National Economy and Public Administration	MoH NHIF	MoH
Saint Lucia	MoH	MoH	MoH & National Insurance Corporation	MoH
Serbia	ALIMS	RZZO	RZZO	MoH
Sint Maarten	Ministry of Public Health	None	Ministry of Public Health & Social Security	Ministry of Tourism, Economic Affairs, Traffic and Telecommunication
Slovakia	State Institute for Drug Control	MoH	MoH	MoH
Slovenia	JAZMP	Slovenia Health Insitute	HIIS (MoH for procedures)	HIIS
Suriname	MoH	None	MoH and Social Security	
Trinidad and Tobago	MoH	MoH	MoH and Regional Health Authorities	MoH
Turkey	Turkish Drug and Medical Devices Agency	MoH, MEEC	SSI SSI Drug Committee: MEEC and RC	MoH / SSI
Uruguay	MSP - División Evaluación Sanitaria	MSP, FNR	MSP, FNR, and MEF	MSP and MEF
Venezuela	Servicio de Contraloría Sanitaria	Instituto Nacional de Higiene	Servicio Nacional de Salud	Ministerio del Poder Popular para el Comercio

Source: Source: Mapping report 2015 (2)

Which type of technology is assessed in CESEE and the Americas?

In the HTA process, all technologies should be potential candidates for HTA (7). The mapping report showed that in most of countries where HTA is used to inform coverage decisions, pharmaceuticals are the most assessed technology.

Figure 4.Technologies assessed in CESEE and the Americas



Source: Mapping HTA report 2015 (2)

Who is the initiator of the HTA decision-making process?

Commonly, in most jurisdictions in Europe, the manufacturer initiates the HTA decision-making process (e.g. Belgium, Germany, Sweden, Denmark, Finland, Italy, and Ireland). However, sometimes, it is initiated by the HTA agency (e.g. Sweden) or other institution such as the Ministry of Health (e.g. England and Spain) depending on the public health issue. In CESEE and Americas' countries, the HTA process usually begins with the submission of an application by the manufacturer. Further information and examples can be found in Chapter II.

Body independence and link to decision-making process and priority setting

The body in charge of HTA in each country can be part of the Ministry of Health or an independent scientific body. Given the complexity of decision-making for health technologies, it is recommended that the HTA process is conducted independently of the body that ultimately will be responsible for the adoption, funding and implementation of the HTA decision (36).

Although there are differences between HTA bodies across the Americas and CESEE countries, few are independent.

Examples

England

The National Institute for Health and Care Excellence (NICE) has been given the status of a non-departmental government body. This means that NICE is accountable to the Department of Health but operationally independent from the Government. An Appraisal Committee comprised of independent experts makes the recommendations for reimbursement.

Poland

The Agency for Health Technology Assessment (AOTMiT) is independent of the body responsible for reimbursement and coverage decisions. Recommendations are made by an appraisal committee or standing advisory committee comprised of independent experts.

Croatia

The Agency for Quality and Accreditation in HealthCare and Social Welfare undertakes the technology assessment while the Croatian Institute for Health Insurance (CIHI) is responsible for the appraisal and reimbursement decision.

Colombia

The Instituto de Evaluación Tecnológica en Salud (IETS) is the body responsible for assessment and appraisal of the health technology and the Ministry of Health (MoH) is in charge of the decision making.

Brazil

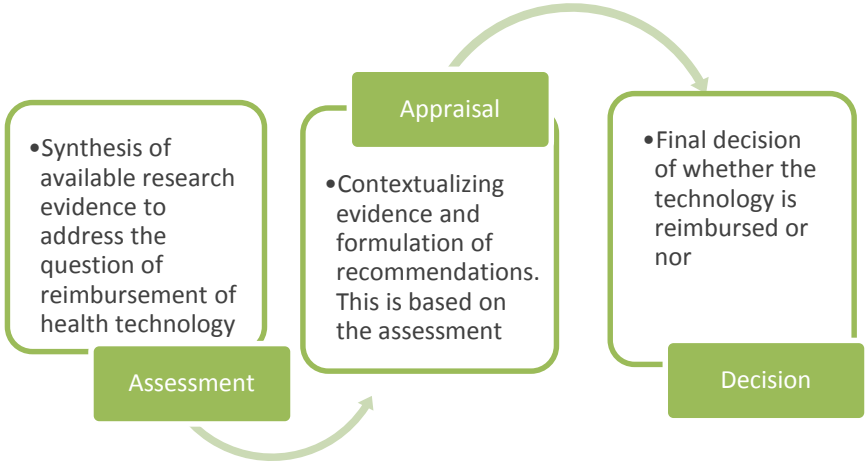
The Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC) is the body responsible for assessment and appraisal of the health technology in the Brazilian National public health system, while the Secretary of Secretaria de Ciência, Tecnologia e Insumos Estratégicos (SCTIE) of the MoH is in charge of the decision making. Up to date, all recommendations made by CONITEC were approved by the Secretary of SCTIE.

Mexico

The body responsible for assessment and appraisal in Mexico is Centro Nacional de Excelencia Tecnológica en Salud (CENETEC), while the MoH or Health Council makes the decisions —depending on who started the process (see Chapter II.1).

The HTA decision making process can be defined in three steps (and can include different organisations): assessment, appraisal and decision-making, as shown below.

Figure 5. Relationships between assessment, appraisal and decision-making



Source: elaborated by the authors

There are countries where all three steps are conducted by different committees that belong to the same organization as is the case in the Czech Republic, Latvia, Slovakia and Slovenia. There are cases where the HTA body only performs assessment and another body is responsible for the appraisal (Croatia and Cyprus); and others, such as in Bulgaria, where the appraisal is performed by one body, or, in other words, the three steps are conducted by different bodies.

Among Americas' and CESEE countries, variation in how HTA is linked to decision-making and priority setting is shown in the pie charts below. While in CESEE countries legislation recommends that HTA reports should be considered for coverage decisions, in the Region of the Americas, the HTA reports are used to support policy making (though this process is not official). Nevertheless, among the Region of the Americas countries, in those that are non-RedETSA members[IV] there is no legislation and decisions are not taken considering HTA findings.

Findings

Countries with legislation mandating use of HTA in the decision making process are Slovakia, Latvia, Greece, Poland, Czech Republic, Estonia, Slovenia, Bolivia, Brazil, Costa Rica (for medical devices at Caja Costarricense de Seguro Social), Uruguay (for high cost medicines) and Bermuda.

Countries where legislation recommends the use of HTA in the decision making process include Colombia, Chile and Suriname.

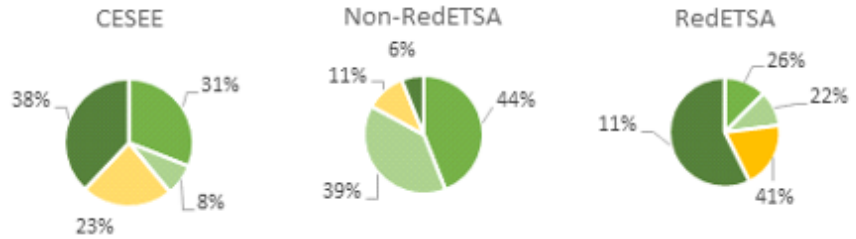
Countries that do not have specific legislation state that coverage decisions should be informed by HTA reports. These include: Croatia, Lithuania,

[IV] Costa Rica and El Salvador were considered as non-RedETSA members' due to the nature of the first mapping report (Advance_HTA project) (2N).

Russia, Hungary, Argentina, Cuba, Ecuador, El Salvador, Mexico, Nicaragua, Panama, Peru, Quebec (Canada), Saint Martin and Trinidad and Tobago.

Countries where the decision is not informed by HTA include: Republic of Serbia, Belize, Costa Rica, Dominican Republic, Guatemala, Haiti, Honduras, Jamaica, Paraguay, Saint Lucia, Uruguay and Venezuela.

Figure 6. How HTA is linked with decision making in CESEE and the Americas



- There is no specific legislation at the present time starting that coverage decisions should be informed by HTA reports, but HTA reports are used to support policy making.
- There is no link and the decision are not informed by HTA.
- There is legislation establishing that HTA reports must be considered in the decision-making process (mandatory).
- There is legislation establishing that HTA reports should be considered to support coverage decisions (recommendation).

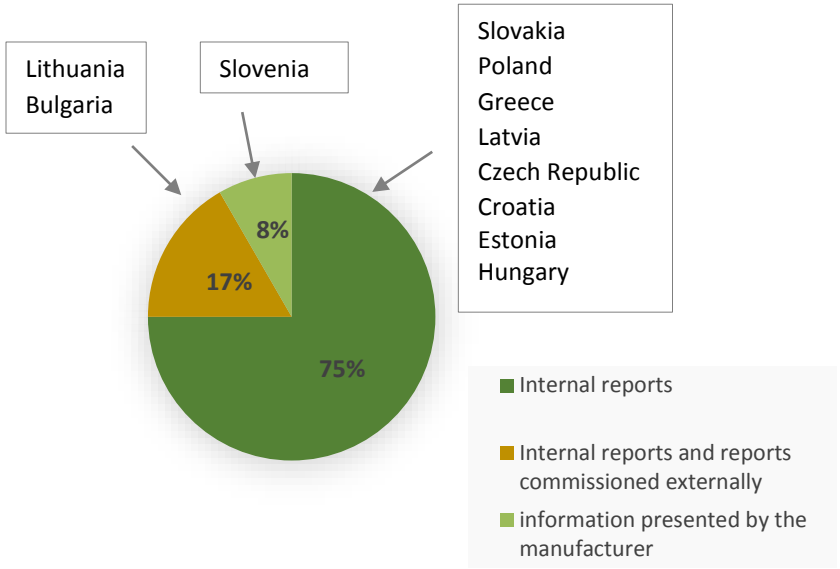
Source: Mapping report 2015 (2)

Production and review of evidence for the HTA decision-making process

In most EU countries with a well-defined HTA process, the production and review of evidence are both developed inside the HTA agency by their own dedicated staff. However, HTA organizations are increasingly commissioning HTA reports to academic centers. At present, England, Ireland, Austria, Ireland, Spain, and Sweden are commissioning reports externally. In the Region of the Americas, this occurs in Argentina, Bolivia, Brazil, Colombia, Chile, Cuba, Mexico and Paraguay.

In CESEE, most of HTA bodies review the information presented by the manufacturer and produce their own report. HTA bodies in Lithuania and Bulgaria commission the reports, while in Slovenia the HTA body only reviews the information presented by the manufacturer (Figures 7 and 8 below).

Figure 7. Type of information taken into account when assessing technologies in the CESEE countries.



Source: Mapping report 2015 (2)

Figure 8. Type of information taken into account when assessing technologies in the Region of the Americas

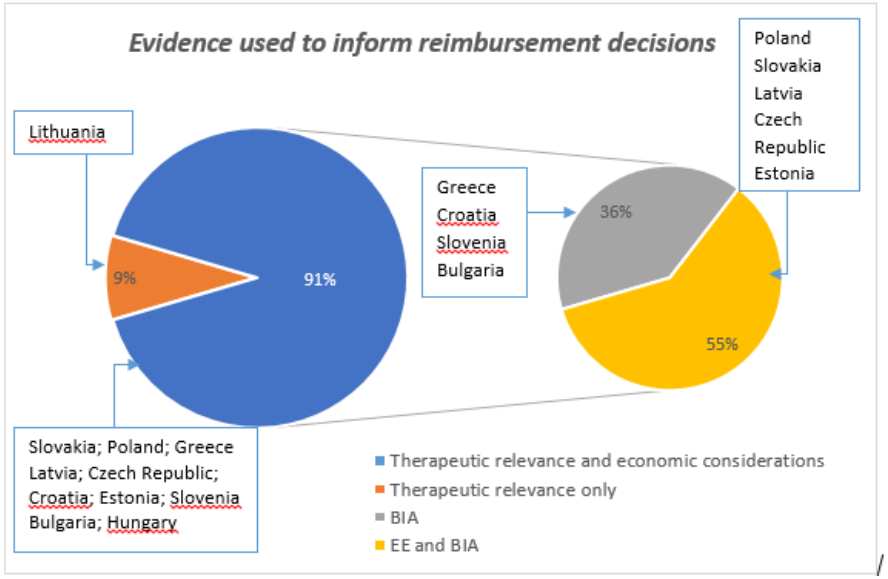
Source: Mapping report 2015 (2)

Main criteria used to inform reimbursement decisions

In general, most of the European countries include an economic evaluation and/or budget impact analysis as a requirement for the HTA decision. Countries such as England, Germany, Scotland, Poland, and Italy require an economic evaluation for the final decision of reimbursement. By contrast, countries such as France, Belgium and Ireland only use budget impact analysis as a criterion added to therapeutic relevance to take the final decision.

However, there are many barriers against the adoption of health economic evaluations as formal tools for decision making in low- and middle-income countries as shown in the graph below.

Figure 9. Evidence used to inform reimbursement decision in CESEE countries



BIA: Budget impact analysis; EE: Economic Evaluation.
Source: Mapping report 2015 (2)

Transparency and stakeholder involvement

In order to have an HTA process well established in a jurisdiction, it is important that all parties are engaged and interested in the process. Therefore, HTA should be an unbiased and transparent exercise, according to principle 2 of Drummond et al (7).

By including all stakeholders such as health professionals, patient representatives and industry representatives in the HTA process, bias is reduced (7). However, HTA organizations differ widely in the degree to which stakeholders can participate in the process and interact with the decision-makers. Mapping exercises showed wide stakeholder involvement from Latvia, Poland, Czech Republic, Lithuania, Russia and Estonia.

The HTA body in the Czech Republic allows stakeholders to comment on a draft HTA whereas in Poland, stakeholders can only comment at the final stage of the assessment process. HTA bodies from Slovakia, Latvia and the Czech Republic allow stakeholders to appeal against recommendations/decisions. Slovakia, Latvia, the Czech Republic and Bulgaria have a decision making process, including the rationale behind technology reimbursement decisions, which is open to public scrutiny.

Example

In England stakeholders are fully involved in the HTA process. NICE formally requires stakeholders to be engaged in its activities by encouraging or requiring submissions of evidence from them. Also, NICE allows them to make comments on the assessment reports at the draft stage and encourages them to appeal against the final appraisal recommendation. It is important to mention that NICE's HTA appraisal committee also includes a wide stakeholder representation. Other countries with a similar stakeholder involvement are Poland, Scotland, France, Germany and Belgium.

In Brazil stakeholders are required, by law, to participate in the HTA process. Representatives from wider society and medical professionals are also required to take part. The recommendation is available for public consultation for 20 days and after this period, contributions are analysed for final appraisal and recommendation. IETS, in Colombia, asks for contributions to their website at the beginning of the process (when the research question is being formulated) in the assessment and appraisal steps. The HTA body in Quebec (INESSS) involves representatives from patients, physicians and society in the appraisal committee. For further information, refer to Chapter II.3.

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II. Building the HTA Function

1. Types of HTA Bodies/Organizations and their Responsibilities

In order to have a transparent and unbiased decision-making process it is important to determine the type of HTA body healthcare managers interact with.

In most jurisdictions several agencies/organizations/units are involved in preparing and making reimbursement decisions for health technologies (mostly for pharmaceuticals). Institutions (generally government-dependent units) whose primary purpose is technology regulation (ANVISA, Brazil), reimbursement (TAHD, Hungary) or pricing regulation (CIHI, Croatia), ultimately have an explicit or implicit HTA function.

However, on the other hand, some organizations that have been set up primarily to conduct HTAs. These are generally independent, "arms' length" HTA bodies.

HTA functionality can be classified as:

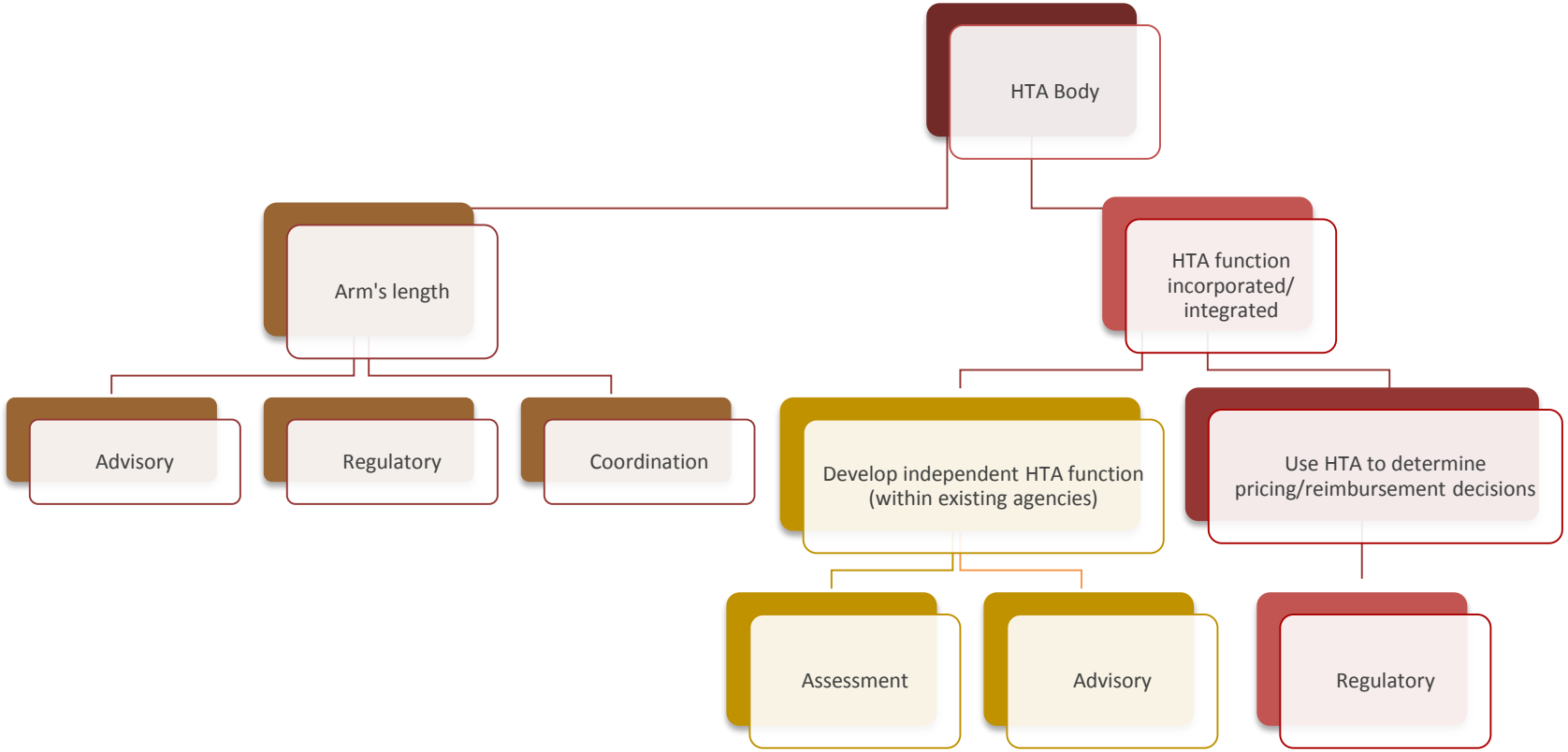
Advisory: provide reimbursement or pricing recommendations to a national or regional government, a ministerial department, or self-governing body.
Example: NICE accountable to the NHS however, it can be classified as an "independent" body (since it has autonomy to perform HTA functions) of an advisory nature.

Regulatory: responsible for listing, pricing and reimbursement of health technologies; an example is TLV in Sweden.

Coordination: responsible for coordinating HTAs, including research on HTA, developing clinical guidance, and producing and disseminating HTA reports. An example of this is SBU in Sweden.

HTA bodies involved in HTA activities in the rest of Europe, countries with a more developed HTA process are described elsewhere (1-3).

Figure 1. Division/classification of HTA bodies and their HTA functions



Source: Sorenson C et al 2008 (3)

Table 1. Types of HTA bodies/ organizations involved in HTA activities & their responsibilities identified in the Region of the Americas

Country	Institution	Type of HTA body (according to prime function in HTA)	Responsibility of the HTA entity and website
Argentina*	IECS	Arms' length	Coordination (research) & Advisory http://www.iecs.org.ar/
	Ministerio de Salud de la Nación	HTA integrated	Advisory http://www.msal.gov.ar/
	UCEETS	Arms' length	Coordination & Advisory (Not available)
Bolivia*	UNIMED	HTA integrated	Coordination & Advisory http://unimed.minsalud.gob.bo/unimed/index.html
Brazil*	CONITEC	Arms' length	Coordination & Advisory http://www.conitec.gov.br/
	ANVISA/CMED	HTA integrated	Regulatory (ANVISA: CMED) http://portal.anvisa.gov.br/wps/portal/anvisa-ingles
	ANS	Arms' length	Regulatory (private healthcare system) http://www.ans.gov.br/
Canada*	CADTH	Arms' length	Coordination & Advisory https://www.cadth.ca/
	INESSS* (Quebec)	Arms' length	Coordination & Advisory https://www.inesss.qc.ca/accueil.html
Chile*	Comisión Nacional de ETESA**	Arms' length	Coordination & Advisory (HTA) http://web.minsal.cl/evaluacion_tecnologias_salud
	ISP	HTA integrated	Coordination http://www.ispch.cl/
	Secretaría AUGE	HTA integrated	Coordination (produces clinical practice guidelines) http://web.minsal.cl/no_ges_secretaria_tecnica

Country	Institution	Type of HTA body (according to prime function in HTA)	Responsibility of the HTA entity and website
	División de Planificación Sanitaria	HTA integrated	Coordination & Advisory focused on health policies http://web.minsal.cl/salud_planificacion_sanitaria
Colombia*	IETS	Arm's length	Coordination & Advisory http://www.iets.org.co/
	MoH	HTA integrated	Advisory http://www.minsalud.gov.co/Paginas/default.aspx
	INVIMA	MoH	Regulatory regulation of health technologies https://www.invima.gov.co/
Costa Rica*	CCSS	HTA integrated	Coordination & Advisory http://www.ccss.sa.cr/
	Ministerio de Salud	HTA integrated	Regulatory http://www.ministeriodesalud.go.cr/
Cuba*	Ministerio de Salud	HTA integrated	Coordination & Advisory
Ecuador*	Dirección Nacional de Inteligencia de Salud	HTA integrated	Advisory http://www.salud.gob.ec/direccion-de-inteligencia-de-la-salud/
El Salvador*	Dirección Nacional de Medicamentos	HTA integrated	Coordination & Advisory http://www.medicamentos.gob.sv/index.php/
Mexico*	Consejo de Salubridad General	HTA integrated	Advisory http://www.csg.gob.mx/
	CENETEC	Arm's length	Coordination http://www.cenetec.salud.gob.mx/
Peru*	Instituto Nacional de Salud	HTA integrated	Coordination & Advisory http://www.ins.gob.pe/portal/jerarquia/4/825/publicaciones-unagesp/jer.825
Uruguay*	Ministerio de Salud Pública	HTA integrated	Coordination & Advisory http://www.msp.gub.uy/

Country	Institution	Type of HTA body (according to prime function in HTA)	Responsibility of the HTA entity and website
	FNR	HTA integrated	Coordination & Advisory http://www.fnr.gub.uy/
Venezuela	CONETS	Arm's length	Advisory http://www.mpps.gob.ve/

Note: *Member countries of RedETSA (2); **ETESA – Evaluación de Tecnologías Sanitarias (Comisión intersectorial dependiente del Ministerio de Salud (MINSAL).
Source: Mapping report 2015 (5)

Table 2. Types of HTA bodies/ organizations involved in HTA activities & their responsibilities identified in CESEE countries

Country	HTA body/ organization/ institution	Relationship with Government	Responsibility of the HTA entity and website
Albania	NCQSA	HTA Integrated	Coordination (clinical guideline, HTA, Evidence-Based Medicine) http://qkcsaish.gov.al/activities.htm
	Reimbursement Department at HII in collaboration with Pharmaceutical Directorate in MoH	HTA Integrated	Regulatory# (It is responsible for pharmaceutical reimbursement)
Belarus	RSPC MT	HTA Integrated	Coordination (Clinical practice guideline, HTA) http://rnpcmt.belcmt.by/index.php?option=com_content&view=article&id=15&Itemid=17
Bulgaria	NCPR	HTA Integrated	Regulatory# http://ncpr.bg/en/home
Croatia	Agency for Quality and Accreditation in Health Care and Social Welfare	HTA Integrated	Coordination http://aaz.hr/en/about-us
	CIHI (Drug Committee and Medical Devices Committee)	HTA Integrated	Regulatory# http://www.hzzo.hr/en/
Cyprus	Drug Committee (MoH)	HTA Integrated	Regulatory± http://www.moh.gov.cy/Moh/phs/phs.nsf/dmlindex_en/dmlindex_en?opendocument#
Czech Republic	SÙKL	HTA Integrated	Regulatory# http://www.sukl.eu/
Estonia	University of Tartu Department of Public Health	HTA Integrated	Advisory http://www.arth.ut.ee/en/hta/health-technology-assessment-estonia
	EHIF	HTA Integrated	Regulatory# http://www2.haigekassa.ee/eng/ehif

Country	HTA body/ organization/ institution	Relationship with Government	Responsibility of the HTA entity and website
Greece	EOF	HTA Integrated	Regulatory# http://www.eof.gr/web/guest;jsessionid=3ac0b2099eba4dad3e9ed781671f
	EOPYY	HTA Integrated	Regulatory# http://www.eopyy.gov.gr/Home/StartPage?a_HomePage=Index
Hungary	TAHD	HTA Integrated	Advisory http://www.eski.hu/index_en.php
Latvia	CHE	HTA Integrated	Coordination and Regulatory http://www.vmnvd.gov.lv/en/news
Lithuania	VASPVT	HTA Integrated	Coordination (systematic reviews http://www.vaspvt.gov.lt
	Diseases, Pharmaceuticals and Medical aids Reimbursement commission and National Health Insurance Fund	HTA Integrated	Advisory http://www.vlk.lt/sites/en/healthcare-in-lithuania/reimbursable-pharmaceuticals-and-medical-aids
Former Yugoslav Republic of Macedonia	MoH	HTA Integrated	Regulatory# http://vlada.mk/node/353?language=en-gb
Moldova	MoH	HTA Integrated	Regulatory# http://www.ms.gov.md/
Montenegro	MoH	HTA Integrated	Regulatory* http://www.mzdravlja.gov.me/en/ministry
Poland	AOTMiT	Arm's length	Advisory http://www.aotm.gov.pl/www/
Romania	MoH	HTA Integrated	Regulatory# http://www.ms.ro/

Country	HTA body/ organization/ institution	Relationship with Government	Responsibility of the HTA entity and website
Serbia	RZZO	HTA Integrated	Regulatory★ http://www.eng.rfzo.rs/
Slovakia	SLOVAHTA	Arm's length	Coordination± (not available)
Slovenia	ZZZS	HTA Integrated	Regulatory# http://www.zzzs.si/indexeng.html
Turkey	SSI	HTA Integrated	Regulatory http://www.sgk.gov.tr/wps/portal/en SSI is in charge of final decision
	MEEC, RC	HTA Integrated	Advisory (MEEC is responsible for assessment, RC is responsible for appraisal)

Note: # the subject of this regulation is the reimbursement determination, for which health economic evidence or HTA may be one of the criteria used; *decision are not informed by HTA; ±:it has had little influence to date in decision making processes, with primarily a strong pharmacoeconomic influence on reimbursement.

Source: Mapping report 2015 (5)

Examples of HTA Bodies/Organizations

Brazil

CONITEC is part of the Ministry of Health (MoH) and aims to advise the MoH on assignments for incorporation, exclusion or modification of health technologies by the federal healthcare system in Brazil (SUS), and the constitution or alteration of Clinical Protocols and Therapeutic Guidelines in the country. CONITEC is an independently functioning government body and its role is coordination and advisory.

Following the submission of an application by a manufacturer, there is a statutory period of 180 days (extendable by a further 90 days) for a decision to be made.

CONITEC is structured by a Secretariat and a Plenary Board. The Secretariat is responsible for managing and coordinating the activities of CONITEC, while the Plenary Board is responsible for issuing recommendations for the MoH. All recommendations issued by the Plenary are submitted for public consultation. The public's consultation suggestions are added in the CONITEC's final report, which is forwarded to the Secretary of Science, Technology and Strategic Inputs (SCTIE) for decision making. The Secretary of SCTIE can also request a public hearing prior to his/her decision.

The Plenary Board consists of 13 members from the following jurisdictions:

- Representatives of each Secretariat of the MoH (7 in total)
- Federal Council of Medicine
- Federal Council of Health
- National Council of State Departments of Health
- National Council of the Municipal Departments of Health
- National Regulatory Agency for Private Health Insurance and Plans
- Brazilian Health Surveillance Agency

The quorum for holding plenary meetings is seven members and the deliberations are adopted by consensus. In case of no consensus, members will be required to vote and a decision will be reached by a majority choice. Members must sign a confidentiality term and declare any conflicts of interest (CoI). Members should declare themselves ineligible to vote if such a conflict arises.

Applicant

The respective society or organization and the MoH.

Topic Selection

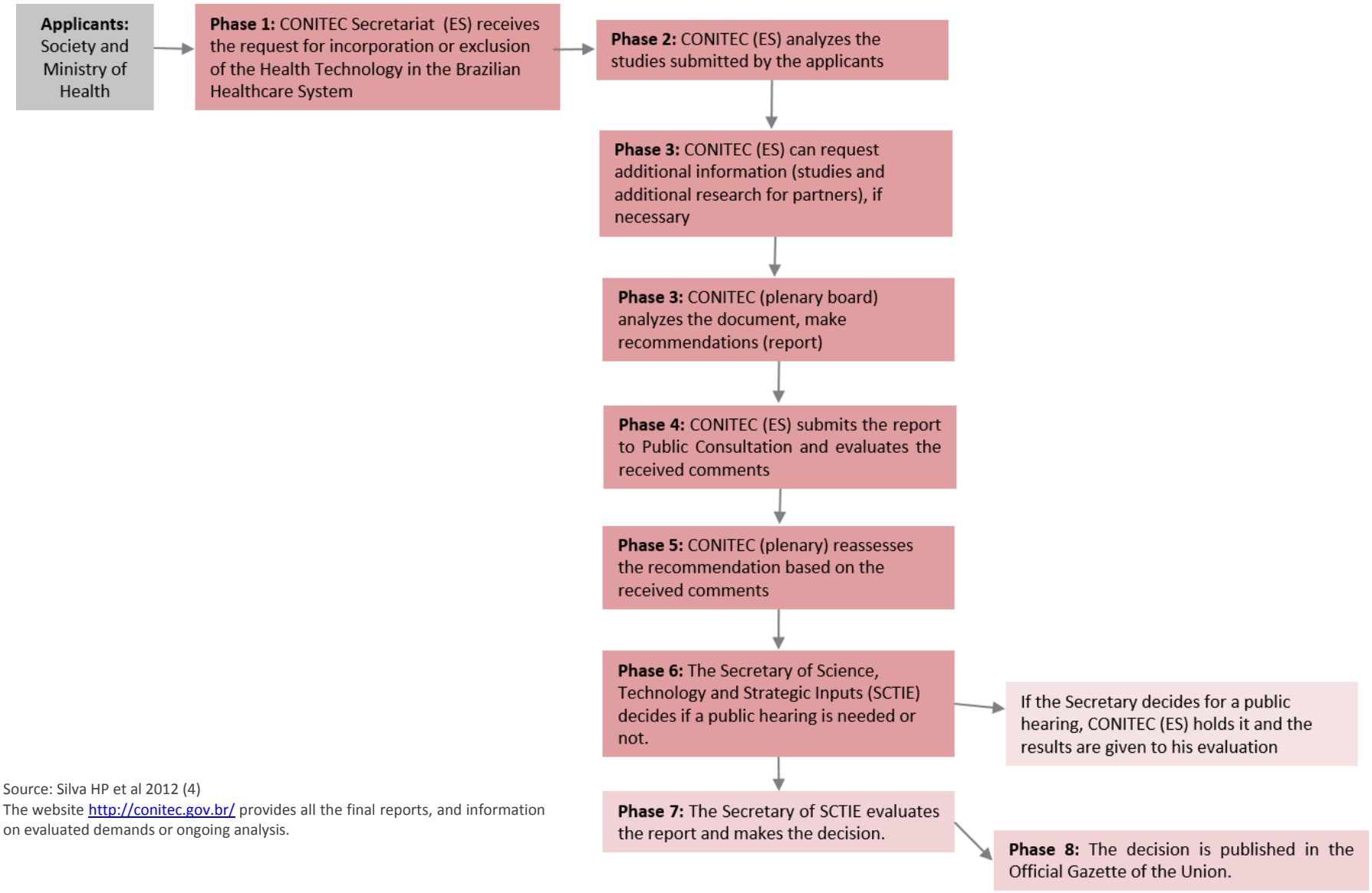
The prioritization process involves technical areas of the MoH and external researchers, based on:

- Epidemiological relevance;
- Policy and Health services relevance;
- Social demand / as requirement of judicial actions of the State.

Price Regulation

The Brazilian experience of an inter-ministerial body for economic regulation of medicines (Câmara de Regulação do Mercado de Medicamentos - CMED) is important because it shows significant efforts to adopt clinical and cost-effectiveness criteria when applying for drug registration. Currently, for a drug to achieve a price higher than the existing alternative in the market for the same indication, it is essential to show (through evidence-based medicine) that the new drug has superior efficacy, similar efficacy with significant reduction in adverse events, or similar efficacy with reduced cost of treatment.

Figure 2. HTA process at CONITEC – Brazil



Source: Silva HP et al 2012 (4)
The website http://conitec.gov.br/ provides all the final reports, and information on evaluated demands or ongoing analysis.

Mexico

CENETEC is a decentralized body of the MoH, which reports directly to the Vice-Minister for Health Integration and Development of the Health. Its main purpose is to produce objective, reliable and timely information based on the best health technology evidence available. CENETEC satisfies HTA needs and management by providing advisory and sectoral coordination by focusing on four areas:

- HTA
- Management of medical devices
- e-Health
- Clinical practice guidelines development

CENETEC aims to use HTA as a tool for issues pertaining to health technologies, which have a significant societal and public health impact. The HTA process in based on the clinical, economic, organizational and social evidence through the HTA reports in order to support decisions to facilitate effective access to health services.

Applicant

Ministry of Health and General Health Council (CSG).

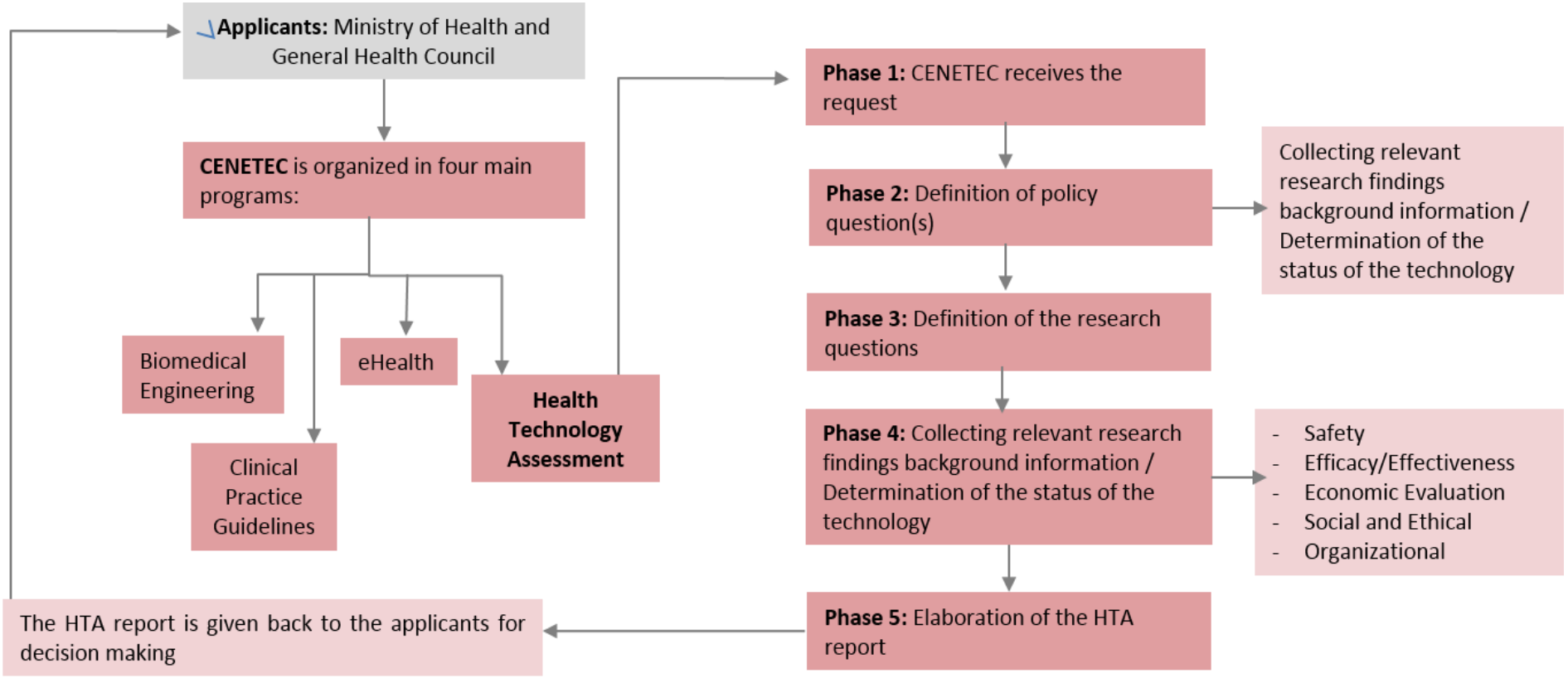
CSG is the decision making body. It receives topics from pharmaceutical companies and other source requests. CENETEC develops the HTA study and delivers it to members of specific committees from the CSG.

The specific committees are who take the decision to incorporate or not the technologies into the positive list.

Topic Selection

Regarding the health programs, the MoH selects the topic accordingly what are considered relevant for the population at the time; CSG analyzes the health supplies as soon as they are submitted.

Figure 3. HTA process at CENETEC-Mexico



Source: CENETEC
The website www.cenetec.gob.mx provides the final reports for HTA and CPG.

Colombia

IETS is a nonprofit corporation, defined as a mixed public-private partnership. It aims to evaluate health technologies in an evidence based way and produce guidelines and protocols on medicines, medical devices, procedures and treatments. IETS makes recommendations to the relevant authorities on technologies that should be covered by public funds through the Sistema General de Seguridad Social en Salud (General System of Social Security in Health).

IETS members include:

- Ministerio de Salud y Protección Social (Ministry of Health and Social Protection)
- Instituto Nacional de Vigilancia de Alimentos y Medicamentos – Invima (Colombian Health Agency)
- National Institute of Health
- Colciencias (Administrative Department of Science, Technology and Innovation)
- ASCOFAME (Colombian Association of Medical Schools)
- Colombian Association of Scientific Societies

IETS has two committees: the Technical Committee, which deliberates on the quality and content of the best available evidence for effectiveness, clinical aspects, cost-effectiveness and possible budgetary impact of different technologies under evaluation. Recommendations are then made to the Health Regulation Commission, and/or other competent authorities.

Technical Committee members

Patient organizations, medical, scientific and related associations, health insurance institutes, institutions providing health services and pharmaceuticals.

- Members may vary depending on the complexity and the content of the topic.
- The committee will be led by a coordinator who must be a physician with knowledge of the technology that is being evaluated and proven experience of managing interdisciplinary groups.
- Both members and the coordinator shall be elected by the Executive Director of IETS.
- Members must declare any conflict of interest at any phase of the evaluation of health technologies and/or production of clinical practice guidelines.
- Members of the Technical Committee may not be the same as the Review Committee.

For each evaluation IETS develops, one technical committee with different experts in the technology under assessment.

The Review Committee only required when the Technical Committee cannot reach any conclusion regarding its report.

Review Committee members are as follows: patient organizations; medical, scientific and related associations, health insurance institutes, institutions providing health services and pharmaceuticals.

- Members may vary depending on the complexity and the content of the topic.
- The committee will be coordinated by the Executive Director of IETS or his delegate.
- Members shall be elected by the Executive Director of IETS.
- Members must declare any conflict of interest at any phase of the evaluation of health technologies and/or production of clinical practice guidelines.
- Members of the Review Committee may not be the same as the Technical Committee.

Applicant

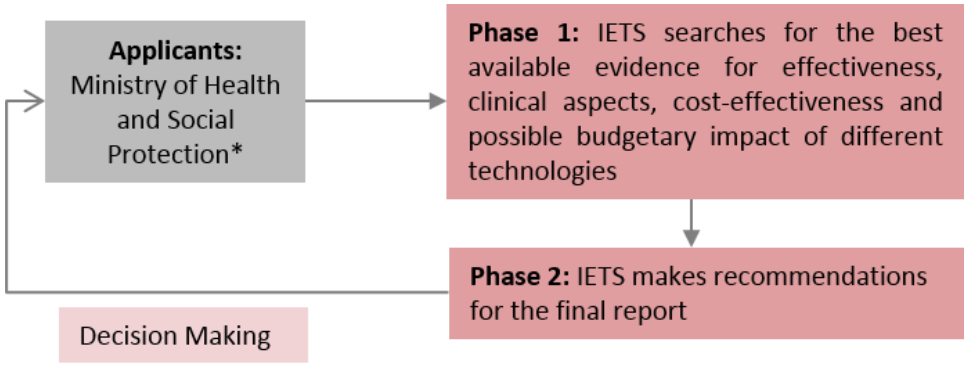
MoH, which is in charge of concentrating all requests made by the pharmaceuticals, scientific societies and other stakeholders in the system.

Topic Selection

MoH has weighting methodology criteria for selecting health technologies to assess, available on MinSalud website (only in Spanish).

The criteria applied in 2013 were burden of disease, reimbursement by approved value and reimbursement by frequency. According to those criteria, MoH published a list of 61 health technologies that should be assessed in 2014 (available on MinSalud website and only in Spanish).

Figure 4. HTA process at IETS-Colombia



*Ministry of Health and Social Protection is in charge of concentrating all requests made by the pharmaceuticals, scientific societies and other stakeholders in the system.

Sources: IETS website and MinSalud website.
The website http://www.iets.org.co/Paginas/inicio.aspx provides the final reports for HTA.

England and Wales

NICE is an independent organization, set up by the Government in 1999. Since 2005, the National Health Service (NHS) in England has been legally obliged to provide funding for medicines and treatments recommended by NICE.

NICE provides guidance on the use of health technologies within the NHS for new and existing medicines, treatments and procedures. In addition to the technology appraisals, it also develops clinical guidelines and quality standards assessments for healthcare services.

It produces four types of guidance: technology appraisals, clinical guidelines, public health guidance and reports on interventional procedures. In producing its guidance, NICE considers both clinical and cost-effectiveness.

Topic selection

- Technologies are selected for appraisal according to the following selection criteria:
  - Burden of disease (population affected, morbidity, mortality).
  - Resource impact (cost impact on the NHS or the public sector).
  - Clinical and policy importance (whether the topic falls within a government priority area).
  - Presence of inappropriate variation in practice.
  - Potential factors affecting the timeliness for the guidance to be produced (degree of urgency, relevancy of guideline at the expected date of delivery)
  - Likelihood of guidance having an impact on public health and quality of life, the reduction in health inequalities, or the delivery of quality programs or interventions.

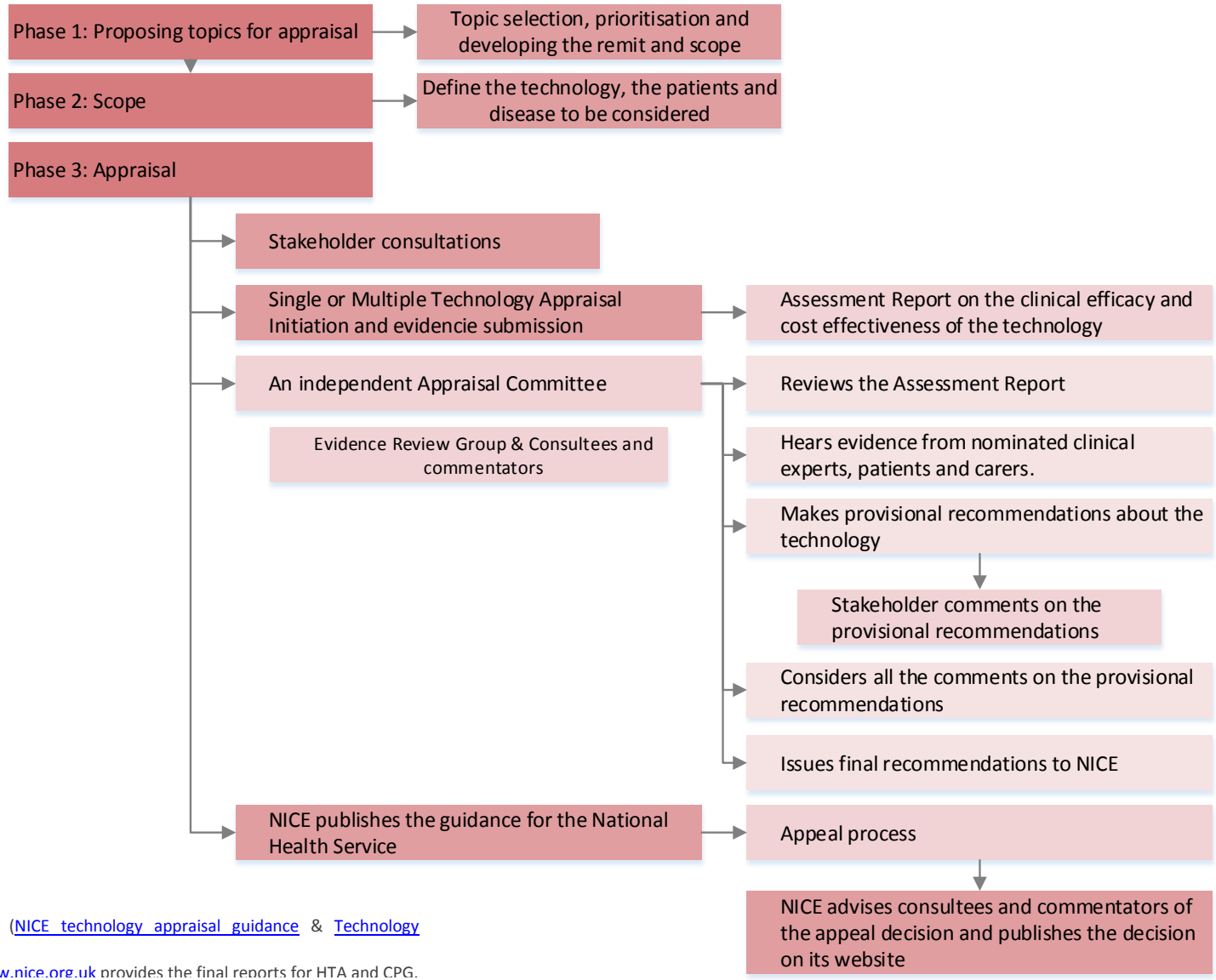
Technology appraisals are recommendations on the use of new and existing medicines and treatments within the NHS. These can be the following: medicines, medical devices (e.g. hearing aids or inhalers), diagnostic techniques (e.g. tests used to identify diseases), surgical procedures (e.g. repairing hernias) and health promotion activities such diabetes management.

NICE usually commissions an independent academic centre to prepare the technology assessment reports for consideration by the Technology Appraisal Committee.

The Technology Appraisal Committee is an independent advisory committee in charge of making the technology appraisal recommendation. Committee members are appointed for a three-year term, and are drawn from:

- The NHS
- Patient and Care Organizations
- Academia
- Pharmaceutical and medical devices industries

Figure 5. HTA process at NICE-England and Wales



Sources: NICE website (NICE technology appraisal guidance & Technology appraisal committee)
The website https://www.nice.org.uk provides the final reports for HTA and CPG.

Poland

The Agency for Health Technology Assessment and Tariff System (AOTMiT) was established in 2005 as an advisory body to the MoH. Since 2009 AOTMiT has been a legally defined body.

The role of AOTMiT is to assess and appraise all medical technologies and services claiming public funding. Recommendations, statements and opinions issued by AOTMiT are based on additional, officially published data, expert opinions, manufacturers' submissions and Polish public payer (National Health Fund) evaluation.

The AOTM assesses and appraises all medical technologies, medicines, medical devices, public health interventions, national and local government health care programmes and other interventions that require public financing.

Topic selection

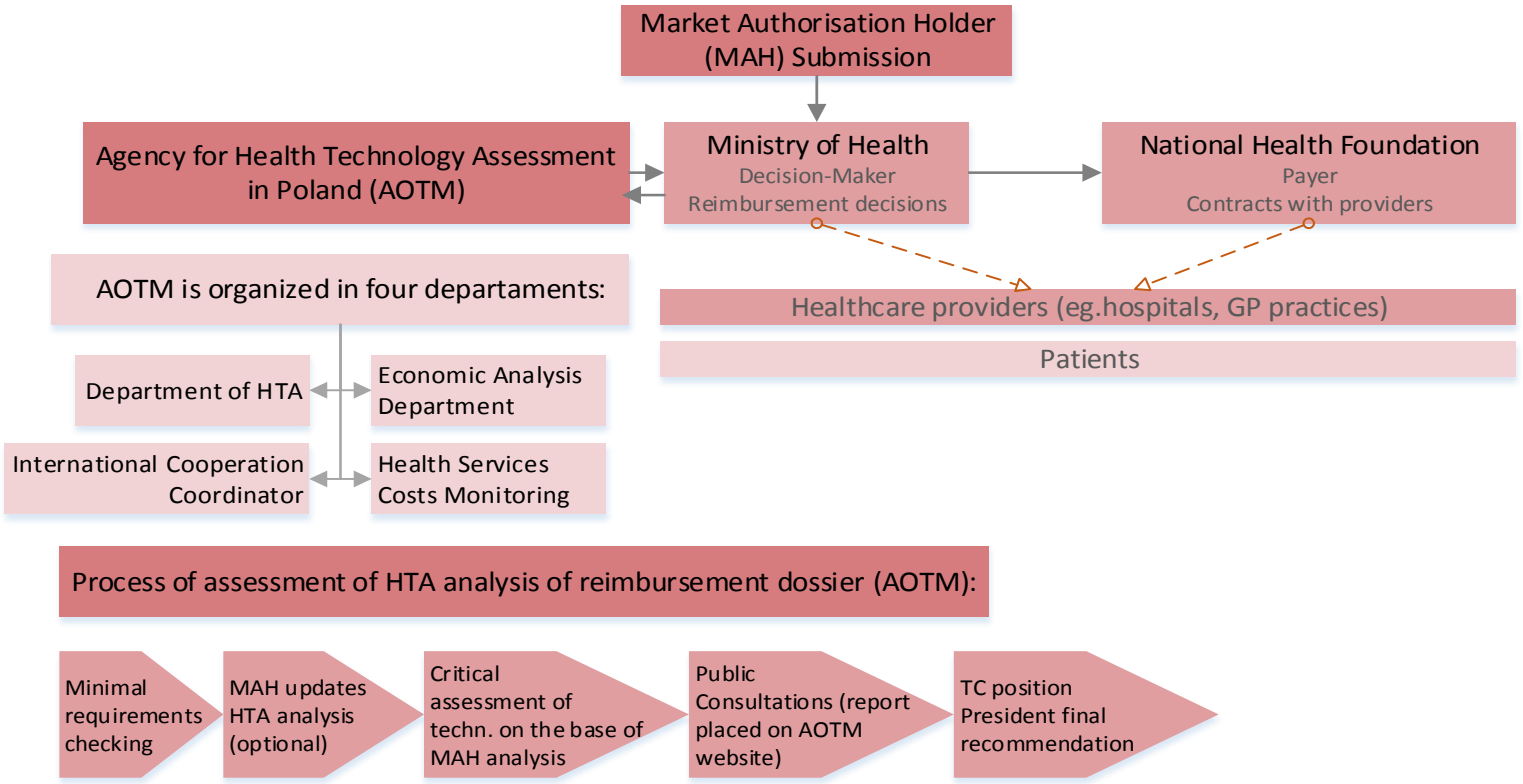
Criteria for selecting technologies to be assessed using HTA are the following:

- Frequency of the clinical condition (prevalence, incidence) (as by law).
- Burden of disease (mortality, morbidity and quality of life related to a clinical condition —LYG, QALY—) (as by law).
- Cost of illness (direct cost health care for a patient per year) (as by current capacity).
- For submission of a manufacturer of medicine/medical device/food supplement.

Assessment is provided by an Analytic Team, using Polish HTA guidelines.

The Consultative Council (CC) is an independent, advisory body with ten highly qualified members appointed by the MoH. Appraisal is prepared by the CC and the President of AOTMiT. Its assessment includes impact of alternative options, social consequences, organizational implications, relative priorities and wider social and ethical aspects.

Figure 6. HTA process at AOTMiT-Poland



Sources: Mapping report 2015 (5) and AOTMiT website

The website sss.aotm.gov.pl or www.aotm.eu provides full-text versions of HTA reports (available in Polish, with abstracts in English)

2. Advantages of HTA Networking

In 1985, the European Office of WHO published several targets for its member states, including one on HTA that stated *"(...) all member states should have established a formal mechanism to systematically assess the appropriate use of health technologies and to verify that they respond to the national health program needs"* (6). In 2012, the Member States of the PAHO approved the first Resolution on HTA and decision-making where the importance of working in networks is specifically mentioned (7). In May 2014, WHO restated its support for sustainable health financing structures and universal coverage, including rational use of medicines and medical devices (8).

Therefore, in an effort for funders and HTA agencies to assume a growing role in priority-setting and health policy processes, the need has also become evident to harmonize the methodology and share evidence and results. This has led to the emergence of various international initiatives whose main objectives are to avoid duplication of efforts. Thus, HTA-networking brings together scientific institutions and experts to promote synergies and achieve the best value of scientific excellence[I]. *"International coordination of the regulatory approval of diagnostics, medical devices, and medical equipment is less well developed, although discussions are currently in progress internationally and within the EU"* (9).

HTA development is closely linked to Ministries of Health, HTA agencies, public health insurance programs and broader academic networks. HTAi examples include: The International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the International Network of Agencies for HTA (INAHTA), the European Network for Health Technology Assessment (EUnetHTA) Joint Action project representing public sector HTA agencies in Europe, the RedETSA (Health Technology Assessment Network of the Americas (Red de Evaluación de Tecnologías en Salud de las Américas) in Latin America and HTAsiaLink (Asian Health Technology Assessment Network) in Asia. Beyond the above, HTA development is linked to international organizations, such as the World Bank or the European Commission (EC). These have garnered an important role in the use and development of HTA in Europe and a number of developing countries (5).

The European Commission has played an increasingly significant role in HTA in its twenty-eight Member States. This is evident in the European Union Commission's High Level Group on Health Services and Medical Care, which in November 2004 concluded that, "HTA has become a political priority and there is an urgent need for establishing a sustainable European network for HTA"(11). In fact, EUnetHTA *"as a result was envisioned as a sustainable European Network for Health Technology Assessment to inform policy decisions, and to connect public national HTA agencies, research institutions, and health ministries, enabling an exchange of information and support of policy decisions by member states"*(6). In some developing countries, four projects have markedly improved coordination of HTA efforts: EUR-ASSESS, HTA-EUROPE, European Collaboration on Health Technology Assessment (ECHTA) and EUnetHTA. Furthermore, important initiatives, and research and

[I] Swiss Network for Health Technology Assessment

collaborative networks belong to the EU's Seventh Framework Programme for Research: AdHopHTA, INTEGRATE-HTA, Advance_HTA and MedtecHTA.

The World Bank has also been active in the field of HTA. It has sponsored several consultations and conferences on HTA, and included HTA in many of its recommendations to countries concerning their health services and countries such as Malaysia, Poland, Romania, the Russian Federation or Serbia have received substantial support from the Bank to develop HTA.

In 2012, the Member States in the Region of the Americas approved the first Resolution on Health Technology Assessment and decision making. At that time, they realized there was a need for establishing Decision-making processes based on HTA, strengthening institutional frameworks and integrating HTA into public policies on health technologies in the Americas (2).

Since then, some advances in the institutionalization of HTA in the region have been noticed, both at national and regional levels. Examples of countries include:

- Argentina, witnessing the creation of a national HTA network (RedARETS) and the consolidation of a coordinating unit (UCEETS);
- Brazil, showcasing the strengthening of a national appraisal commission (CONITEC) and the expansion of a national HTA network (REBRATS) with more than 75 members;
- Colombia, experiencing the strengthening of a national HTA institute (IETS); and
- Chile, creating a national HTA commission (Comisión Nacional Ministerial, ETESA).

Some of the most important international initiatives and HTA Collaborative Projects, from Europe and Latin American regions, are listed below.

Adopting Hospital based HTA in the EU

- Under the 7th Framework Research Program, it brings together 10 partners from nine different countries (hospitals and national agencies): Spain, Denmark, Finland, Switzerland, Italy, Turkey, Estonia, Norway and Austria.
- This project promotes the adoption of technologies with proven value in hospitals, making available the knowledge and tools to facilitate adoption of hospital based HTA initiatives. Also, this project will develop tools for formal coordination among existing hospital-based HTA initiatives and for improved liaison with national and regional HTA agencies
- More information in http://www.adhophta.eu

European Network for Health Technology Assessment

- EUnetHTA performs the function of the scientific and technical cooperation of the HTA Network. It aims to create an effective and sustainable network for HTA across Europe, to help developing reliable, timely, transparent and transferable information to contribute to HTAs in European countries.
- EUnetHTA supports collaboration between more than 50 European HTA organisations through facilitating efficient use of resources available for HTA, creating a sustainable system of HTA knowledge sharing and promoting good practice in HTA methods and processes.
- More information in www.EUnetHTA.eu

The International Information Network on New and Emerging Health Technologies

- It is a collaborative network of 18 member agencies for the exchange of information on important emerging new drugs, devices, procedures, programmes, and settings in health care.
- EuroScan collaborates with organisations with related activities in order to: disseminate information on early awareness and alert systems and activities, avoid duplication, share experiences, methods and outputs and promote the introduction and diffusion of safe, effective and cost effective health technologies in health systems around the world.
- More information in http://euroscan.org.uk/

Advance-HTA

- It is a research project funded by European Commission's Research Framework Programme led by the London School of Economics – LSE Health.
- It is a partnership of 13 members.
- It aims to advance and strengthen the methodological tools and practices relating to the application and implementation of HTA.

EUnetHTA Joint Action 2 (2012-2015) have published a report entitled "Recommendations on the implementation of a sustainable European cooperation on HTA" in which the main factors influencing the scientific and technical cooperation, organizational, governance and technical aspects of the European cooperation on HTA are described. In this document, the different levels of participation in the scientific and technical cooperation on HTA are outlined and discussed:

- *Level 1*. Sharing and exchanging information and methods applied individually, by participating organizations.
- *Level 2*. Contributing to the development, support and application of common tools (e.g. databases, models for structuring and reporting of HTA information and capacity-building activities) and scientific methods (e.g. methodological guidelines and templates) to support HTA production processes.
- *Level 3*. Contributing to the production of joint assessment reports and application of the results of joint assessment reports in the national/regional HTA production processes.

Health Technology Assessment International

- Is the global and international scientific and professional society for all those who produce, use, HTA Network Strategy or encounter HTA.
- HTAi has approximately 1000 members from over 65 countries and embraces all stakeholders, including researchers, agencies, policy makers, industry, academia, health service providers, and patients/consumers. It´s a neutral forum for collaboration and the sharing of leading information and expertise.
- More information in http://www.htai.org/

The Health Technology Assessment Network

- It is a voluntary Network set up under Article 15 of Directive 2011/24. It gathers mainly Ministries of Health or competent authorities responsible for HTA, appointed by Member States. Its scope of activities is on strategic issues.
- It is composed of 28 members, and observer members and observer stakeholders.
- More information in http://ec.europa.eu/health/technology_assessment/policy/network/index_en.htm

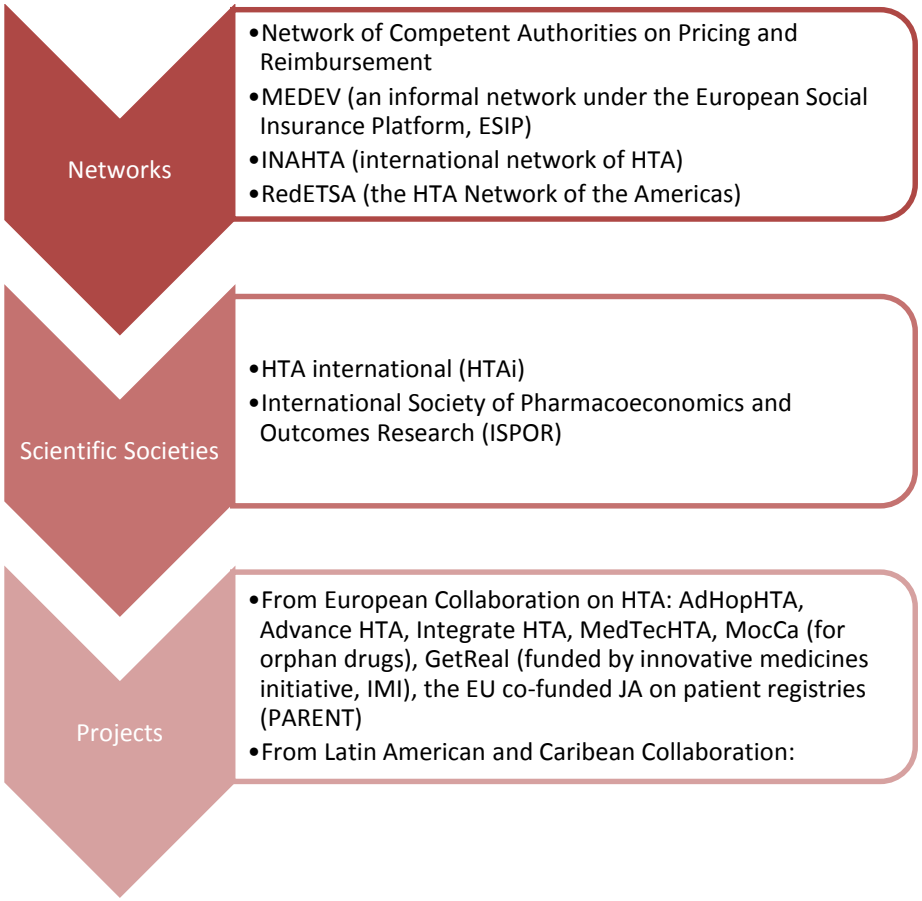
In responses to HTAi demand, a Sub-Group on Developing Countries has been created to share experiences, contribute and support work towards initiation/maintenance of HTA activity in developing countries. HTAi has also a Sub-Group on Information Resources (IRG), which provides the information resources, conducts research, and addresses information management issues that support HTA decision making. Members of the IRG are HTA staff members, from government departments, agencies, for profit and not for profit firms, consultants, experts, and all those who use, provide, or otherwise support HTA information needs. This subgroup have developed the HTAi Vortal, a web based source of HTA information available to anyone.

The International Network of Agencies for Health Technology Assessment

- INAHTA is a network of 55 HTA agencies (from 32 countries including North and Latin America,Europe, Africa, Asia, Australia, and New Zealand) that support health system decision making that affects over 1 billion people in 33 countries around the globe.
- This network connects these agencies to cooperate and share information on the production and dissemination of HTA reports for making evidence-based decisions. It also identifies the methods used and their relation to the formulation of national and regional policies.
- More information in http://www.inahta.org/

The HTA Network in its publication "The Strategy for EU cooperation on Health Technology Assessment (HTA)" has characterized the activities of the HTA Network as follows:

Figure 7. Classification of HTA networking by activities



Source: adapted from HTA Network Strategy

In April 2015, the HTA Network produced a reflection paper on the "Reuse of joint work in national HTA activities". This supports the implementation of the HTA strategy and provides recommendations on how joint work should develop to facilitate national and regional HTA bodies to reuse assessments in national activities.

INAHTA collaborates with the international HTA community and broader global health organizations, including: the World Health Organization (WHO), Health Technology Assessment International (HTAi), The Guidelines International Network (G-I-N) and EuroScan or EUnetHTA.

Integrate-HTA

- Under the EU 7th Framework Research Program, and using palliative care as a case study, this project aims to develop concepts and methods that enable a patient-centred, comprehensive assessment of complex health technologies.
- The INTEGRATE-HTA consortium consists of 7 partners from 5 different countries.
- More information in http://www.integrate-hta.eu

Health Technology Assessment Network of the Americas

- The HTA Network of the Americas has members from 27 institutions and 14 countries (Argentina, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Mexico, Paraguay, Peru and Uruguay)
- Recent activities include the mapping of HTA capacity in the region and opportunities for further development of human resources in HTA. It aims encourage incorporation of health technology based on HTA , as well as development of clinical guidelines and protocols for new technologies. RedETSA has invested in training its members by virtual meetings (webinars) and also short professional exchanges among RedETSA institutions
- More information in http://redetsa.org/

The International Society for Pharmacoeconomics and Outcomes Research

- Founded in 1995 as an international multidisciplinary professional membership society, ISPOR advances the policy, science, and practice of pharmacoeconomics (health economics) and outcomes research. ISPOR is a non-profit public organization for educational and scientific purpose. It is an unbiased organization of 9,500 individual and student members from 114 countries, and over 8,700 affiliate members.
- ISPOR Regional Initiatives Groups (Consortia and Networks) work on developing health economics and outcomes research at a local and / or regional levels (Asia, Latin America, Africa, Arabian, and CEE).
- More information in www.ispor.org

Methods for Health Technology Assessment of Medical Devices

- Under the EU 7th Framework Research Program, this project has the partner of 6 universities and 1 scientific association from Austria, Germany, Italy, Slovenia and UK.
- It is focused on improving the existing methodological framework within the paradigm of HTA for medical devices, and to develop this framework into a tool that provides structured, evidence-based input into health policies. It is expected contribute significantly to decisions on cost-effectivenes, appropriate use and patient access, to medical devices.
- More information in http://www.medtechta.eu/wps/wcm/connect/site/medtechta/home

MEDEV- The Medicine Evaluation Committee

- MEDEV represents the drug experts and pharmacologists of the national social health insurance organisations and other such bodies in 14 EU Member States
- Its purpose is to provide the national health insurance organisations with timely analyses about drug related trends and innovations, both at national and European level. Also, it aims to support the EU activities in formulating drug policies and can offer expert advice to all EU bodies from the earliest stage of the pharmaceutical decision making process to help them analyse the possible impact of drug-related policies on national health schemes.
- More information in www.esip.org

Mechanism of Coordinated Access to Orphan Medicinal products

- The purpose of MoCA working group was to find collaborative ways to identify and assess the value added of orphan medicinal products. Agreement was reached on a final report. This includes "Key conclusions and recommendations", and an indicative set of criteria, such as available alternatives or response rate against which value could be assessed, so as to ultimately facilitate access for patients.

The platform on access to medicines in Europe was one of the three work areas of the Process on Corporate Responsibility in pharmaceuticals. It gathered a number of concrete initiatives intended to facilitate the pricing and reimbursement of innovative treatments after their marketing authorization, or to contribute to a responsible environment for access (within the current legal framework).

These initiatives were translated into several projects allowing all stakeholders to test ideas and develop new concepts. Specifically, the MoCA working group objective was to find collaborative ways to identify and assess the added value of orphan medicinal products. Agreement was reached on a final report. This included "Key conclusions and recommendations", and an indicative set of criteria, such as available alternatives or response rate against which value would be assessed, so as to ultimately facilitate access for patients.

PAtient REgistries iNitiaTive

- The objective is to support the EU Member States in developing comparable and interoperable patient registries in fields of identified importance with the aim to rationalize the development and governance of patient registries. It is also to support the EU Member States in providing information on the relative efficacy of health technologies to enable the rationalization of the HTA process. This avoids duplication of assessments and increases availability and quality of previously localized patient registries data.
- More information in http://patientregistries.eu/parent

HTAsiaLink

- Is a network to support collaboration between Asian HTA agencies, with a focus on facilitating HTA research by accelerating information and resource sharing and developing an efficient methodology for HTA in the region.
- In January 2011, the agreement was reached on establishing the HTAsiaLink and to undertake collaborative research between its 15 members. The founding organizational members are Taiwan Center for Drug Evaluation (CDE), the Health Intervention and Technology Assessment Program (HITAP), and the National Evidence-based healthcare Collaborating Agency (NECA). The HTAsiaLink Newsletter is currently distributed three times a year.
- More information in http://www.htasialink.org/

The Guidelines International Network

- Is an international not-for-profit association of organisations and individuals involved in the development and use of clinical practice guidelines. It facilitates networking, promotes excellence and helps our members create high quality clinical practice guidelines that foster safe and effective patient care. Its networking role is enhanced through annual conferences, region-specific communities and topic-specific working groups in which participants exchange knowledge and improve methodology.
- It is a global network, and since beind founded in 2002, has grown to 100 organisations and 131 individual members, representing 48 countries from all continents
- More information in http://www.g-i-n.net/

3. Social Values and Perspectives of Different Social Actors in Decision-making

As the HTA definition includes an ethical dimension, it is expected that the HTA full report incorporates ethical aspects. To add further complexity to the decision making process, other equally relevant elements that may be classified as social values must be included alongside clinical and economic aspects. Social value is a large concept that includes the subjective elements of the citizen's well-being (12).

When making decisions, one is required to make judgments regarding social and scientific values. While scientific judgments interpret the quality and significance of the available evidence, social values judgments are those related to society (13).

Ethical aspects to incorporate in a Full HTA Report

The appropriate use of (new) health technologies may raise ethical questions. A set of 33 moral questions that are relevant in the HTA was proposed in 2005 by Hofmann, and has guided several ethical analyses. They are presented in the following table:

Table 3. Ethical questions raised in the context of HTA

Ethical questions raised in the context of HTA		
Moral Issues	Q1	What are the morally relevant consequences of the implementation of the technology?
	Q2	Does the implementation or use of the technology challenge patient autonomy?
	Q3	Does the technology in any way violate or interfere with basic human rights?
	Q4	Does the technology challenge human integrity?
	Q5	Does the technology challenge human dignity?
	Q6	Will there be a moral obligation related to the implementation and use of a technology?
	Q7	Does the technology challenge social values and arrangements?
	Q8	Does the widespread use of the technology change our conception of certain persons (e.g., with certain diseases)?
	Q9	Does the technology contest religious, social, or cultural convictions?
	Q10	Can the use of the technology in any way challenge relevant law?

Ethical questions raised in the context of HTA		
	Q11	How does the assessed technology relate to more general challenges of modern medicine?
	Q12	Are there any related technologies that have turned out to be morally challenging?
	Q13	Does the technology in any way challenge or change the relationship between physician and patient?
	Q14	How does the implementation of the technology affect the distribution of health care?
	Q15	How does the technology contribute to or challenge professional autonomy?
	Q16	Can the technology harm the patient?
Stakeholders	Q17	What patient group is the beneficiary of the technology?
	Q18	Are there third-party agents involved?
	Q19	What are the interests of the users of the technology?
	Q20	What are the interests of the producers of technology (industry, universities)?
The Technology	Q21	Are there moral challenges related to components of a technology that are relevant to the technology as such?
	Q22	What is the characteristic of the technology to be assessed?
	Q23	Is the symbolic value of the technology of any moral relevance?

Ethical questions raised in the context of HTA		
Moral aspects of Methodological choices	Q24	Are there morally relevant issues related to the choice of end points in the assessment?
	Q25	Are there morally relevant issues related to the selection of studies to be included in the HTA?
	Q26	Are the users of the technology in the studies representative of the users that will apply it in clinical practice?
	Q27	Are there morally relevant aspects with respect to the level of generalization?
	Q28	Are there moral issues in research ethics that are important to the HTA?
Technology Assessment	Q29	What are the reasons that this technology is selected to be assessed?
	Q30	What are the interests of the persons participating in the technology assessment?
	Q31	At what time in the development of the technology is it assessed?
	Q32	Are there related technologies that have or have not been assessed?
	Q33	What are the moral consequences of the HTA?

Source: adapted from Hofman 2005 (14)

Tools for Ethical Analysis

The Unit of HTA in Madrid (Unidad de Evaluación Tecnologías Sanitarias. Agencia Laín Entralgo[II]) developed a guideline for providing decision makers with a tool to design, implement and create an HTA report that includes evaluation of its ethical aspects. The document (in Spanish) is available on the internet.

INAHTA's Ethics Working Group

The International Network of Agencies for Health Technology Assessment (INAHTA) has an ethics working group that deals with ethical issues in HTA analysis. This group has developed a report comprising eight questions and how to address them, in developing an HTA report or managing the human resources that deal with ethical analysis (15,16).

Table 4. INAHTA's ethical questions for HTA report

	Question
Q1	Can there be a procedure for handling ethical issues concerning technologies being assessed?
Q2	If yes, what would such a procedure look like?
Q3	If no, why not and what else can be done to assure good quality of the assessment of the ethical aspects of a technology?
Q4	What kind of ethical issues and questions are relevant with respect to a given technology?
Q5	How far should HTA go in: a) Displaying values involved in the HTA-process itself? b) Highlighting relationships between knowledge and norms? c) Making recommendations with respect to ethical issues?
Q6	What is the relevance of addressing ethical issues with respect to achieving a successful dissemination? a) With respect to professionals? b) With respect to health policy?
Q7	What kinds of methods might be used to tackle these kinds of issues in an HTA and how might INAHTA help to assist with appropriate methodologies and quality checks?
Q8	What can be done to find or develop skills that would be required by HTA agencies undertaking ethical analyses?
	Does the economic evaluation of the technology contain any ethical problems?
	What are the ethical consequences related to the assessment of the technology?

Source: Adapted from INAHTA's Working Group on Handling Ethical Issues (2005)

INAHTA's Working Group on Handling Ethical Issues – Final Report (2005) can be accessed from INAHTA website.

[II] The HTA Unit from Madrid (Unidad de Evaluación Tecnologías Sanitarias (Agencia Laín Entralgo) no longer exists.

The EUnetHTA Ethical Analysis Model

The European Network for Health Technology Assessment (EUnetHTA) launched a model on ethical analysis (17,18) with six topics and 19 issues that integrate ethics and HTA, presented in the table below.

Table 5. Ethical analysis model by EUnetHTA

Topic	Issue
Beneficence/ non-maleficence	What is the severity level of the health condition the technology addresses?
	What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?
	What are the benefits and harms of the technology for other stakeholders (relatives, other patients, organizations, commercial entities, society etc.)?
	Are there any other hidden or unintended consequences of the technology and its applications for different stakeholders (patients/users, relatives, other patients, organizations, commercial entities, society etc.)?
Autonomy	Is the technology used for patients/people that are especially vulnerable?
	Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles?
	Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used?
	Does the implementation or use of the technology affect the patient's capability and possibility to exercise autonomy?
Respect for persons	Does the implementation or use of the technology affect human dignity?
	Does the implementation or use of the technology affect the user's moral, religious or cultural integrity?
	Does the technology invade the sphere of privacy of the patient / user?
Justice and Equity	How does implementation or withdrawal of the technology affect the distribution of health care resources?
	How are technologies with similar ethical issues treated in the health care system?
	Are there factors that could prevent a group or person from gaining access to the technology?

Topic	Issue
Legislation	Does the implementation or use of the technology affect the realization of basic human rights?
	Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?
Ethical consequences of the HTA	What are the ethical consequences of the choice of endpoints, cut-off values and comparators/controls in the assessment?
	Does the economic evaluation of the technology contain any ethical problems?
	What are the ethical consequences related to the assessment of the technology?

Source: Adapted from EUnetHTA WP8 – HTA Core Model 2.0

Ethics in the Decision Process

The key to successful ethical analysis is integrating it into the HTA so that ethical issues are considered reflectively during the whole assessment process, starting from the planning stage.

(World Health Organization)

Ethics in the decision process is based on three understandings: (16,19,20)

- First, adopting health technologies is related to the consequences of applying the technology in a context, which justifies performing an ethical analysis in the context of HTA.
- Secondly, technologies may influence moral principles, norms, values and/or rules of society that should be addressed by HTA.
- Thirdly, HTA itself is a value-laden process.

When introducing (new) technologies into healthcare systems, resource allocation is critical and may be accompanied by devaluing, abandoning or divesting from other technologies. Decision makers have to balance individual and societal interests and needs. Ethics-based analysis within HTA can provide insights into this and help decision makers interpret information in a practical policy manner (12,21,22).

Tools to Include the Equity Perspective

The principle of equity holds that, all things being equal, all patients have an equal right to receive necessary health care (23). The table below exemplifies equitable decision-making processes.

Table 6. Decision making process considering equity perspective

Description	Example
During [disease scenario], tough decisions will need to be made about which health services [technologies] to fund and which [technologies] to postpone introducing. *Decision makers must attempt to*: • Preserve the equity principle as much as possible between the interests of patients [afflicted with the disease] and those who need urgent treatment for other diseases • Ensure procedural fairness in decision making	*In allocating scarce resources, the value of equity could guide in developing fair criteria for allocation while consideration is given also to compensation for those who will not meet inclusion criteria, yet are entitled to receive care.*

Source: adapted from Thompson 2006 (11)

The Equity-Oriented Toolkit

The Bruyère Research Institute from University of Ottawa is a WHO Collaborating Center for Knowledge Translation and Equity in HTA. It has developed a system whereby emerging countries can implement a "needs-based technology approach", by connecting people's needs and priorities to policy development and implementation. This system is an Equity Oriented Toolkit (23) for HTA, which is an online instrument based on clinical and population health statuses, considering issues of gender, social justice, community participation and socioeconomic differences in health.

The toolkit takes into consideration four main elements with comparative assessment of tools. These elements are: burden of illness, community effectiveness, economic evaluation, and knowledge translation and implementation. It helps equip decision makers with the tools and information required when choosing health technologies that focus on distributional issues to promote equitable health.

Participation of Different Social Actors in the Decision Process

WHO recommends that all stakeholders are identified and nominate an ethics expert. EUnetHTA recommends that an ethical expert should take part in the HTA analysis and is responsible for reporting on the ethical challenges (12). This increases transparency and reduces bias (10).

The second edition of "Social Value Judgments: Principles for the Development of NICE Guidance" describes the principles and judgments that NICE and its advisory bodies should follow:

- In designing or revising the processes it uses to develop its guidance and recommendations
- In making decisions about the effectiveness and cost effectiveness of interventions, especially where such decisions affect the allocation of NHS resources.

Therefore, these principles are intended for three audiences: those involved in designing or revising the processes for developing NICE guidance, NICE's advisory bodies responsible for developing individual items of NICE guidance, and NICE's stakeholders and the wider public. These principles enable the audiences to understand the social values that underpin NICE guidance.

NICE subscribes to the widely accepted moral principles that underpin clinical and public health practice, taking also into account the problem of distributive justice, or how to allocate limited healthcare resources fairly within society. This is in addition to the legal obligations and fundamental principles underlying HTA guidance.

Methods by which to improve resource allocation are included in stating that "HTAs should adopt a broad societal perspective to optimize efficiency and societal benefit and to avoid and identify potentially distorted clinical decisions and health policies resulting from adoption of narrower perspectives used by various healthcare systems stakeholders" (24). Therefore, there are advantages in using a broader perspective for HTA, even for decision-making bodies with limited budgetary means. HTA must meet the needs of multiple decision makers, taking into account the benefits and costs associated with various components and facilitating the validity of the overall analysis (26).

Patient Perspective & Citizen Participation

It is important to clarify that the patient is different from the public. While patients have narrower disease interests, the public may have broader interests as they do not – necessarily – suffer from a condition.

Public and patient involvement in the decision making process is widely recognized as crucial, mainly because patients are those who reap the rewards of health technology approval (27). Adding the patient perspective in the HTA outputs has been a challenge to many, if not most, HTA bodies (28). Among Americas' countries, Brazil, Canada and Colombia are examples of countries that involve citizens and patients in their processes. In Brazil, CONITEC has guaranteed public engagement through public consultation since 2012. By law, representatives from society, which includes patient associations, have to take part in the advisory board. Also, after the recommendation is provided, the report is available online and citizens can voice their opinion through public consultation. This contribution is made online and one can choose between 2 formularies: contributing with experiences/ sharing opinion, and contributing with scientific inputs. CADTH in Canada has included patient input to the Common Drug Review since 2010. On their webpage, CADTH publishes both the Common Drug Review and the deadlines for filling patient comments for each drug. For oncological drug reviews, a guide for patient advocacy groups is offered in CADTH's website (also available in pdf format). In Quebec, the Stakeholder Consultation is part of the good practice of INESSS and pursues different objectives to developing clinical practice guidelines, HTA and social services. In Colombia, according to IETS' regulation, citizen participation is guaranteed. Neither health technologies, nor clinical guidelines are evaluated and/or developed without the participation of the stakeholders to whom they are addressed.

The public can submit comments through the internet at any stage of the HTA process and the elaboration of CPGs (29).

In Europe, some examples were found in England, France and Scotland. In Scotland, Patient and Public Involvement Group (PAPIG) requested the Scottish Medicines Consortium (SMC) to hold explanatory discussions. These aim to explain the role of the SMC regarding the access to medicines in the country, how patient opinion is considered in their decisions, and learn about their understanding of and expectations for the provision of medicines in the national healthcare system.

The Role of HTAi Interest Sub-Group on Patient and Citizen Involvement in HTA

HTAi (Health Technology Assessment international) is a global and international scientific and professional society for all those who produce, use, or encounter HTA. The HTAi Interest Sub-Group on Patient and Citizen Involvement in HTA was established in 2005 aiming to provide patients with an understanding of their role in the decision making processes and also of their expectations (30-32). In 2008, HTAi Interest Sub-Group on Patient and Citizen Involvement in HTA launched a guideline explaining patients' role in the decision making process in lay terms. This publication is available online in numerous languages through the following link or in English.

Examples of Patient and Citizen Involvement

CONITEC – Brazil

As part of the decision making process, CONITEC performs a mandatory public consultation of all HTA recommendations (see Chapter II.1). Subsequently, the inputs are analyzed, added to the HTA report and may (or may not) change the previous recommendations. Below are some examples where the inputs received from these public hearings impacted directly on CONITEC's recommendations:

1. Erlotinib for non-small cell lung cancer*:* the Erlotinib assessment report recommended against its incorporation into the Brazilian healthcare system and was sent to public consultation (open online for 20 days). Eighty contributions were received during this period, of which 41 were patients and patient association inputs (most of them were willing to express and share personal experiences about the treatment success). Other inputs criticizing the report included QALYs and prices of the comparative drug in the national healthcare system.

These contributions were analyzed and added to the HTA report. The final recommendation was in favour of incorporating Erlotinib in the Brazilian healthcare system. Further information:

CADTH – Canada

CADTH receives a drug submission, and posts a Call for Patient Input on their website. Patient groups can submit their input about the technology under evaluation. Typically, only patient groups may submit input, however there is currently a pilot process for submissions from individual patients and caregivers. The *Patient input template* is available for patients who want to submit their opinion.

1. Tocilizumab for the treatment of rheumatoid arthritis: the Canadian Drug Expert Committee (CDEC) recommended subcutaneous tocilizumab to be listed for the treatment of patients with moderately to severely active rheumatoid arthritis (RA). Patient input information is described in the report.
2. OnabotulinumtoxinA (Ona A) for Overactive Bladder: the Canadian Drug Expert Committee (CDEC) recommended Ona A to be listed for the treatment of patients with overactive bladder. Patient input is described in the report and was taken into consideration in the recommendation (available from CADTH website).

INESSS - Canada

1. Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes - In order gain users' and health professionals' experiences with the pump, a self-questionnaire (patients) and face-to-face interviews (professionals) were conducted. All information is presented in the report and helped the agency (AETMIS) in its recommendation.

CENETEC – Mexico

1. Screening for the detection of prostate cancer in a population using Asymptomatic Prostatic Specific Antigen (PSA) and Digital Rectal Exam (DRE) - Both ethics and social aspects were taken into account in this HTA report.
2. Stent for abdominal aortic aneurysms - In this HTA report, both ethics and social aspects were taken into account when analyzing the cost-effectiveness of the technology in the context of the Mexican healthcare system.

IETS – Colombia

1. Mometasone (nasal inhalation) as rhinitis treatment – A study question and protocol was published on IETS' website to receive comments from stakeholders.
2. Validity of proof of glucocerebrosidase enzyme activity for Gaucher disease – A study question and protocol was published on IETS' website to receive comments from stakeholders.

According to IETS, in both cases, patients participated in the formulation of the research question and therefore had direct impact on the methodology of the evaluation.

NICE – England

1. Ranibizumab for treating diabetic macular oedema- The Appraisal Committee understood from patient experts that visual impairment has a substantial negative impact on quality of life and activities of daily living in people with diabetic macular oedema. Patient experts also emphasised the loss of independence and its implications for employment. They described the significant impact of visual impairment on emotional wellbeing, which can lead to depression and, in some instances, suicidal thoughts. The Committee understood that any relief from these problems would have a positive impact on the lives of people with diabetic macular oedema (available from NICE website)

2. Treatment for Psoriasis - Clinical research showed that the severity of psoriasis was the most important factor affecting patient's quality of life. However patients indicated the location of psoriasis on their body was more important (e.g. face or joints). The Appraisal Committee took into account the patient perspective from which they were able to review the evidence and question the relevance of the clinical research findings (20) (available from NICE website).

Transferability

Both the EUnetHTA model and Moral Questions were developed as an international collaboration considering relevant and transferable values and issues (21). However, when ethical issues are country-specific, or related to factors like a 'social contract', the country's healthcare financing system or the country's GDP growth prospects, the transferability can be properly judged (12).

Judicialization

An increasingly common phenomenon among Americas' Region countries is '*judicialization', which carries with it considerable ethical and budgetary implications.* This is a litigation process in which there has been an increase of claims for health interventions before the courts by rights guaranteed by the Constitution of each country. This type of litigation commonly occurs in countries where the health system is structured under principles of universality, equity and equality of health services; principles which resonate with the healthcare systems in the Americas. The three countries with the highest rates of judicialization in the region are Brazil, Costa Rica and Colombia.

Reivez et al analyzed and compared (34) the judicialization scenario among these three countries. The authors found out that prescriptions are the main support of the judges' decision and the majority of the claims are favorable to the claimant. Furthermore, regarding the ethical aspects of this litigation, many judges determine the right to health as an individual, not collective, right.

Therefore, it is important to encourage interdisciplinary work between judiciary and medical areas and heavily invest in the educational training

of the judiciary framework. This will help achieve decisions that are in line with collective, or population, benefit.

Costa Rica

The jurisprudential orientation in Costa Rica only accepts prescriptions as evidence.

> "In repeated statements, the Court has pointed out to the Caja Costarricense de Seguridad Social (Costa Rican Department of Social Security) ,which has to prevail the judgment of the treating physician as to the administration of drugs that are not part of the Official List of Drugs, considering violation of the fundamental rights of health and life, and the right to social security, the refusal to provide it"

Colombia

According to the Colombian Constitutional Court, judges do not have jurisdiction to order drugs that have not been prescribed by the physician. A significant majority of the claims are favorable to the claimants (34).

In its website, the MoH recognizes that, despite being high, the rate of judicial demands for health services has been stable over the last three years (35).

Brazil

In Brazil, according to its Constitution, *"Health is everyone's right and the State's duty."* Guided by this article, many judges recognize the individual rights over the collective. As a result, the number of lawsuits for health services has increased (36,37).

There has been substantial research in this area, mainly because when considering the mandatory purchase due to judicial sentences, the MoH loses its power of bargaining and that incurs in an over budget expenditure. On top of that, many lawsuits regard high cost medicines (37,38).

The Brazilian Network for HTA (REBRATS – Rede Brasileira de Avaliação de Tecnologias em Saúde) maintains up-to-date information on this topics, to disseminate awareness through its website.

Initiatives

SaluDerecho is a collaborative learning initiative on rights to health and universal health coverage in Latin America, led by The World Bank. In 2014 an online book was released, mainly focused on the judicialization phenomenon in Latin America.

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III. HTA Products

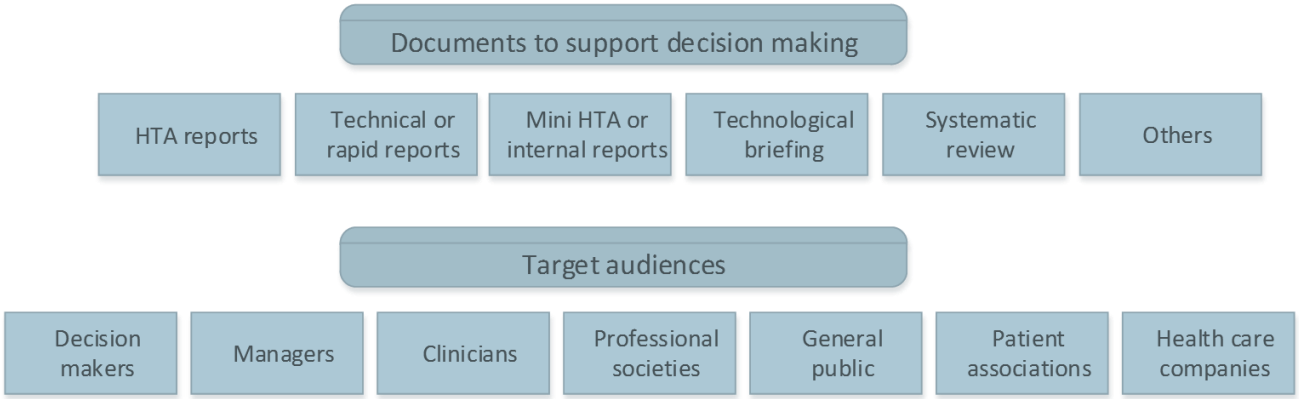
1. Types of Study or Evidence for the Decision-Making Process

Documents to Support Decision-Making

There are more than 200 public and private organizations undertaking HTA, including bodies created by ministries of health, private agencies, professional organizations and universities. All of them aim to aid decision making around the introduction and appropriate use of new and existing technologies (1).

Guidance is created in different contexts using different approaches. They also vary considerably in scope and methodology, according to the perspective, setting and end-user target, be it clinicians, administrators, decision makers, insurers or public bodies. They are published in many formats as assessment reports (ARs), technical reports (TRs), technological briefing (TBs) and clinical practice guidelines (CPGs) (1).

Figure 1. Types of documents to support decision-making and target audiences



Source: Strategies for the diffusion and dissemination of health technology assessment (HTA) products (1)

The main product in an HTA is the classic HTA report. This is based on a systematic literature search, a clinical and economic assessment of the health technology, and some assessments on other relevant aspects (organisational, social or legal). A classical HTA-report usually includes a discussion of the results and limitations, or with a recommendation for decision makers (2).

Table 1. Examples of documents to support decision making of organizations

Country	Organization	Document to support decision making	Example
Brazil	CONITEC	Technical Report with economic evaluation	Abatacept for Rheumatoid Arthritis therapy (3)
Colombia	IETS	Technical Report	Diagnostic utility of molecular exams for Alzheimer Disease (4)
Argentina	IECS	Technical Report	

Source: Elaborated by the authors

Most studies are systematic reviews based on a summary of primary studies, and take the form of ARs, TRs, TB and CPGs. In all studies, a specific health technology is assessed/ appraised based on efficacy, effectiveness, efficiency, safety and its impact on the healthcare system (1).

In CESEE countries, Croatia, for example, to publish a full HTA report and its summary in English. It would also publish short advice to different stakeholders (Minister of Health and Social Welfare, Croatian Institute for Health Insurance, hospitals, health professionals and patients) in different languages (Croatian and layman) (5). From countries in the Americas Region, HTA reports are found in many formats, such as systematic reviews, economic evaluation, technical / rapid reports (the latter being the most common) (6). Examples can be easily found onlineas IETS in Colombia, CONITEC in Brazil and IECS in Argentina, all produce technical reports.

Some of the main types of HTA report and its distinctive features are described in the following table:

Table 2. Main types of HTA report and its distinctive features

Type of HTA report	What is/are	Objective	End-users	Dissemination vehicles
Technical reports (TRs), Rapid Reviews and Rapid Assessments	Documents in which systematic reviews are used to assess specific aspects of a technology	To assess specific aspects of a technology To respond to specific queries	Health care managers, health professionals, patient associations, the general public and industry	Internet publication of agency web pages, e-mailing and publication in journals
Technological Briefing (TBs)	Brief documents that summarizes the most relevant scientific evidence on new and emerging technologies, so as to provide support for decision-making.	To detect new technologies Prioritisation in research Control, adoption and diffusion of technologies in the promotion phase, whether by the health care industry, professionals or opinion leaders.	Health care managers, regulatory bodies, research funding entities, insurers, health professionals, patient associations, general public and industry.	Internet publication on web pages of the respective issuing agencies, with TB being sometimes published in journals of international scope, vaguely connected to health technologies specialised databases: The International Information Network on New and Emerging Health Technologies (EuroScan) Other non-EuroScan institutions (the University HealthSystem Consortium, UHC, in the USA)

Source: adapted from Strategies for the diffusion and dissemination of health technology assessment (HTA) products (1)

The mutual and differential elements in each type of common technical HTA report are summarized in the following table from INAHTA website.

Table 3. Mutual and differential elements in each type of common technical HTA report according to INAHTA, 2015

Elements	HTA report	Mini-HTA	Rapid Review
Describe the characteristics and current use of the technology	Always	Always	Always
Evaluate safety and effectiveness issues	Always	Always	Always
Determine the cost-effectiveness of the technology e.g. through economic modelling (when appropriate)	Always	N/A	N/A
Provide information on costs/financial impact	Always	Always	N/A
Discuss organisational considerations	Always	N/A	N/A
Conduct a comprehensive systematic literature review or a systematic review of high level evidence	Always	Always	N/A
Conduct a review of only high level evidence or of recent evidence and may restrict the literature search to one or two databases	N/A	N/A	Often
Critically appraise the quality of the evidence base	Always	Always	Optionally
Address ethical, social and legal considerations	Optionally	Optionally	N/A
Provide information on costs/financial impact	N/A	N/A	Optionally

Source: adapted from INAHTA (7)
N/A: Not applicable.

The time required for preparation of the report varies according to the type of the report and the amount of evidence available regarding the technology being assessed. A HTA-broad report, based on a complex problem or area of disease, has a time frame between 1.5 to 2.5 years. An HTA-focused report, based on a specific problem and focused on one technology can be developed within a short time frame (1 year). In both of them, external peer review provides quality assurance (8).

The EUnetHTA collaborative project has developed the so called "HTA Core Model", a general understanding of contents and structures of different HTA reports. The HTA Core Model currently comprises five applications, organized according to their primary use (diagnostic technologies, medical and surgical interventions, pharmaceuticals or screening technologies). The application differs from Core and Rapid HTA, depending on whether it contains an extensive assessment of health technology or, on the contrary, a narrower analysis of the health technology.

In NICE in the UK, the technology appraisals take one of two forms: single or multiple technology appraisal (STA and MTA) (9). The main differences can be observed in the table below:

Table 4. Main differences between single and multiple technology appraisal held by NICE

Technology appraisal	Cover	Timelines	Stakeholders (evidence)
Single	Single technology for a single indication Normally covers new technologies	37 weeks	The company The Evidence Review Group Consultees Clinical Experts Patient Experts
Multiple	More than one technology, or one technology for more than one indication	54 weeks	An independent academic group Consultees Clinical experts NHS commissioning experts Patient experts

Source: adapted from NICE website

CADTH develops two different types of Health Technology Management Products, besides the HTA report. The *rapid response service* provides rapid reviews of health technologies to support timely health care decision making and the *optimal use* delivers a HTA report with recommendations from an expert panel.

In addition to HTA reports in the several forms mentioned above (including short or rapid response reports, mini-HTA, etc.), there are agencies that have also specialized in the production of other reports (10) in order to:

- Develop consensus information. These reports are prepared on specific topics of common interest, in which there is insufficient scientific evidence or it is contradictory; they can be part of clinical practice guidelines.
- Report on emerging technologies. These are synthesis documents in which a brief description of the emerging technology and an estimate of its potential impact is performed (in terms of health, costs and organizational impact). Early warning of new technologies early in their "life cycles" alerts decision makers of future technologies. It has a time frame of 2-4 months.
- Produce "patient decision aid" tools - It provides accurate information on clinical options and outcomes relevant to patients' health. It is based on available scientific information and adapted into plain language to empower citizens in the decision making process.

SBU in Sweden classified its HTA reports in Yellow and Alert Reports (11). Both are systematic assessments, but while the first one focuses on an entire medical field, the second assesses an intervention that is usually new or in the process of being introduced. The extension of the report and the number of experts involved are different, while the publicity of the report or the procedures to approve the final assessment are similar. The other type of HTA report, the SBU remarks, are summaries with comments on current reviews of international medical knowledge. This facilitates decision makers' and health professionals' access to current and relevant international knowledge.

Guidelines

A guideline is a document that contains recommendations and is designed to help users choose among several potential possibilities (12). HTA guidelines must include the principles and methodological requirements for conducting HTA in a country. These guidelines are important to facilitate consistent decision-making and assist manufacturers in preparing their submissions. Most of the existing guidelines focus on the economic evaluation part of the HTA report.

Economic Evaluation (EE) guidelines are included in a reimbursement application, a guide for designing and conducting a study, or a template for evaluating the economic study reports (13).

Many countries around the world have published EE guidelines to support reimbursement decision. EE are very similar, however differ in discount rate values, perspective of the analysis, time horizon, or type of sensitivity analysis required (13).

Where can HTA/EE Guidelines be found in the Americas' Region?

Recently, formally incorporating EE in health assessment as a decision making tool has in the region of the Americas (14). Methodological guidelines regarding HTA and/or EE were found in websites of the Ministry of Health, HTA bodies and institutions of the following countries: Argentina, Brazil, Canada, Chile, Colombia, Mexico and Uruguay, as shown in Table 5. According to a survey conducted in 2013/2014 (15), Bolivia, Costa Rica, Cuba, Paraguay and Peru confirmed use of methodological guidelines for EE (16); however this document is not available on Internet. The information was endorsed by phone contact with respondents. Bermuda and Venezuela stated the guidelines were being developed by the time this document was completed.

Barbados, Belize, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Jamaica, Nicaragua, Panama, St. Lucia, Saint Martin, Suriname and Trinidad and Tobago are countries that do not have any guidelines for HTA or EE. The Bahamas and Venezuela were working on their HTA guideline by the time this toolbox had been developed.

Table 5. List of institutions in the Americas' Region, by country, that have any economic evaluation guideline

Country	Institution	Has EE Guidelines?	Guidelines available on internet?
Argentina	MoH	Yes	https://sisa.msal.gov.ar/sisa/#sisa
Bolivia	MoH	Yes	No
Brazil	MoH	Yes	http://rebrats.saude.gov.br/diretrizes-metodologicas
Canada	CADTH	Yes	https://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf
	INESSS	Yes	https://www.inesss.qc.ca/en/publications/documents-methodologiques.html
Chile	MoH	Yes	http://desal.minsal.cl/wp-content/uploads/2013/09/EE_FINAL_web.pdf
Colombia	MoH	No	
	IETS	Yes	http://iets.org.co/MANUALES
Costa Rica	MoH	No	No
	CCSS	Yes	
Cuba	MoH	Yes	No
Mexico	MoH	Yes	http://www.csg.gob.mx/descargas/pdfs/2015/GCEEE_2015.pdf
Paraguay	MoH	Yes	No
Peru	MoH	Yes	No
Uruguay	MoH	Yes	No

Source: Mapping report 2015 (6)

Argentina

Argentina has two guidelines: one for EE and one for the Preparation of Reports of Health Technology Assessment. Both documents are MERCOSUR based. The Economic Evaluation Guideline (Directrices Metodológicas para Estudios de Evaluación Económica de Tecnologías Sanitarias) was approved in 2009 (17,18). The MoH/ UCEETS have developed a checklist for critical reading of an EE report. It aims to help

decision makers assess the methodological quality and applicability of (local and international) EE. This is part of the ongoing assessment of health technology for the rational and equitable use of resources in the country.

Brazil

The first edition of the Brazilian Guideline for Technical Scientific Report was published in 2007 and it is now in its fourth edition (19). Besides this, Brazil has seven more guidelines: Guideline for Economic Evaluation (20), Guideline for Systematic Reviews and Meta-Analysis of Diagnostic Accuracy Studies, Guideline for Budget Impact Analysis (21), Tools for Adaptation of Clinical Guidelines (22), Guideline for Systematic Review and Meta-Analysis of Comparative Observational Studies on Risk Factors and Prognosis, Guideline for GRADE System (Manual of the Graduation of Evidence Quality and Strength of Recommendation for Health Decision-Making) (23) and Monitoring the Technological Horizon in Health (24) within the Brazilian HTA Network. The latest one concerns disinvestment and is on public consultation from July 23rd to Oct 1st 2015. However, the content can be accessed online through the link (see Chapter V.2 Disinvestment/Reinvestment& Countries Examples).

Canada

CADTH in Canada has a Guideline for Economic Evaluation of Health Technologies and also a Guideline for the Costing Process. INESSS, which is the *Institut National d'Excellenceen Santé eten Services Sociaux* in Quebec, Canada, does not have a guideline for economic evaluations but it has a guideline for study interpretation. The institute also has a guideline to interpret systematic review studies (25,26).

Chile

In March 2013 Chile approved its methodological Guideline for Economic Evaluation of Health Interventions financed entirely by the Chilean Ministry of Health (27).

Colombia

In Colombia, the only guideline found for the economic evaluation of healthcare technologies was launched by the *Instituto de Evaluación Tecnológica en Salud* – IETS in 2014. This institute is a private, nonprofit corporation with mixed participation, created in Law 1438 in 2011. Its members are the Ministry of Health and Social Protection, the INVIMA, the National Institute of Health, Colciencias, ASCOFAME and the Colombian Association of Scientific Societies (28).

Mexico

In February 2015, Mexico launched the Guideline for Driving Economic Assessment Study for Updating the Basic Catalog Input in Health Sector (29).

Bolivia, Paraguay and Uruguay

Like Argentina, other Latin American countries such as Bolivia, Paraguay and Uruguay use the Guideline for Reporting of Health Technology Assessment launched by MERCOSUR in 2008 (12,13).

ISPOR is an international multidisciplinary professional membership society founded in 1995 that aims to disseminate the advances of policy, science, and practice of pharmacoeconomics/health economics and outcomes research (30).

ISPOR has a global repository of all existing pharmacoeconomics guidelines that are annually updated on its website (13).

Where can HTA/EE Guidelines be found in the European Countries?

In CESEE countries, HTA institutions from Slovakia, Poland, Estonia, Croatia, Slovenia, Russian Federation and Hungary have published guidelines to outline the methodological requirements for conducting HTA in the country. There is also a Baltic guideline for EE of pharmaceuticals used in Latvia, Lithuania and Estonia. Most guidelines describe process and data requirement for reimbursement process.

The European network for Health Technology Assessment (EUnetHTA) has recently published a draft guideline for a general framework for conducting EEs among EUnetHTA members (31). The main purpose of the guideline is to set a general framework for EUnetHTA to increase its transferability among EUnetHTA members. This guideline also provides information about the similarities and differences between guidelines for EEs used in European countries. These guidelines are based on commonalities between members. The Information of European guidelines is listed below.

Table 6. EU countries with methodological guidelines for conducting HTA

Country	Institution	Name of document and access to the website
Austria	BIQG LBI-HTA	Methodenhandbuch für HTA Version 1.2012, Bundesinstitut für Qualität im Gesundheitswesen (BIQG) und Gesundheit Österreich GMbH, 2012 Guidelines on Health Economic Evaluation, Consensus paper, Institute for Pharmacoeconomic Research, 2006.
Belgium	KCE	Belgian guidelines for economic evaluations and budget impact analyses: Second edition, KCE Report 183C, Belgian Health Care Knowledge Centre, 2012
Croatia	AAZ	Guide for the Economic evaluation of health technologies, In: The Croatian Guideline for Health Technology Assessment Process and Reporting, 2011
Czech Republic	SUKL	SP-CAU-028 – W. Postup pro hodnocení nákladové efektivity
Denmark	DHMA	Health Technology Assessment Handbook
		Report on Guidelines for Health economic analyses of medicinal products, Sunhedsstyrelsen
England	NICE	Guide to the methods of technology appraisal 2013
		Medical Technologies Evaluation Programme Methods guide
		Diagnostics Assessment Programme, 2011 manual
Finland	THL	Preparing a health economic evaluation to be attached to the application for reimbursement status and wholesale price for a medicinal product, Application instructions TTS 10.6.2013
	Ministry of Social Affairs and Health, Pharmaceuticals Pricing Board	Guidelines for preparing a health economic evaluation, Annex to the Decree of the (201/2009)
France	HAS	Choices in Methods for Economic Evaluation 2012
Germany	IQWiG	General Methods for the Assessment of the Relation of Benefits to Costs (Version 1.0 dated 19/11/2009)

Country	Institution	Name of document and access to the website
Hungary	GYEMZI	Az Emberi Eroforrások Minisztériuma szakmai irányelve az egészség-gazdaságtani elemzések készítéséhez (The Technical Guideline for the Making of Health-Economic Analyses by the Ministry of Human Resources) Egészségügyi Közlöny 2013/ 3. 1314-1334.
Ireland	HIQA	Guidelines for the Economic Evaluation of Health Technologies in Ireland,), 2014 Guidance on Budget Impact Analysis of Health Technologies in Ireland Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland
Italy	AIFA AGENAS ASSR	Italian Guidelines for Economic Evaluation Italian Association of health care economists, 2009
Latvia Lithuania Estonia	NHS VASPVT Department of Public Health of UTA	Baltic guideline for economic evaluation of pharmaceuticals 2002
The Netherlands	ZIN	Guidelines for Pharmacoeconomic Research in the Netherlands, 2006
Norway	NOKC	Guidelines on how to conduct pharmacoeconomic analyses, Norwegian Medicines Agency (NOMA), 2012 Økonomisk evaluering av helsetiltak – en veile der, Helsedirektoratet, 2012
Poland	AOTMIT	Guidelines for conducting Health Technology Assessment (HTA) (Polish guidelines), Agency for Health Technology Assessment, Version 2.1 (Part 4 & 5), 2009 REGULATION OF THE MINISTER OF HEALTH of 2 April 2012 on the minimum requirements to be satisfied by the analyses accounted for in the applications for reimbursement and setting the official sales price and for increasing the official sales price of a drug, a special purpose dietary supplement, a medical device, which do not have a reimbursed counterpart in a given indication (Polish regulation), Minister of health, 2012

Country	Institution	Name of document and access to the website
Portugal	INFARMED	Guidelines for Economic Drug Evaluation Studies, INFARMED, 1998
Russian Federation	ANO NC HTA	Protocol on the Procedure for Clinical and Economic Evaluation of Drugs which are submitted for inclusion into reimbursed drug lists, Moscow (2010)
Scotland	SMC	Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF), Scottish Medicines Consortium, 2013
Slovakia	Ministry of Health of the Slovak Republic	Guidelines for Economic Evaluation of Health Care Interventions (December 2011)
	IER	Regulation on classifying drugs onto positive list for public financing, Health Insurance Institute of Slovenia
Spain	MoH	Spanish Recommendations on Economic Evaluation of Health Technologies (Spanish version: Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias), 2010
	Catsalut	Guía y recomendaciones para la realización y presentación de evaluaciones económicas y análisis de impacto presupestario de medicamientos en el ámbito del CatSalut, Catsalut, 2014
Sweden	SBU	General guidelines for economic evaluations from the Pharmaceutical Benefits Board, The Dental and Pharmaceutical Benefits Agency (TLV), 2003 Guide for companies when applying for subsidies and pricing for pharmaceutical products, Version 2.0, Decided 2/3/2012, Utvärdering av metoder i hälso- och sjukvården – en handbok, Swedish Council on Health Technology Assessment (SBU), 2013
Switzerland	Swiss Federal Office of Public Health	Handbuch betreffend die Spezialitätenliste (including Appendices), Bundesamt für Gesundheit, 2013 Handbuch zur Antragstellung auf Kostenübernahme bei neuen oder umstrittenen Leistungen

Sources: ISPOR website (2), Mapping report 2015 (6), EUnetHTA EE guideline (20)

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Transnational HTA

According to mapping results, many countries frequently use reports from other settings to help in their decisions. They are usually in line with findings from other authors' (31-37) health technology assessments (HTA) produced in another context. They are usually updated and adapted to the local scenario so that it can be used for the decision-making (29,32,38).

The aim of adaptation is to allow an HTA body in one country to apply an HTA report produced in another. This saves time and money by avoiding inefficiencies of duplication and enables transfer of knowledge between countries (31,39). Toolkits and guidelines regarding adaptation of HTA reports for use in different settings have been developed worldwide (31-37).

IETS (Instituto de Efectividad Clínica y Sanitaria), an Argentinian academic and independent non-profit institution devoted to research, education, and technical cooperation in healthcare, was identified in LAC region as an HTA institution that has contributed with the dissemination of transferability issues in the region (14-31). According to the institute, in Latin America HTA reports produced in other countries have been used when developing local reports and also by decision makers to guide their decisions (29,31).

Transferability of economic evaluations across settings can be an issue, considering that many variables as such as local incidence, burden of disease, availability of healthcare resources, prices, costs, preference values and standards of care may vary among jurisdictions (29,14). However, analysts should evaluate if settings are sufficiently similar to have their economic data grouped and analyzed together (38,29,40). Some countries have their own methodological economic evaluation guidelines where they mention the usage of economic data produced outside their local context. Nonetheless, as those documents are updated (and given the importance of the issue) they start to be more restrictive in accepting data from other settings (29).

Opportunities

When adapting HTA reports, the benefits of multiple reports on the same health technology saves time, effort and money. Adaptation is even more important in contexts or countries where resources are scarce and the disease burden is high (31,32).

When that occurs, it is possible to improve general understanding of cultural differences such as societal principles and rules, organization of healthcare and also clinical practice. By adapting HTA reports, the collaboration between HTA agencies, organizations and institutions can be facilitated by exploring strategies for sharing development of documents (32,41).

Problems with Transferability of HTA Reports

Differences in common clinical practice, cultural values, professional issues, legal principles, political matters, budget constraint, threshold values and others that be barriers to adaptation of HTA reports (14,32,39,41). Because of these differences, health technologies can have different profiles of cost effectiveness in different settings and be cost-effective in one place and cost-ineffective in another (37,42).

From the mapping results, it is possible to conclude that due language barriers between geographies, especially in European countries – decision makers may have trouble understanding the report analysis.

The use of HTA reports from other settings without an established methodology may be risky, given the possibility of reproducing any errors the reference report may contain (14,31).

In order to avoid these problems and cooperate in information exchange, certain organizations have been created between HTA agencies and institutions. Examples are discussed in the next topic.

Best Practice to Address the Transferability of HTA Reports

The best way to ensure the transferability of HTA reports is through clear processes with a methodology of adaptation (29,31).

The MoH/ UCEETS have developed a checklist for critically reading economic evaluations. It aims to help decision makers assess the methodological quality and applicability of (local and international) economic evaluations.

Role of ISPOR

In 2004, ISPOR's Health Science Policy Council recommended that the transferability of economic data would be considered by the board of directors. The full article is available at Transferability of Economic Data: When Does a Difference Make a Difference? be considered by the Board of Directors (38). In this document the authors define guidelines for accepting data from another setting considering existing national guidelines (43).

Role of EUnetHTA: the EUnetHTA Work Package

The European Network for Health Technology Assessment (EUnetHTA) (44) has developed a toolkit to support HTA agencies adapt HTA reports from other countries, regions or settings for their specific use. The pdf format is available online. One of its limitations is that it does not manage adaptation of HTA reports that are considered as primary research (32).

The first section of this toolkit has eight questions and aims to evaluate the relevance of a report for adaptation. The second section is called *"main part"* and has five domains: the technology's use, safety, effectiveness, economic evaluation and organizational elements (32,44).

Role of INAHTA: the INAHTA checklist

The checklist consists of 14 questions and was developed as an aid for writing reviewing and adapting new HTA reports in a more transparent way (21). INAHTA checklist questions specifically on adaptation have been incorporated into the EUnetHTA toolkit (32,47). The inconvenience is that only those who are part of the network have access to this document. However, the link below refers to a free online article on how to write a HTA report Toward Transparency in Health Technology Assessment – A checklist for HTA Reports.

References for Transferability of HTAs and EE

- The HTA Adaptation Toolkit (32): this is *a transferability checklist.*
- Transferability of economic evaluations across jurisdictions (38): in this document, *ISPOR Task Force on Good Research Practices proposes a procedure that determines the most suitable methodology for adapting cost-effectiveness across jurisdictions*
- A decision chart for assessing and improving the transferability of economic evaluation results between countries(36): this is *a tool to assess the transferability of economic evaluations that consists of a decision chart and a transferability checklist.*
- Analysis of the eligibility of published economic evaluations for transfer to a given health care system: this is the *definition of five indicators to assess transferability of economic evaluations to different healthcare systems. The authors conclude that to increase the transferability of economic evaluations between different settings, collaboration has to be strengthened, and methodologies standardized.*
- Guidelines for completing the EURONHEED transferability information checklists(33): this is a *transferability checklist.*
- Transferability of health technology assessments and economics evaluations: a systematic review of approaches for assessment and application(37).*This is a review of seven papers focused on approaches to transferability assessment of economic evaluations across different settings. The authors propose a list of critical transferability factors including quality, transparency of methods, the level of reporting of methods and results, and the applicability of the treatment comparators to the target setting.*
- Transferability indices for health economics evaluations: methods and applications (45): this is an *index to measure the degree of transferability of economic evaluations results. (Free text not available online).*

Examples of transferability of EE of health technology

- Jit M, Bilcke J, Mangen MJ, Salo H, Melliez H, Edmunds WJ, et al. The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe. Vaccine. 2009;27:6121-8.
- Steuten L, Vallejo-Torres L, Young T, Buxton M. Transferability of economic evaluations of medical technologies: a new technology for orthopedic surgery. Expert Rev Med Devices. 2008;5:329-36.
- Wolfenstetter SB, Wenig CM. Economic evaluation and transferability of physical activity programmes in primary prevention: a systematic review. Int J Environ Res Public Health. 2010;7:1622-48.

2. Structure and content of a HTA Report

Structure

Since the Renaissance era, scientists would share their research findings in letters; this process of sharing discoveries has evolved. Thus, in recent decades, publishing scientific papers in the IMRAD format (Introduction, Methods, Results and Discussion) has become the currency of scientific knowledge-sharing (49). As part of its objectives, this standardization facilitates effective collaboration, replication of the results and sharing information. These help overcome two barriers: variation in the extent and scope of the analysis, and the differences in reporting the results.

Thus, although HTA agencies worldwide share a common set of principles and methodological approaches, the structure of HTA reports varies considerably between different organisations according to their national regulations, individual work processes, and context. To facilitate this standardization, some guidelines have been highlighted:

- The HTA Core Model (50).
- Guidelines for Authors of CADTH Health Technology Assessment Reports (51).

Other tools for the appraisal of HTA reports are:

- INAHTA checklist: Hailey D. 2003 (52)

Taking into account the similarities and differences between the documents, a possible structure of a HTA report is presented below:

1. **Authorship**: for the authorship designation, the recommended tool is from The Committee on Publication Ethics (COPE): How to handle authorship disputes: a guide for new researchers.
2. Executive Summary: a summary of all parts of the document presented. It has a delimited extension.
3. Introduction:
    a. Background/setting: provides an overview of the disease, epidemiology, current clinical practice, and the rationale and context within which it was produced.
    b. Health Problem and Current Use of the Technology: this part should describe the following topics of interest: target conditions, target groups, epidemiology and the availability and patterns of technology use.

This part is closely related to the scope. It is important to note that when it comes to making a decision on a technology, international experiences of this technology in other countries are often taken into consideration, therefore, epidemiology and priorities of those countries should be considered.

4. Methodology**:** once the research question has been formulated, the next step is to answer how to deal with it. To facilitate the transferability of results (key principle 9 of Drummond) (53), and improve the transparency of the report (key principle 2 of Drummond) (53) the process should be described in detail:
   - Process for reviews of clinical efficacy/effectiveness reports: the CADTH offers a preferred approach to reviewing clinical efficacy/effectiveness reports; CONITEC also published a methodological guideline on how to develop a rapid HTA. (See Chapter III).
   - Process of economic evaluation: (For guidelines on economic evaluation, see Chapter III.1. For Process of economic evaluation see Chapter III.2).
   - Other processes: to cover other potential aspects of HTA reports.

One should always consider that, depending on the type of HTA reports, all the parts of the document do not necessarily need to be addressed. For example a rapid HTA does not include economic aspects of the technology (see Chapter III.1. Types of HTA).

5. Results**:** see Chapters III.2. Systematic review and III.2. Economic evaluation.
6. Discussion of methods and results should provide information on: summary of results, limitations, generalizability of findings, health services impact (where applicable) and knowledge gaps.
7. Recommended lecture: Docherty M et al 1999 (54).
8. Conclusions**:** provide a brief response to each objective. Make them clear, concise, consistent and compelling and draw conclusions based on the evidence.
9. Dealing with conflicts of interest in HTA process**:** for different actors have confidence in published reports, there must be a clear and transparent process of declaring conflicts of interests when developing an HTA report. The international Committee of medical journal editors has a Form for Disclosure of Potential Conflicts of Interest.
10. References**:** some of the statements and methodological aspects must be supported by a bibliographic reference. You should choose those references that are considered more appropriate for readers to evaluate the results. There are several styles of references, the most commonly used are the Vancouver style references: and APA style references.
11. Annex**:** the Annexes or appendices must contain additional information such as literature search strategies, large tables and figures, etc.

Scope

The selection of the health technology to be evaluated is determined by the agency and is chosen based on cost of illness, prevalence and incidence, burden of disease, ethical implications, and legal features, among others. According to the mapping study the three most mentioned aspects are (6): prevalence/incidence, burden of disease and ethical, legal or social implications.

Taking into account the fact that HTA reports are used as tools to aid decision making, several aspects must be considered: who initiated the report? Who commissioned it? Why is an assessment needed at this point in time? What decision is it going to support? Who represents the primary target audience for the report? (55).

All these elements lead to the definition of the scope. The 'scoping' process determines the appropriateness of the proposed topic and defines in detail the limits of the evaluation process (50). According to the Key principles of Drummond (2008) (53), the goal and scope of the HTA report should be explicit and relevant to its use. The scope must clearly and explicitly identify the decision on which the HTA will be focused.

This is a critical part of the process because it determines the nature and content of the assessment. The purpose of a scope is to provide an evaluation framework. This uncovers the questions to address by considering the clinical variables, cost-effectiveness and other relevant aspects of the health technology. Thus, decisions made during the scoping should be considered throughout preparation and presentation of the HTA report. Furthermore, according to Drummond (2008) the scope must be circulated to all stakeholders in order to constructively critique, and potentially influence the aforementioned process (53). According to the HTA Core Model, the scope is structured in the following way (56):

- Technology and its intended use: a sufficiently detailed description of the technology to differentiate it from other technologies currently available in the country.
- Target condition (disease or health condition): a name and a brief description of the disease or health condition.
- Target population: individuals who have the disease or who are in (low/high) risk of having the disease. People who could benefit from the incorporation of technology.
- Comparison: it is necessary to specify how the comparison is being made (against another specific technology, management pathway without the technology, usual care, not doing anything, or a placebo intervention). An HTA report is used to display the results of the comparison between technology/technologies that are already established in the market to a new one.
- Main outcomes for each domain: to ensure overall clarity of the project scope (see Chapter III.2. Efficacy, Effectiveness, Safety).

For the definition of scope, it is important to consider the ethical aspects and conduct an ethical analysis accordingly. The ethical domain considers prevalent social and moral norms and values relevant to the technology in question. It involves an understanding of the consequences of implementing (or not) a health technology (see Chapter II.3. Social Values and Perspectives of Different Social Actors in Decision Making).

Efficacy, Effectiveness, Safety

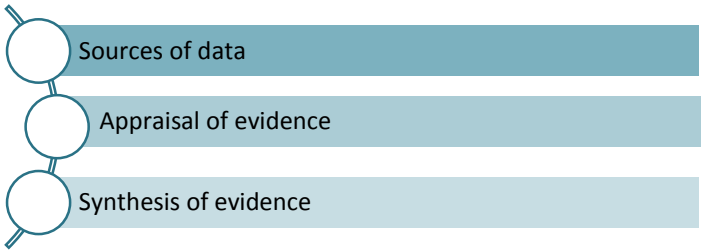
Efficacy and Effectiveness are the basic starting points in HTA and are defined as the benefit of using a technology, programme or intervention in a specific situation under ideal conditions or under general or routine conditions.

The evaluation of both concepts is linked to safety. HTAs assess benefits, risks and harms. The approach used is that ofnet benefit approach, indicating benefits minus harms, caused by a technology and the certainty of the evidence.

Benefit-Risk-Balance or Benefit-Harms-Balance is defined as *"an evaluation of the positive therapeutic effects of the medicinal product in relation to its risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment"* (57,58). Hence, the guiding question, considering the elements of efficacy or effectiveness, safety, net benefit and cost is*, "is it worth it?"*(53).

In the process of assessment, the aspects of safety and efficacy or effectiveness should be taken into account when defining the research questions, and to that end, the common steps to all three stages (59):

Figure 2. Process assessment



Source: elaborated by the authors.

For a broad definition of these concepts, please refer to the Glossaries published by various organisations. International Health Technology Assessment (HTA) Glossary, National Information Center on Health Services Research and Health Care Technology (NICHSR), or Glossary for Core HTA adaptation by EUnetHTA.

Drummond et al (53) states that one of the basic principles of HTA should be to consider a wide range of evidence and outcomes. For that, HTA requires use of data from experimental, quasi-experimental, observational, and qualitative studies. Furthermore, integration of both endpoint and validated surrogate data, and assessment of the incremental impactand trade-offs of multiple clinical, economic and social outcomes in clinically relevant populations (60).

Safety

In HTA, safety means any unwanted or harmful effects caused by using a health technology from the perspective of risk-benefit or net benefit for individual patients, but also to inform policy makers (59). There are many possibilities of within safety evaluations. Focusing on one or another aspect will depend on the type of technology being evaluated. The next table shows the safety domain and an example of the research questions:

Table 7. Safety domain and an examples of the research questions

Domain	Examples of research questions
Patient safety	How safe is the technology in relation to the comparator(s)?
Occupational safety	What kind of occupational harms can occur when using the technology?
Environmental safety	What kind of risks for public and environment may occur when using the technology?
Safety risk management	How does the safety profile of the technology vary between different generations, approved versions or products?

Source: adapted from HTA Core Model 2.1-EUnetHTA 2015 (57)

From the safety domain perspective, technology assessment is an assessment of the potential harms (adverse events) that can be caused by the use of that technology. Various elements can be identified (57):

- Direct (morbidity/ disability directly related to the use of technology) or indirect harm (insufficient training or experience, inappropriate patient selection).
- Harms classified according grade of fatality or intensity: mild, moderate, serious or severe (61).
- Operator- or setting-dependent and patient-dependent harms: knowledge, skills and behavior.
- Individuals or group harms: patients and/ or family, health care professionals, public and the environment.
- Harms classified according to dose- relatedness or time-relatedness.
- Known or unexpected harms.
- Risk is an estimate of the probability of the harms.
- Causality of harms.

Though Randomized Clinical Trials (RCTs) are considered to have the most sound methodological base of trial designs, they are not always the most appropriate to report adverse events (62). This calls into question the most appropriate trial design to determine safety for HTA. The context in which trials are carried out is not in routine clinical practice, the number of patients is usually small, follow up period is short and there are difficulties in quantifying latency periods, amongst other limitations. Observational studies often report relevant information about both common and rare adverse events.

Data sources for outcomes related to safety are routinely collected, such as from regulatory authorities such as the FDA or other clinical databases. (53). Thus, review of the different databases is encouraged to complement other sources.

Main document databases query

- Centre For Reviews And Dissemination Of University Of York (Crd)
- The Cochrane Library
- Trip Database
- Embase
- Ovid
- Medline
- The Joanna Briggs Institute,
- Summarized Research In Information Retrieval For Hta (Sure Info), EUnetHTA

Safety can be summarized as, the frequency of adverse effects, relative risk, or the number needed to treat to proceed to one episode of harm (63).

Safety is one of the key elements to consider when adapting HTAs to different contexts (64). In this regard, NICE has published a toolkit offering a number of recommendations on adaptation of HTA, highlighting a list of questions to ask when considering the adaptation of information and/or data on safety (More information in Development of a toolkit and glossary to aid in the adaptation of health technology assessment (HTA) reports for use in different contexts by NIHR HTA programme and EUnetHTA HTA Adaptation Toolkit).

Efficacy

Evaluating efficacy requires review of data from RCTs. To that end, the Cochrane Collaboration conducts systematic reviews, considered of high methodological quality, for the evaluation of HTA. If during the HTA process, a systematic review showcasing the effectiveness of the health technology is found, then extending the search will probably not be necessary. If the review is of high methodological quality, the most recent publication should be updated (59).

Types of studies appropriate for HTA use produce results that may be extrapolated to daily clinical practice. The most recommended studies are pragmatic RCTs because of their high level of methodological quality. Pragmatic trials seek to answer the question, *"does this intervention work under usual conditions?"*, whereas explanatory trials are focused on the question, *"can this intervention work under ideal conditions?"* (65). Explanatory RCTs would target efficacy evaluation (66).

Interesting resources

- Systematic Review Data Repository (SRDR) by AHRQ
- Browse the Health Technology Assessment Database by Cochrane Library

Effectiveness

Evaluating efficacy is not always feasible which is why effectiveness is distinguished. Drummond et al (53) state that important information relevant to HTA is obtained from quasi- or non-experimental data and observational studies.

The most commonly used effectiveness measures are those related to mortality, morbidity, and quality of life. Some examples of research questions linked to these measures are as follows:

Table 8. Examples of research questions linked to effectiveness measures

Domain	Examples of research questions
Mortality	What is the effect of the technology on the mortality due to causes other than the target disease?
Morbidity	How does the technology affect symptoms and findings (severity, frequency…) of the disease or health condition?
Test – treatment chain	Is there an effective treatment for the condition the test is detecting?
Change – in management	How does the technology modify the need for hospitalization?
Function	How does the use of the technology affect activities of daily living?
Quality of life	What is the effect of the technology on disease – specific quality of life?
Patient satisfaction	Was the use of the technology worthwhile?
Patient safety	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?
Test accuracy	Is there evidence that the replacing test is more specific or safer than the old one?
Benefit – harm balance	What are the overall benefits and harms of the technology in health outcomes?

Source: adapted from HTA Core Model 2.1-EUnetHTA 2015 (57)

A number of measures are used to describe the treatment effect. The most frequently used measures are comparison of groups; generally the intervention group versus the control group or new technology and the gold standard. The measure of risk is ratio or relative risk, relative risk reduction, and absolute risk reduction or number need to treat.

A key element in the HTA process is the selection and definition of endpoints. Needs Based ToolKit for Health Technology Assessment (67) includes a number of questions relevant for the critical assessment (methodological standards) for Studies of the Efficacy of Therapeutic or Preventive Health Interventions (68).

The effectiveness (including efficacy) domain is a consideration in the adaptation of HTA reports for use in different contexts (see Chapter II.1 and links included in section Safety domain related with adaptation of HTA).

Interesting resource

- Effective Health Program by AHRQ

Endpoints

The selection of outcome variables or endpoints[1] is established by the evaluation objective. The next table shows good endpoint characteristics:

Table 9. Examples of characteristics of good endpoints

Characteristics of a good endpoint	
Objective	Active follow-up
Reproducible	Easy to interpret
Sensitive/specific	Free of errors of ascertainment or measurement
Unbiased	Stable
Clinically relevant	Observable independent of assignment
Chosen a priori	

Source: adapted from Day S 2008 (68)

[1]Health Information and Quality Authority (HIQA) (2011): *An endpoint must be clearly defined and measurable. It must be reliable and valid. An endpoint should be relevant to the condition being treated and sensitive to change*

Clinical Endpoints

The choice of clinical endpoint must be justified on the basis of a clear link between the disease process, technology and endpoint (69). Clinical endpoints can be intermediate or final. The measures most commonly used for the assessment of efficacy or effectiveness are mortality, morbidity, and health related quality of life.

Efficacy studies tend to favour condition-specific endpoints with strong links to the mechanism of action. This is also related to the fact that follow up times of the intervention/technology tend to be short. Effectiveness studies tend to require more time for follow up and comprehensive endpoint measures that reflect the range of outcomes. These include treatment benefits relevant to the patient and payer, including improvement in ability to function and quality of life (70).

In the evaluation of clinical endpoints in HTA, HIQA (69) proposes the following critical questions:

Table 10. Critical questions

Critical questions
Is the clinical endpoint clearly defined?
Is there a clear mechanism of action between the technology and the clinical endpoint?
Is the clinical endpoint objectively or subjectively measured?

Source: HIQA 2011 (69)

Surrogate endpoints

A surrogate or intermediate endpoint[II] must have a clear biological or medical rationale, or have a strong or validated link to a final endpoint of interest. The magnitude of the effect on the surrogate should be similar to that of the final endpoint (69). These are related to biomarkers and intermediate endpoints, which are more common in clinical trials than in observational studies. They are also used in assessing partial results of the benefits or risks of the new technology (71).

The advantages of using the Surrogate endpoints in the assessment of efficacy or effectiveness are listed below:

[II] "A measure that is used as a substitute for a clinical endpoint of interest such as morbidity and mortality. They are used in clinical trials when it is impractical to measure the primary endpoint during the course of the trial, such as when observation of the clinical endpoint would require long follow-up. A surrogate endpoint is assumed, based on scientific evidence, to be a valid and reliable predictor of a clinical endpoint of interest. Examples are decrease in blood pressure as a predictor of decrease in strokes and heart attacks in hypertensive patients".

Table 11. The advantages of using the surrogate endpoints

Advantages of using the Surrogate endpoints	
Faster and easier to study	Cheaper
Follow up time required shorter than for others clinical outcomes	Proving effect on direct endpoint may not be feasible
Faster drug development	

Source: Sullivan EJ (72)

HIQA (69) proposed the following critical questions regarding surrogate endpoints to evaluate the adequacy of these measures:

Table 12. Critical questions to evaluate the adequacy of surrogate endpoint measures

Critical questions
Has a surrogate endpoint been used for convenience?
Does the surrogate have a clear biological or medical rationale or have a strong or validated link to a final endpoint of interest?
Can the biomarker be reliably detected?
Is the magnitude of the effect on the surrogate similar to that on the final endpoint?

Source: HIQA 2011 (69)

Some examples of subrogate endpoints

- Hypertension: arterial blood pressure: surrogate for CVA, MI, heart failure.
- Cholesterol and triglyceride levels for atherosclerotic disease.
- HIV: CD4 count or viral load: surrogate for complications of HIV.
- Glaucoma: intraocular pressure: surrogate for loss of vision.
- Diabetes Mellitus: blood sugar: surrogate for survival / complications.
- Thrombolytic therapy for MI: clot lysis, patency rate, LVEF: surrogates for survival / functional status.

Source: FDA. Guidance for Industry. Patient-Reported Outcome Measures 2009 (71)

Often, in the process of HTA extrapolation of results of some studies takes place, with the potential biases and limitations that this may entail.

Thus, Drummond et al (53) state the importance of undertaking a suitable review of relevant information in HTA. Especially with regards to outcome measures of study designs, weighing the evidence according to its estimated validity and generalizability, and handling errors and biases.

Composite Endpoints

This type of measure consists of two or more single events combined in one outcome measure showing overall treatment effect. A change in a composite endpoint should be clinically meaningful. All of the individual components of a composite must be reliable and valid endpoints (69).

According to some systematic reviews in RCTs, the use of this type of endpoint tends to be problematic (73,74) since the combination of objectives and measures may create certain confusion. Components are often unreasonably combined, inconsistently defined, with no standard definition, and inadequately reported (75). The authors (73-75) argued that treatment effects often vary, and typically, the effect would be less significant for the most relevant component and vice-versa.

HIQA (69) proposed the following critical questions regarding composite endpoints to evaluate the adequacy of these measures.

Composite endpoints Examples:

- Cardiovascular death or hospitalization for heart failure.
- "MACE" (Major Adverse Cardiac Events): cardiovascular death, non-fatal MI, and non-fatal stroke. Although the MACE composite endpoints are used in research on cardiovascular events, some authors recommend not using it (75).

Table 13. Critical questions to evaluate the adequacy of composite endpoint measures

Critical questions
Does the composite endpoint really measure treatment effect for a disease?
Does the use of a composite endpoint solve a medical problem or is it just for statistical convenience?
Are the individual components of the composite endpoint valid, biologically plausible, and of importance for patients?
Are the results clear and clinically meaningful? Do they provide a basis for therapeutic decisions? Does each single endpoint support the overall result?
Is the statistical analysis adequate?

Source: HIQA 2011 (69)

Patients Reported Outcomes (PROs) or Patients Reported Outcomes Measures (PROMs)

In the Cochrane Handbook, PROs are defined as "any reports coming directly from patients about how they function or feel in relation to a health condition and its therapy, without interpretation of the patient's responses by a clinician, or anyone else" (76). These measures show what aspects affect and matter to patients, and include: signs, symptoms, impairments and other aspects of well-being, functional status or disability related to behaviours and abilities, general perceptions about health or feelings of well-being, satisfaction with treatment, Quality of life (QoL) or Health related quality of life (HRQoL)convenience, tolerability and

adherence. Health status and quality of life outcomes are an important category of PROs.

Table 14 shows some examples about terms and definitions related with PROs:

Table 14. Terms and definitions examples related with Patients Reported Outcomes

Term	Definition
Well-being	Subjective bodily and emotional states; how an individual feels; a state of mind distinct from functioning that pertains to behaviors and activities.
Functional status	An individual's effective performance or ability to perform those roles, tasks, or activities that are valued (e.g. going to work, playing sports, or maintaining the house).
Quality of life (QOL)	An evaluation of all aspects of our lives, including, for example, where we live, how we live, and how we play. It encompasses such life factors as family circumstances, finances, housing and job satisfaction.
Health-related quality of life (HRQOL)	Personal health status. HRQOL usually refers to aspects of our lives that are dominated or significantly influenced by our mental or physical well-being.

Source: Definitions of selected terms related to quality of life in Handbook Cochrane 2011 (61)

PROs are most important when externally observable patient-important outcomes are unavailable, or rare. With difficult outcome measures, for example fatigue, pain or insomnia, the use of PROs is recommended.

The use of these measures is relevant in HTA and for further information we recommend the following documents prepared by the Cochrane Patient Reported Outcomes Methods Group, Patient Reported Outcomes Measurement Group of the University Oxford.

US FDA has prepared recommendation guidelines on the use of PRO instruments to measure treatment benefit or risk in clinical trials.

Patient Reported Outcomes Measurement Group proposes the following elements for the selection of PROs (77):

Table 15. Proposed elements for the selection of Patient Reported Outcomes

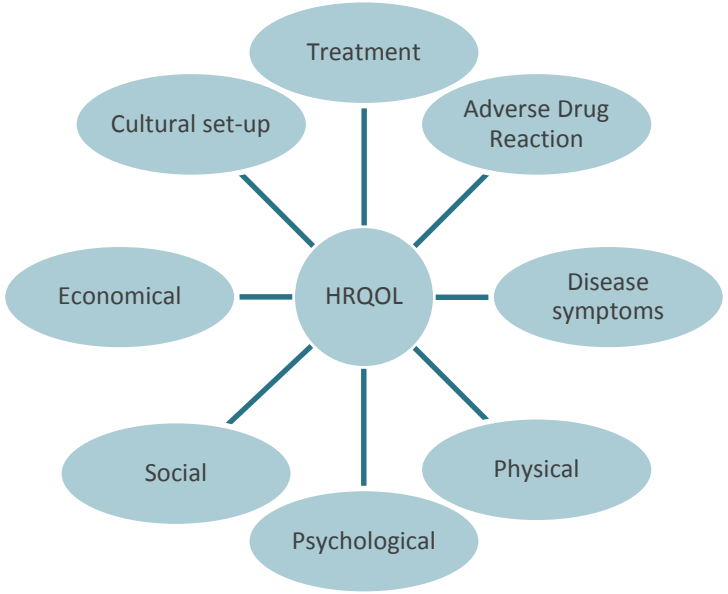
Elements for the selection of PROs	
Appropriateness	Is the instrument content appropriate to the questions which the application seeks to address?
Acceptability	Is the instrument acceptable to patients?
Feasibility	Is the instrument easy to administer and process?
Interpretability	How interpretable are the scores of the instrument?
Precision	How precise are the scores of the instrument?
Reliability	Does the instrument produce results that are reproducible and internally consistent?
Validity	Does the instrument measure what it claims to measure?
Responsiveness	Does the instrument detect changes over time that matter to patients?

Source: Patient Reported Outcomes Measurement Group by University of Oxford (77)

Health-Related Quality of Life (HRQOL)

The use of Health related quality of life (HRQL) has significantly increased due to the need for new ways of assessing the level of people's health beyond the onset of events, diseases and/or survival (78). Assessment of the quality of life may be approached using any of the following questionnaires.

Figure 3. Factors affecting health related quality of life



Source: adapted from Deshpande Pr 2011 (78)

There are two approaches to measure quality of life following Generic questionnaires or Specific questionnaires for specific health-related issues.

Table 16. Types of Patient Reported Outcome (PRO) measures

Types of PRO measures	Examples
Generic	EuroQol SF 36
Disease specific	St. George's Respiratory Questionnaire, SGRQ Western Ontario and McMaster Universities Osteoarthritis Index WOMAC Minnesota Living With Heart Failure Questionnaire Specific questionnaires for Cancer: EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Group
Dimension specific	Physical Activity Index (PAI)
Utility measures from generic-based measures	Health Utilities Index Mark 2 (HUI2) Health Utilities Index Mark 3 (HUI3) EuroQL-5D Value set Short Form-6 Health Survey (SF-6D)

Source: elaborated by the authors

Interesting experience

The PRO in the NHS

Monthly Patient Reported Outcome Measures (PROMs) in England. A guide to PROMs methodology

The generic PRO measures are frequently used in the economic evaluation of health interventions. Other measures such as the impact of treatment or ill-health on a multidimensional scale and can be combined with data on survival in the form of Quality-Adjusted Life Year (QALYs).

Some websites offer a bank of resources regarding general PRO and HRQL measures. Some relevant websites are shown in the next table:

Table 17. List of websites that offer a bank of resources regarding general PRO and HRQL measures

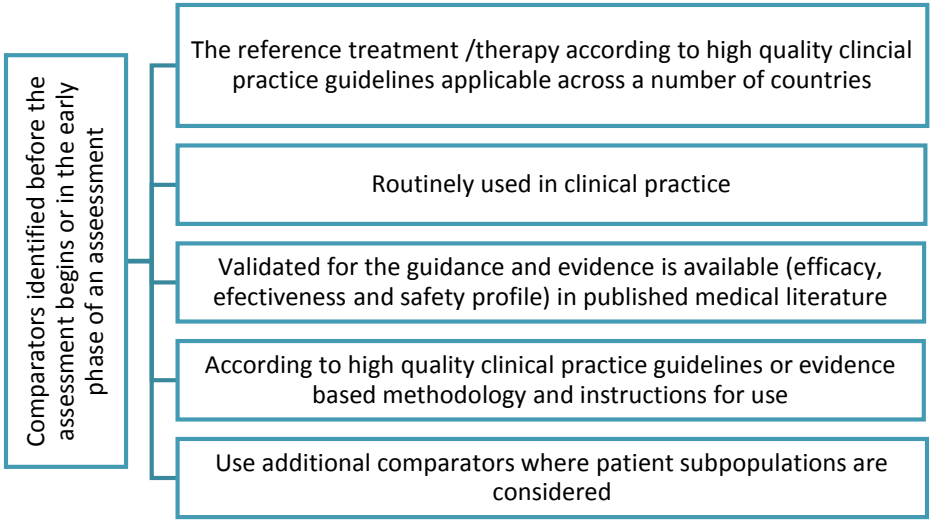
Web	Description
Biblio Pro	Online library of international scientific reference for questionnaires in Spanish for Patient Reported Outcomes (PRO). Currently working on additional data regarding Latin America
Progolid	They offer translations, copyrights, and access to instruments important
NIH Common Fund: Clinical Outcomes Assessment: PROMIS	Patient Reported Outcomes Measurement Information System
Mapi Research Trust	They offer access to information in the fields of Patient-Centered Outcomes, promoting the use of scientific approaches
Patient-Reported Outcome Consortium	A partnership between the Critical Path Institute, U.S. FDA, and the medical products industry, the Consortium develops, evaluates, and qualifies PRO instruments with the FDA for use in clinical trials designed to evaluate the safety and efficacy of medical products
AHRQ	Agency for Healthcare Research and Quality included a section: Patient-Reported Outcomes for Quality Improvement of Clinical Practice
Patient Reported Outcomes Measurement Group by University of Oxford	They offer resources available free to anyone having an interest in the use, availability and development of PROMs
Cochrane Patient Reported Outcomes Methods Group	They are helping people to make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions

Source: elaborated by the authors

Criteria for the choice of the most appropriate comparator(s)

The following criteria should be taken into account when choosing the most appropriate comparator/s (79):

Figure 4. Comparators identified before assessment or at early phase of assessment



Source: adapted from EUnetHTA. Guidelines Comparators & comparison 2013 (79)

Together with these criteria which provide a hierarchy in the selection process as proposed by EUnetHTA, are number of elements are to be considered:

The natural history of the condition without suitable treatment

- Cost – effectiveness
- The licensing status of the comparator
- National procedural rules

The evidence appraisal process undertaken by NICE establishes the appointment of an Appraisal Committee which is in charge of, amongst other responsibilities, selecting the most appropriate comparator(s). Please refer to NICE website for a detailed description of the process for selecting comparators.

Validity and bias

Internal validity

This term is defined as the extent to which the results of a study are correct for the circumstances being studied, or extent to which systematic error (bias) is minimized in clinical studies (80,81). It is interchangeable with Risk of bias. Assessments of internal validity are frequently referred to as *"assessments of methodological quality"* or *"quality assessment"*.

Internal validity ≠ External validity ≠ Precision

Table 18. Components of internal validity/risk of bias of controlled clinical trials

Components of internal validity of controlled clinical trials:
Selection bias: biased allocation to comparison groups
Performance bias: unequal provision of care separate from treatment under evaluation
Detection bias: biased assessment of outcome
Attrition bias: biased occurrence and handling of deviations from protocol and no follow up

Source: Jüni P et al 2001 (81)

Selection bias

Selection bias refers to systematic differences in baseline characteristics between the groups. Some recommendations to decrease the selection bias include:

- Various comparison groups
  - At least two comparison groups
- Equivalence between groups
  - Except independent variables
  - Random sequence generation
  - Allocation concealment
  - Initial equivalence: random assignment or pair maching
  - Equivalence throughout the study

Performance bias

This bias occurs if additional treatment interventions are provided preferentially to one group. Some recommendations to decrease this risk of bias include:

Recommendations
Blinding of participants and personnel. More information in Cochrane handbook
Assessments should be made for each main outcome (or class of outcomes). More information in Cochrane handbook.

Source: Cochrane handbook 2011 (61)

Related keywords: Risk, Risk of bias, Quality assessment, Quality of evidence

More Information

- Chapter 8: Assessing risk of bias in included studies and Criteria for judging risk of bias in the 'Risk of bias' assessment tool by The Cochrane Collaboration
- *Guide in 2012 about Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions* by Agency for Healthcare Research and Quality (AHRQ)
- Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals by EUnetHTA

More resources:

- Seuc A. Randomization to protect against selection bias in health-care trials: RHL commentary (last revised: 1 January 2012). The WHO Reproductive Health Library; Geneva: World Health Organization.
- Chapter 8: Assessing risk of bias in included studies by The Cochrane Collaboration
- Assessing risk of bias in relation to adequate or inadequate allocation sequence concealment
- Adequate methods of sequence generation
- Random Sequence Generator

Detection bias

Detection bias refers to systematic differences between groups in how outcomes are determined.

Recommendations
Blinding of participants and personnel. More information in Cochrane handbook
Assessments should be made for each main outcome (or class of outcomes). More information in Cochrane handbook.

Source: Cochrane handbook 2011 (61)

Attrition bias

Attrition bias refers to systematic differences between groups in withdrawals from a study. Withdrawals from the study lead to incomplete outcome data (82).

Recommendations
Loss to follow-up can lead to bias in randomized trials
Imbalance resulting from this attrition is often hidden
Baseline characteristics of participants loss to follow-up and those included in the analysis should be reported separately
Assessment of the effect of differences between groups on the results is mainly subjective

Source: Dumville Jc et al 2006 (83)

Criteria used in quality assessment of randomized controlled trials. The Cochrane Collaboration's tool for assessing risk of bias

Applicability of evidence in the context of a relative effectiveness assessment

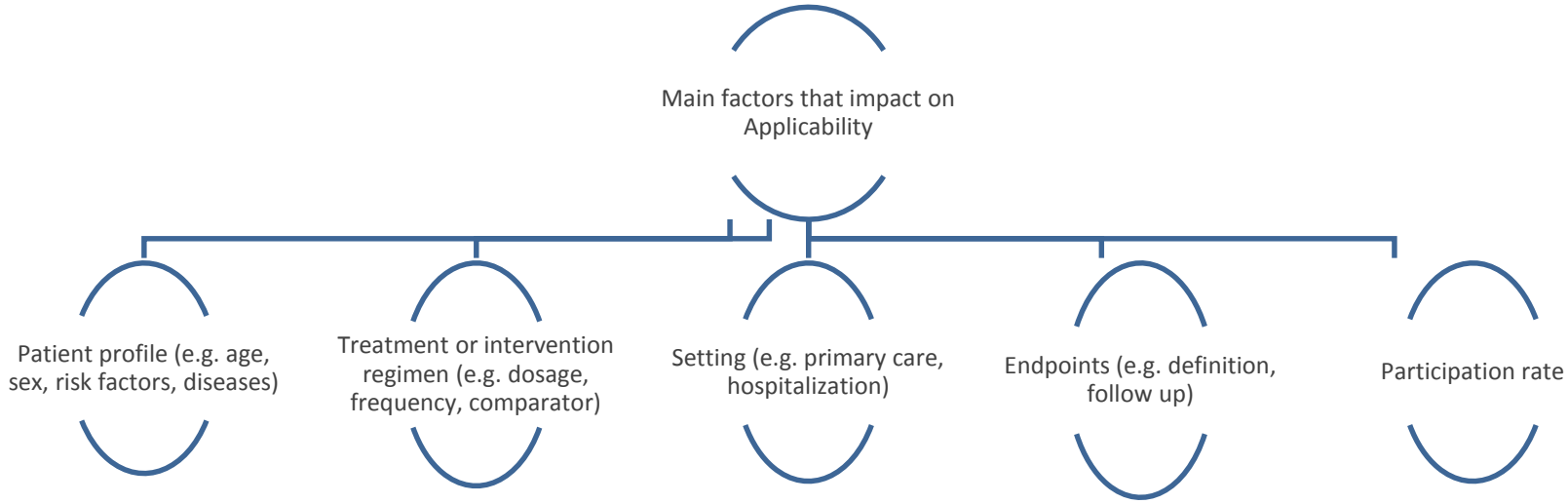
After the compilation of all available evidence on the assessment of the technology that is to be evaluated, the next step is to check whether this evidence is applicable to other settings or populations. By this, we refer to the concept of Applicability. Atkins D, et al (84) defined it as *"the extent to which the effects observed in published studies are likely to reflect the expected results when a specific intervention is applied to the population of interest under 'real-world' conditions. Internal validity is a prerequisite for the applicability"*.

The first step in exploring applicability is to identify factors that may influence or affect it (53).

Due to specific RCT features, sometimes the transfer of technologies or interventions has a number of limitations. EUnetHTA recommends usage of data from trials with a pragmatic approach (57).

The most important factors are:

Figure 5. Main factors that impact on applicability



Source: adapted from HIQA 2011 (69)

Figure 6. Key points and applicability of studies

PICO	¬ Evaluate and contrast the PICO questions ¬ Contain factors related with the applicability
Clinical experts and stakeholders	¬ Consult with experts to identify key elements to be considered in the assessment of the applicability
Studies design	¬ Some specific types of studies allow greater applicability than others. ¬ Population-based surveys, pharmacoepidemiologic studies, and large case series or registries/ health records services are more adequate
Assess possible differences	¬ Assess any possible variations and their effects on the expected results according to differences in patients' characteristics or the intervention
Section "Comments" or "Limitations"	¬ Review these sections of individual studies since here is where keys regarding applicability are provided
Sub-analyzed	¬ Review information about Meta-regression, sub-group analysis and/or separate applicability summary tables
All studies	¬ Evaluate all available evidence to assess applicability

Source: adapted from Atkins D et al. (84)

Websites of interest for Evidence-based Practice Centers (EPCs):

Table 19. List of websites of interest for Evidence-based practice Centers (EPCs)

Evidence-based Practice Centers (EPCs)
Brown University, Center for Evidence-based Medicine, Providence, RI
Centers for Medicare & Medicaid Service Technology Assessments
Duke Evidence-based Practice Center—Duke University
ECRI Institute–Penn Medicine Evidence-based Practice Center, Plymouth Meeting, PA
Evidence Based Health Practice
Johns Hopkins University Evidence-based Practice Center, Baltimore, MD
Kaiser Permanente Research Affiliates
Mayo Clinic Evidence-based Practice Center, Rochester, MN
Medicare Coverage Database
Pacific Northwest Evidence-based Practice Center—Oregon Health & Science University
RTI International—University of North Carolina (UNC) at Chapel Hill, NC
Southern California Evidence-based Practice Center—RAND Corporation, Santa Monica, CA
University of Alberta, Edmonton, Alberta, Canada
University of Alberta Evidence-based Practice Center (UAEPC)
Minnesota Evidence-based Practice Center, Minneapolis, MN
Vanderbilt University, Nashville, TN
University of Connecticut Evidence-based Practice Center

Source: adapted by the authors from different websites

Systematic review

Related keywords:

External validity, applicability, generalizability/ generalisability, transposability, directness, relevance

More Information

Atkins D, Chang S, Gartlehner G, Buckley DI, Whitlock EP, Berliner E, Matchar D. Assessing the Applicability of Studies When Comparing Medical Interventions. Agency for Healthcare Research and Quality; January 2011. Methods Guide for Comparative Effectiveness Reviews. AHRQ Publication No. 11-EHC019-EF

Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals by EUnetHTA

Methodological guideline for REA of pharmaceuticals: Applicability of evidence in the context of a REA by EUnetHTA

Health technology assessment (HTA) is described as the bridge between the world of research and decision making. HTA authors have to manage scientific accuracy with timely report publication, political sensitivity, the decision-makers themselves and how best to disseminate the results (85). A systematic review provides the best evidence source for decision makers (86).

According to the Cochrane glossary, a systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyses the data from the collection of research. Where appropriate, combining the results of several studies gives a more reliable and precise estimate of an intervention's effectiveness than a single study. On the other hand, reviews that do not follow a systematic process are called narrative reviews and cannot be considered a formal research process, but simply a form of scientific literature mainly based on opinion (87). Multiple guides and handbooks to help in the process of systematic reviews can be found in the scientific literature. Some recommended handbooks or papers:

- Cochrane handbook for systematic reviews of interventions (88)
- CRD's Guidance for Undertaking Reviews in Health Care (82)
- Gough D, 2012 (89)
- Systematic review and meta-analysis: when one study is just not enough (89)
- Garg AX, 2008 (91)

1. **Before you start** preparing the systematic review, the following must be taken into account:

   a) The working group must have the right knowledge and experience of the topic under review. Different profiles are required when undertaking a systematic review, such as librarians

(to identify databases, design the search strategy, etc.), statisticians (to analyse data), etc.

b) Conflicts of interest of the working group must be identified

c) Task allocation and schedule (92).

2. **Writing the protocol**. The systematic review protocol must include the different aspects of the methodology to be used. Each of these aspects is explained below.

Recommended paper:

- Best Practice in Systematic Reviews
- Institute of Medicine has standards to conduct systematic reviews
- There is a database for registering systematic review protocols PROSPERO

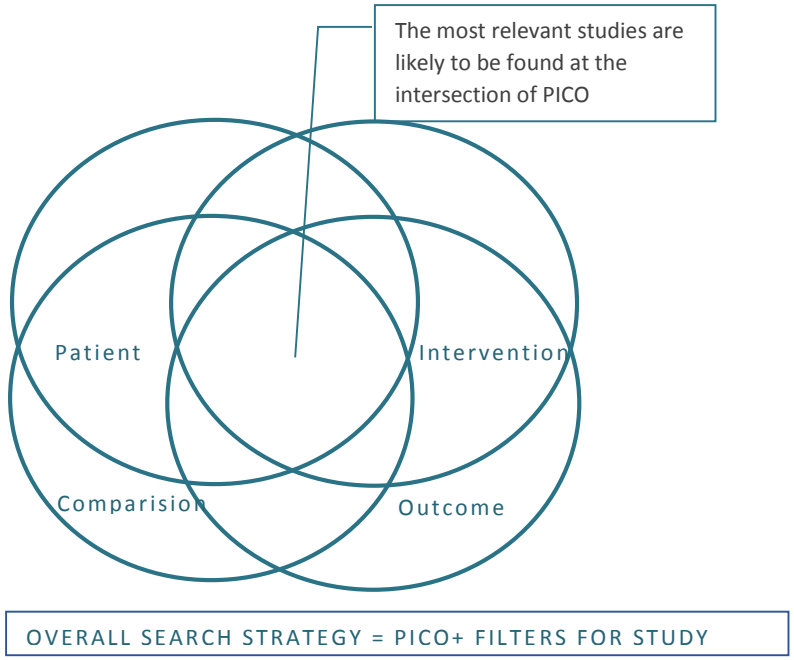
2.1. Formulating a researchable question using PICO criteria. This is a very important aspect and must be carefully considered. A tool to aid in the formulation of the research question should meet the following criteria: (FINER: Feasibility, Interesting, Novel, Ethical and Relevant) (93).

The detailed specification of the review question requires consideration of several key components. To this end, PICO format is a useful tool. There are different variants to the PICO format, one of which is PICOT, which uniquely takes time (T) into account. Templates and definition for PICOT questions can be found in the article from Stillwell SB. 2010 (94).

2.2. Designing the literature search. The search study should be built around a PICO framework to enable the searcher to identify the best studies for the review. Constructing an effective combination of search terms involves breaking down the review question into concepts. Main databases using descriptors are: MeSH (PubMed), EMTREE (EMBASE) and DeCS (Bireme)

Some sources to delimit the search strategy are as follows:

Figure 7. Search strategy



Source: elaborated by authors

SIGN:

- McMaster University, according to the study design.
- The InterTASC Information Specialists' Sub-Group (ISSG).

To appraise a search, the recommended paper is: Wong R, 2013 (95).

2.3. Information search process. Before conducting the search, examination of other systematic reviews is important for two purposes: firstly, it helps ensure that the work has not already been done; second, it provides examples of search strategies for the topic. Bearing in mind time and budget constraints, it is important to strike a balance between comprehensiveness of search and efficiency. Furthermore, bias must be minimised including publication and language bias that may result from narrowing the search in different ways. The following links include lists of different databases:

- Health and Biomedical Databases. University of Columbia.
- Health Sciences Library. University of Buffalo.

It is advisable to use COSI model search protocol to identity sources of information.

Using just one search engine is not considered adequate. Studies show that only 30%–80% of all known randomized controlled trials (RCTs) are identifiable using Medline. Since the overlap in journals covered by Medline and Embase is estimated to be 34%, at least two search engines ensure more comprehensive results.

2.4. Study selection and data extraction. It is advisable to conduct a pilot test with a specific number of references. This checks for homogeneity in assessment of eligibility criteria among people involved in the process. It helps avoid error and subjectivity.

The data extraction forms should contain only information required for descriptive purposes or for analyses later in the systematic review. Information on study characteristics should be sufficiently detailed to allow readers to assess the applicability of the findings to their area of interest. Recommended readings include:

Systematic Reviews CRD's guidance for undertaking reviews in health care. York; University of York, 2008 (see Chapter 1.3).

- Avoiding Bias in Selecting Studies.

2.5. Assessment of the studies. There are a number of tools for assessing risk of bias for articles in the review. Some recommended readings include:

What is critical appraisal?

The following links include some tools for assessing risk of bias:

- Critical Appraisal Skills Programme (CASP)
- Study Quality Assessment Tools

Likewise, some tools have been selected for designs.

- Randomized controlled trials: Higgins 2011 (96).
- Cohort and case control
- Studies of diagnostic accuracy. Whiting P, 2003 (97).

As suggested by Katikireddi SV, et al. (2014) (98), assessing the risk of bias in specific settings involves the adaptation of a tool when a previously published tool was modified by the authors for their review purpose, thus achieving a better adaptability of the tool or even a 'bespoke tool' when a new tool was created by the authors.

3. Synthesis and presentation of the information

3.1. Reference management systems. Detailed information on the best-known reference managers may be found here:

- Referencing
- RevMan

3.2. Meta-analysis. Using statistical techniques, results are quantitatively combined into a single point estimate. There are various programmes for performing meta-analyses, among them:

- EpiData Software and Templates
- OpenMeta [Analyst]

Methodological guidance for performing meta-analysis:

- Meta-analysis of Diagnostic Test Accuracy Studies
- Online effect size calculator
- MetaEasy - A meta-analysis add-In for Microsoft Excel
- MA routines and macros for R Software

For indirect Meta-Analysis, the recommended papers are:

- Jansen JP. 2014 (99)
- Mills EJ. 2012 (100)

3.3. Reporting. There are guidelines and recommendations for presentation and publication of systematic reviews that provide a checklist of the different aspects to be considered. Among these, two guidelines include:

- MOOSE (Meta-Analysis of Observational Studies in Epidemiology) is a checklist for reporting observational studies. It was developed following a workshop on addressing the problem of increasing diversity and variability of meta-analysis reporting of observational studies. (Stroup et al., 2000). Checklist:
  - PRISMA guidelines for reporting meta-analyses of randomized clinical trials.
  - Cochrane

Economic Evaluation for Decision-Making in HTA and Budget Impact Analysis

Economic evaluation (EE) has become a key tool within the HTA process, for the evaluation and reimbursement of healthcare technologies (53). Including EE in the HTA (53,101) allows decision makers to improve efficiency by spending the limited healthcare budget on those health technologies with the greatest health outcome value for money (101).

Increasingly, pharmaceutical and medical device industries include economic evidence as a part of their submission to the authorities for the inclusion of health technology into the health system. This has become a standard requirement in many countries as a part of the decision making process (30,102).

Types of Economic Evaluation

According to Drummond et al (101), economic evaluation is a comparative analysis of alternative courses of action (health care technologies) for both costs and consequences. All types of economic evaluation assess cost, but differ in the way they measure and value the consequence of the technologies. The scope of the outcomes included in an EE will depend on the research question, but might include healthcare resource use, costs, survival, non-fatal clinical events, and quality of life among others (see Table 20). Selection of the appropriate type of economic evaluation is usually based on the nature of the research question, the condition of interest, and the availability of data on outcomes. For comparability, most EE aim to measure health outcomes by Quality-Adjusted Life Years (QALYs). However, EE guidelines in LAC and European countries have different recommendations on EE to be used (see Chapter III.1. Guidelines)

Many papers describe in detail which type of EE, and methodologies must be used for HTA decision making. In the table below, there are some key documents that provide useful descriptions and examples of each type.

Table 20. Types of EE and main characteristics of each type

Type of analysis	Characteristic	Consequence measurement (outcome)
Cost minimization analysis (CMA)	Find the technology with least cost between alternatives with equivalent health results.	Equivalent desired effects (benefit) and undesired effects (risks/harms).
Cost-effectiveness analysis (CEA)	It compares the cost and consequence of health interventions in terms of cost per natural unit (outcome). Supply information about the greatest effect for a given cost. Its major limitation is the inability to compare interventions with different natural effects.	Natural units (e.g.: life years gained) or subrogated outcomes (e.g.: functional status e.g.: units of blood pressure or cholesterol).
Cost-utility analysis (CUA)	It is a variant of CEA. Consequences are measured in terms of preference-based measures of health (utility).	Health status (e.g.: Quality adjusted life year gained – QALY- ; disability adjusted life year -DALY-).
Cost-consequence analysis (CCA)	It examines cost and consequence of interventions in which the outcome can be measured in different units. It can be useful when multiple consequences are to be weighed together simultaneously.	Different consequences measured in different ways (e.g. intervention costs, hospital costs, clinical benefits, and adverse events).
Cost-benefit analysis (CBA)	Involves measuring costs and benefits in commensurate terms, usually monetary. It allows comparing different interventions using the net benefit criterion. Difficult to define monetary value for consequences in healthcare.	Monetary unit (productivity gains). Willingness to pay.

Source: Drummond et al 2008 (53), Drummond et al 2005 (101), Husereau D et al (103)

Table 21. Source of information with more detailed information about each type of EE and examples

To learn more about:	Source of information
Introduction to economic evaluation of health technologies	Walker et al 2011 (104) Larsen RJ 2003 (105) Kobelt, G 2013 (106)
Cost minimization Analysis (CMA)	Briggs et al 2001 (107) Dakin H (108) Newby D 2003 (109) Robinson R 1993 (110)
Example of CMA in HTA	Argenta C et al 2011 (111) CONITEC – Brazil March 2015 (112)
Cost effectiveness analysis (CEA)	Gray AM et al 2010 (113) DTB 2012 (114) Adang E et al 2005 (115) Baltussen R et al 2005 (116)
Example of cost-effectiveness analysis in HTA	Pedersen BG et al 2005 (117) CONITEC – Brazil April 2015 (118)
Cost utility analysis (CUA)	Robinson R 1993 (119) de Neeling JND 2003 (120)
Examples of cost utility analysis in HTA	Ward S et al 2007 (121) Urueña A et al 2011 (122)
Cost benefit analysis	Brent RJ 2004 (123) Islam SMN 2006 (124) Layard R 2005 (125)
Example of cost benefit analysis in HTA	Nichol KL 2001 (126) AETMIS 2010 (127)
Cost consequence analysis	Mauskopf JA et al 1998 (128) McIntosh E 1999 (129)
Example of cost consequence analysis in HTA	Gage H et al 2006 (130) Moreno M et al 2014 (131)

Source: elaborated by the authors

General requirements for economic evaluation for decision-making

The aim of an economic evaluation of health technologies is to provide information about the effect of the new treatment on health outcomes and costs, with the maximum achievable precision given the existing evidence. Carrying out such a task is usually a multidisciplinary project that includes input from health economists, statisticians, health science researchers and clinical experts. There are some recommended requirements for using economic evaluations in HTA decision-making (see Box 1) (101,132,133)

Box 1. Requirement for economic evaluation fot HTA decision-making (101,132,133)

- Clear statement and measurement of the objective function. A key requirement for decision-making is the need for a clear measure of health gain for the new technology.
- A consistent perspective. It is important to establish an appropriate cost and benefit perspective on the option choices.
- Appropriate definition of the decision problem. There is a need for a clear and consistent articulation of the decision problem (which patient population will be considered?, which alternative options of the health technology are available?, etc.).
- Appropriate time horizon. From a normative perspective, the time horizon of an analysis should be sufficient to indicate when cost and consequence differences between health technologies are stable. For example, for any health technologies that may have a plausible effect on mortality will require a lifetime horizon. In those cases, a discount rate must be taken in account.
- Evidence synthesis. The study setting should provide an analytic framework within which all relevant evidence can be brought together. It is recommended that clinical effectiveness data is collected by systematic review of the literature and meta-analysis (see Chapter III.2. Systematic review)
- Evaluation. The analysis needs to identify the optimal decision according to the defined decision rules for cost-effectiveness analysis.
- Uncertainty. The analysis needs to quantify the uncertainty associated with the decision. In addition, the study setting should facilitate an assessment of the various types of uncertainty relating to the analysis.
- Additional evidence. The results of analysis should provide a basis for prioritising future research, which can generate further evidence to re-assess the study question in the future.

Valuing Outcomes

As described at the start of the chapter, all types of economic evaluation assess cost, but differ in the way in which consequences of technologies are measured and valued. The scope of the outcomes included in an EE will depend on the research question, but might include healthcare resource use, costs, survival, non-fatal clinical events and quality of life.

Outcomes measured in natural units

A distinction is made between **Intermediate endpoints** (surrogate measures, eg: reduction in H1Abc levels, cardiovascular event avoided) and **final endpoints** (years of lived gained, live salved, cardiovascular disease free years of life gained). Intermediate endpoints are only an acceptable outcome measurement when clinically relevant, accepted by clinical experts, and used as a proxy for the final endpoint (101) (see Chapter III.2. Efficacy, Effectiveness and Safety). Most of European guidelines of EE recommend the use of intermediate endpoints only when final outcomes/endpoints are missing (30).

Quality-adjusted life years

In CUA, the outcome measurement used is the quality-adjusted life years (QALY). This measurement is routinely used as a summary measure of health outcomes, which incorporates the impact on both the quantity and

quality of life (134). It is an attractive measure in HTA decision-making because it allows comparison across different disease areas and populations. Most of the jurisdictions in Europe recommend using CUA as a modality of EE, and QALYs for valuing outcome (30).

In order to generate QALYs, health utilities (or HRQoL weights) are needed. There are two methods to generate HRQoL weights: direct and indirect (also called generic preference-based measures) (135). The table below describes some tools and sources of information for a more detailed description of each method. The method most commonly used for derivation of HRQoL is an indirect instrument, such as EQ5D or SF6D.

Table 22. Methods and tools to generate HRQOL weights

Method	Tools and some source of additional information
Direct method	
Time trade off / Standard gamble / Visual Analogue Scale	**Description of methods:** Whitehead SJ et al 2010 (134) Sinnott PL et al 2007 (135)
Indirect methods (generic preference-based measures)	
EQ-5D health questionnaires	**Description of method:** Brooks R et al 2003 (136) **Tools**: EQ-5d-3L and EQ-5d-5L (questionnaire and value sets) Brazilian researches have been working on 5Q-5D and 6F-6D questionnaires and they developed a Utility Table for the country
SF-6D preference score.	**Description of method:** Brazier JE et al 2002 (137) **Tools**: University of Sheffield (access to questionnaire, syntax files and further references) Campolina AG et al 2010 (138) (SF 6d brazil questionnaire and method) Brazilian researches have been working on EQ-5D and SF-6D questionnaires and they developed a Utility Table for the country
Health utility index (HUI 2 HUI 3)	HUI 2 HUI 3 (questionnaire and method)
15D health questionnaire	**Description of method:** Sintonen H. 2001 (139); Sintonen H. 1994 (140) ; Sintonen H. 1995 (141) **Tools**: Questionnaire and registration forms
Other resources	
Databases: **CEA registry** (database of CUA and utility weights) **ScHARRHUD (**database of health utilities evidence)	 Access to database **CEA registry** Access to database **ScHARRHUD**
Other articles	Bell CM et al 2001 (142) ; Brauer CA et al 2006 (143); Dolan P et al 2005 (144); McDonough CM et al 2007 (145); Tsuchiya A et al 2005 (146);

Source: elaborated by the authors

Willingness to pay

The monetary value of the outcomes in the CBA is usually obtained by applying a willingness to pay (WTP) approach (147,148). The method primarily used in WTP studies is contingent valuation (preferred —30—) and conjoint analysis (also known as discrete choice experiments –DCE). These methods use surveys in which individuals are asked about their willingness to pay for a treatment. DCE can include population and patient preferences in HTA decision-making (148).

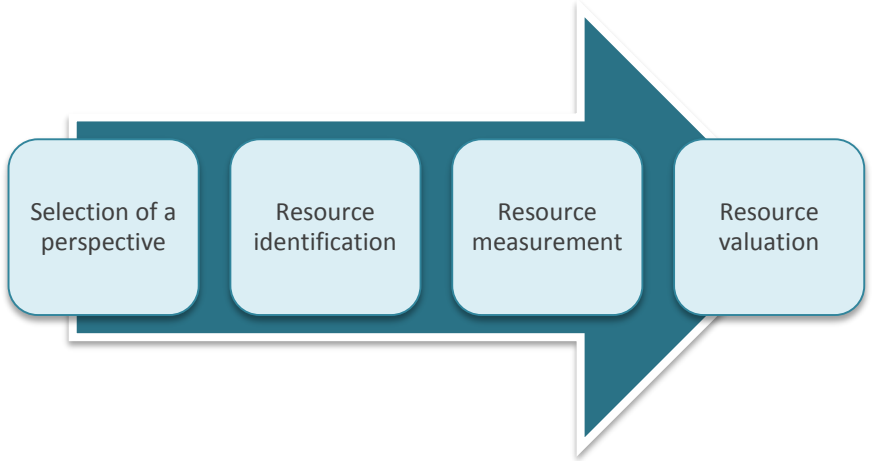
Although WTP is increasingly used, the method is still under development. It is not frequently used in HTA decision-making and most guidelines do not mention it as a potential outcome (30,102). In Europe, EE guidelines from Finland, Portugal, Russia, Spain and Sweden, include CBA as a possible form of EE that can be used; others like Denmark, France and Poland recommend its use as a complementary analysis.

Cost estimation and perspective analysis

All the resources used in the production process of the new technology are considered. These resources cover the whole time horizon to take into account the long term cost consequences of interventions. Costs that are considered unrelated to the new technology are excluded (101).

To be useful to the decision maker as well as to form the basic input for a health economic model, these estimated costs must be reported in sufficient detail and appropriately adapted to the context. We can consider four stages in assessing cost in a health economic evaluation:

Figure 7. Stages in assessing costs in a health economic evaluation



Source: elaborated by the authors

Selection of a perspective and resource identification

Costs included in health economic evaluations depend on the perspective the analysis is conducted from. The broadest perspective is societal perspective, where all relevant costs and consequences of the health technologies evaluated must be included in the analysis, regardless of who will incur them. Other narrower perspectives include public payer, health care service, the hospital or the patient itself (149).

In Europe, countries such as Belgium, Croatia, Czech Republic, England, Estonia and Latvia, Germany, Ireland, Italy, Scotland, Slovakia, Slovenia, and Switzerland recommend a health care perspective analysis, whereas countries like Denmark, Finland, the Netherlands, Norway, Portugal, Spain and Sweden recommend societal perspective (30). EUnetHTA guideline recommends that EE should at minimum be conducted from healthcare system perspective, but resources used that are related to other sectors can be included in a complementary analysis (30).

The type of cost and resource associated with the each perspective is detailed in Table 23.

Resources should be identified, measured, and valued.

Table 23. Perspectives, type of cost and resource consumption

Perspective				Type of Cost	Example of resource consumption
Societal	Public payer	Health care services	Hospital	Hospital Direct cost	Health professionals, hospital services, Drugs, medical devices Equipment, space, facilities, and associated overhead costs. Medical services, including procedures, Hospital services, Emergency visits, Ambulance services
				Direct cost in other health care sector	Cost incurred in primary health sector: consultation with general practitioner, physiotherapist, prescription of a medicine. Rehabilitation in a facility or at home* Community-based services, such as home care, social support* Long-term care in nursing homes
				Direct costs to publicly funded services (other than health care)	Social services, such as home help, meals on wheels* Income transfer payments paid (e.g., disability benefits) Special education
				Indirect costs to patients and their families	Out-of-pocket payments (including co-payments) for drugs, dental treatment. Cost of travel for treatment. Lost time at unpaid work (e.g., housework) by patient and family caring for the patient
				Productivity cost of the patient	Lost productivity due to reduced working capacity, or short-term or long-term absence from work (during friction period); Costs to employer to hire and train replacement worker for patient

* Some of these costs may be incurred by the publicly funded health care system, depending on the precise nature of these costs and the relevant jurisdiction;

Sources: EUnetHTA (30), HTA Handbook 2007 (149)

Resource measurement and valuation

Measuring costs is a rigorous process and relies upon clearly identifying and defining the cost inputs in the analysis. To ensure transparency in the cost analysis, it is recommended to report the use of resources of the compared technologies in physical and natural units, prior to its monetary conversion (101,106).

The valuation of a cost in monetary terms is the result of applying a unit cost to a certain quantity. Resources should be valued at their opportunity cost. There are several ways of valuing resources, including market prices, tariff, administrative fees, direct measurement, and calculation of shadow prices (101). The cost valuation must be assigned using local currency. Costs are converted to the most recent price year by using relevant indices (30). In Table 24, we show an example of cost estimation in health economic evaluation (adapted form Drummond et al (101)).

For more information about cost estimation, the Costing manual from NHS (England) provides an example of the minimum principles for costing in a healthcare system.

In the hyperlinks below are some examples of costing templates:

- *Management of hip fracture*
- *Faecal calprotectin diagnostic test for inflammatory disease of the bowel*

Table 24. Example of cost estimation in health economic evaluation

Resource identified	Possible measurement	Cost estimation
Hospital resources		
Radiotherapy	Number of treatment session could be recorded	Cost per treatment session taken from standard hospital account
Bed days	Number of bed days differentiating type of hospital ward	Average daily cost for different type of wards
Out-patient attendances	Number of attendances	Average cost of charge available from out –patient visit
Overheads	These would probably be related to the number of bed days or other suitable resource item	Overhead can be allocated in each of the cost above, depending of the overhead item
Community care resources		
General practitioner (GP) visit and Nurse visit	Number of GP visit and nurse visit	Physician (or nurse) fees and average cost of a visit
Ambulance	Number and length of trips	Average cost per mile or kilometer traveled
Patient and family resource use		
Patient's time	Time off work	Gross salary
Out of pocket expenses for transport (e.g. car, bus, train, taxi)	Number of bus tickets or distance travelled in private car	Bus fare /cost per mile or kilometer
Resource in other health sector Home visit by social worker	Number of visits	Social worker fees and average cost of a visit

Source: adapted form Drummond et al (101)

Time horizon

Time horizon should be long enough to reflect all important differences in costs and outcomes between the intervention and comparators. Normally a lifetime time horizon is considered for chronic conditions (e.g. chronic kidney disease, diabetes) or when alternatives have different effects in mortality (e.g. statins for prevention of cardiovascular disease) (30,101).

Discounting

Cost and future consequences (beyond one year) should be discounted to reflect society's rate of time preference (150, 151). The choice of discount rate is the decision the jurisdiction in which the EE is performed. Most European countries use a discount rate between 3 to 5% for both cost and effect. However, it is recommended to perform a sensitivity analysis to explore the effects of reducing the rate to zero (4). In Box 2 there is a description of how to obtain discounted costs and QALYs.

Box 2. How to obtain present value of future cost and benefit according to a discount rate.

Formulae:

$$PV = \sum_{n=1}^{n} \frac{FV}{(1+r)^n} \quad \Rightarrow \quad 888.5 = \frac{1000}{(1+0.03)^4}$$

Present value (PV) of future cost or benefit (FV) occurring at year "n" at selected annual discount rate (r)

Example: cost of a cardiovascular event (CV) occurred in 5 years, assuming discount rate of 3%.

Year	Cost of CV event	PV of cost of CVD event	Year	QALY	PV of QALY
0	1,000 €	1000 €	**0**	10	10.0
1	1,000 €	970.9 €	**1**	8,5	8.3
2	1,000 €	942.6 €	**2**	7	6.6
3	1,000 €	915.1 €	**3**	6	5.5
4	**1,000 €**	**888.5 €**	**4**	5	4.4

Roles of modelling in HTA

We can distinguish two phases in the HTA assessment process: gathering evidence and processing evidence (132). All relevant evidence needed for an economic evaluation is rarely available from a single source, thus necessitating the need for a systematic review of literature. The use of decision-analytic modelling provides a framework for synthesizing data from various sources, including data from: clinical trials, observational studies, insurance claim databases, case registries, public health statistics, and preference surveys. It also allows for consideration of all relevant comparators, adopting sufficiently long-time horizons and taking uncertainty into account (101,104,106). Such evidence may include information about the baseline risk of certain clinical events, epidemiology data, resource use, cost, compliance/participation pattern, HRQoL, survival, another time to event outcomes, relative treatment effects and relationships between intermediate and final endpoints (152). Modelling represents the natural history of disease when more than one alternative of treatment exists. The progression of the disease or the *"patient pathways"* must be examined; identifying cost and effect associated with the treatment and observing how they change (153).

Brennan et al (152) identify the roles of modelling in health economic evaluation and discuss its value for each role with examples to illustrate (Box 3).

Box 3. Roles of modelling by Brennan et al (152)

Five perspectives to identify roles and application of modelling:

- Extending results from a single trial
- Combining multiple sources of evidence to answer policy questions: to extend surrogate endpoints to final outcomes- extending to relevant comparators
- Generalizing results from one specific context to other
- Modelling to inform research strategy and design
- Modelling uncertainties in the knowledge base.

Decision-analytic modelling has become a widespread method in HTA, but the extent to which modelling is used differs among international institutions. All guidelines state that the use of decision-analytic modelling is accepted in health EE (102, 30). In particular, HTA guidelines used in Canada and UK provide detailed description required HTA elements and appropriate methods for decision modelling (150).

The Decision Tree and Markov Model are the most frequently used. Other types of decision analytic modelling are detailed in table 25. Useful tools to develop a decision model are provided in table 26.

Table 25. Summary of types of decision model structures Model Type

	General Description	Type of Decision Best Suited For
Decision tree	Diagrams the risk of events and disease states over a fixed time horizon.	Interventions for which the relevant time horizon is short and fixed - Usually for acute diseases.
Markov (cohort) model	Simulates a hypothetical cohort of individuals through a set of health states over time.	Modeling interventions for diseases or conditions that involve risk over a long time horizon and/or recurrent events. Usually for chronic diseases.
Microsimulation (individual) model	Simulates one individual at a time; tracks the past health states of individuals and models the risk of future events stochastically.	Modelling complex disease processes, when Markov models are too limiting.
Dynamic model	System of differential equations that simulates the interactions between individuals and the spread of disease.	Modeling interventions for communicable diseases, such as vaccinations.
Discrete event simulation model	Simulates one individual at time as well as interactions among individuals or within a health care system.	Evaluating alternative health care systems (e.g., workflow, staffing) though flexible enough to address questions in several different areas.

Source: Sainfort et al 2013 (153)

Table 26. Tools for developing a decision-analytic modelling

To know more about:	Source of information
Guidance to choose from the types of decision-analytic model available.	Brennan et al (154)
Developing a decision model	Briggs A et al (155) (textboox). Supporting material for Decision Modelling for Health EE (including exercise templates and solution file): OpenMarkov (software to develop a Markov model) Software EQIS 2.0 (free software to obtain HRQL of populations from EQ-5D, all the calculations, reporting summary results for costs and effectiveness in your population, acceptability curves, and other graphical tools necessary to do a simple but complete EE. User guide EQIS 2.0
Modelling good research practice	ISPOR good practice (156)
Summary about the use of models in many countries of Europe.	EUnetHTA EE Guideline (30)
Framework for quality assessment of decision-analytic models. Attribute of a good model.	Phillips et al (157)
Model validation	Ingalls et al (158)

Source: elaborated by the authors

Estimating uncertainty

In a decision-analytic model, input data are drawn from different sources and the interpretation of the result will largely depend on the level of the confidence or uncertainty. Every economic evaluation will contain some degree of uncertainty because of the model structure or the actual value in the model.

For example, what if the compliance of statins was 20% less than that considered in the decision-analytic model? What if the cost of acute myocardial infarction is 40% higher? What if a discount rate of 4% was applied instead of 3%? (101).

The approach to dealing with model uncertainty in called sensitivity analysis (SA). SA is performed to assess impact in the result of EE when various parameters in the model vary. This analysis should always be

followed by an economic analysis. There are different ways of undertaking SA (see Table 27).

Table 27. Types of Sensitivity Analysis

Type	Description
"one-way"*	Only one parameter is changed at one time. It is a good start to handle uncertainty
"multiway" *	Two or more parameters vary at the same time. The interpretation becomes increasingly difficult and complex as the number of parameters involved increases
Extremes*	Method to assess the confidence around all parameters, by varying all of the parameters in a model to their 'best' and 'worst' case scenarios.
Threshold value*	Identifies the critical values (threshold) for one or more parameters at which the conclusion of the analysis changes. Only usable for continuous variables
Probabilistic	The ranges of parameter variation are assigned according to a probability distribution function, and a Monte Carlo simulation selects values for all variables. It is simulated many times, so a distribution of the result emerges and the variance can be estimated.

*Deterministic sensitivity analysis.
Source: Health Technology Assessment Handbook (149)

The usual approach to estimating uncertainty in models is by *"probabilistic sensitivity analysis"* (PSA). Here, the model inputs are considered random variables composed of a mean value and a stochastic error term (159). The results of the model are repeated using a simulation with input variation. The output of the probabilistic model can be used to construct confidence intervals for costs and QALYs, or to construct *"cost-effectiveness acceptability curves"* (CEAC).

CEACs shows the probability of a technology being cost effective compared with its alternative at various threshold values for willingness to pay (160). Most of the EE guidelines recommend deterministic sensitivity analysis to identify parameters, which may have substantial impact on the results of the. The PSA explores parameter uncertainty, presenting confidence intervals around the incremental cost effectiveness ratio (ICER), scatter plots in a CEE plan or in a CEAC (30).

Threshold and decision rules

When comparing the cost and effect of two technologies, the incremental cost effectiveness ratio (ICER) is calculated. The ICER shows the cost of one extra unit of effect produced with the new technology (161). Where the new technology is more costly and more effective, decisions about its acceptability will depend on the maximum price that the decision maker is willing to pay for the extra effect (ICER threshold values).

Table 28. Explicit, implicit ICER threshold values in some jurisdiction in Europe and America's Region countries

Country	ICER Threshold	Reference
Australia*	AU$45,000 per QALY	Paris V et al (161)
Chile	1xGDP per capita	Guideline (164)
Czech Republic*	3xGDP per capita	Mapping report (6)
Ecuador*	3xGDP per capita	Mapping report (6)
Estonia*	1-3 GDP per capita	Mapping report (6)
Germany	Not used. Alternatively: efficiency frontiers	
Latvia*	The ICER for an additional obtained year of life or progression-free year of life shall not exceed the ICER of pharmaceuticals already included in the Positive list.	Mapping report (6)
Mexico	1xGDP per capita	Guideline (28)
Poland	3x GDP per capita for ICUR/QALY or ICER/LYG	Mapping report (6)
Slovakia	24 x average monthly salary € / QALY; 35 x average monthly salary € / QALY	Mapping report (6)
Spain*	€20,000-€30,000	Sacristan J et al (162)
The Netherlands*	€20,000	Boersma et al (163)
UK	£20,000-£30,000	

Source: elaborated by the authors.

Reporting

Once the ICER is calculated and the different SAs are performed, results must be clearly and transparently incorporated in the HTA report. Results, model design, input data and assumptions must be described in detail in order to be transparent. Writing the report in such a way to match the target audience is recommended. This is challenging as substantial information must be presented to allow full scrutiny of analysis findings.

In order to provide transparency and help for reporting EE analysis, the ISPOR "Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement has been produced. This statement (165) is a 24-item recommendation checklist for EE researchers.

Budget Impact Analysis

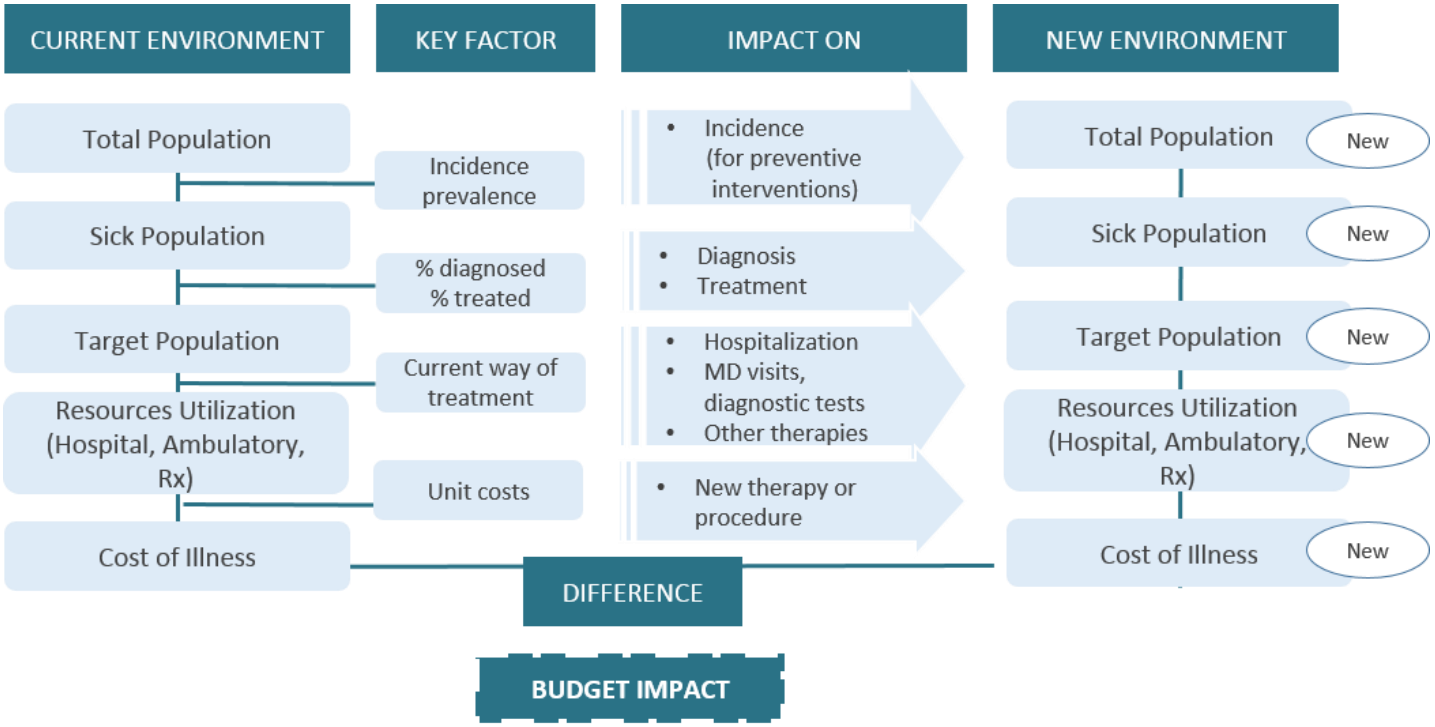
In addition to knowing if a new health technology is cost effective, it is often possible in the HTA report to estimate the spending burden of adoption and diffusion of this new technology. This can be investigated through a budget impact analysis (BIA). Increasingly, BIA is required, along with cost-effectiveness analysis, prior to technology marketing approval or reimbursement approval (166,167).

The main purpose of a BIA is to estimate how the change in the technologies used to a treat particular group of patients will impact the trajectory of spending on that condition (166) (see fig.1).

Here there are some resources to help with budget setting, prescribing planning and medicines management.

- Excel template from NHS (England)
- Budget Impact Analysis Good Practices from ISPOR
- Example of the use of BIA in HTA in Europe (168,169)
  - BIA excel template for Medicines. Brazil, available in Portuguese

Figure 8. Budget impact schematic



Source: Mauskopf et al 2007 (166)

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IV. Beyond HTA

1. Using MCDA to facilitate decision-making and priority setting

When a decision maker needs to select and recommend a health technology, this decision is complex and must take into account different aspects and dimensions of value.

Key considerations of interest can be grouped into five categories (1,2):

1. Maximize general population health.
2. Distribution of health within the population.
3. Specific societal preferences.
4. Budgetary and practical constraints.
5. Political considerations.

On the other hand, the main outcome in a Health Technology Assessment (HTA) is the evaluation of costs and benefits of the new technology compared with the old one. Nevertheless, for decision makers, other dimensions of value and interests must be taken into account, such as ethics, equity, or innovation. These dimensions of value are rarely addressed or incorporated explicitly in an economic evaluation.

Recently, multiple criteria decision analysis (MCDA) has emerged as a prospective alternative to address shortcomings of Health Technology Assessment (HTA) methodologies (3).

MCDA is a set of methods and approaches to assign the relative importance of different criteria, with a view to aiding decision-making. This approach encompasses more perspectives and provides a wider value assessment, which addresses several of the limitations of economic evaluation. It does so by disaggregating a complex problem into simpler objectives, measuring the performance of the different available options against the objectives, weighting up these objectives according to their relative importance, and re-assembling the components by aggregating scores and weights to show the overall picture. A major advantage of MCDA is that it enables open and transparent consideration of all stakeholder views (4).

MCDA is not a tool to substitute decision making but to improve transparency and understanding of decision making processes. Additionally, this method could be used to evaluate an existing health technology as an audit trail. This methodology has been successfully applied in other areas (energy planning, transportation, geographical information systems) whilst being increasingly used in healthcare (4).

The use of the MCDA in the context of healthcare and HTA has been analyzed by three systematic reviews (5-8). All three reviews concluded that further work is needed including the development of methodological guidelines to ensure the validity and reliability of MCDA applications, and the testing of their impact on decision-making.

The *Decision making process mapping in CEE and LAC* report, highlights the need to use criteria and values in the process of an HTA. However, none of the countries surveyed used the MCDA methodology for HTA (9), although Russian Federation has a guide entitled: Methodological Guidance on Application of Multi-Criteria Decision Making Analysis in Russian Healthcare (10).

In Latin America, the MCDA was used by CONITEC (Brazil) for the prioritization of the Clinical Protocols and Therapeutic Guidelines (CPTG) for integral attention to people with rare diseases. Facing a scenario of more than 8,000 rare diseases and the need to prioritize groups of more frequent and important diseases to develop the CPTG, CONITEC opted to apply MCDA methodology among a specialist panel. This process is well described in the Protocol.

A study (11) has several examples of the use of MCDA methods in different settings. Table 1 shows a summary example of MCDA for use in prioritization:

Table 1. Example of MCDA for use in prioritization

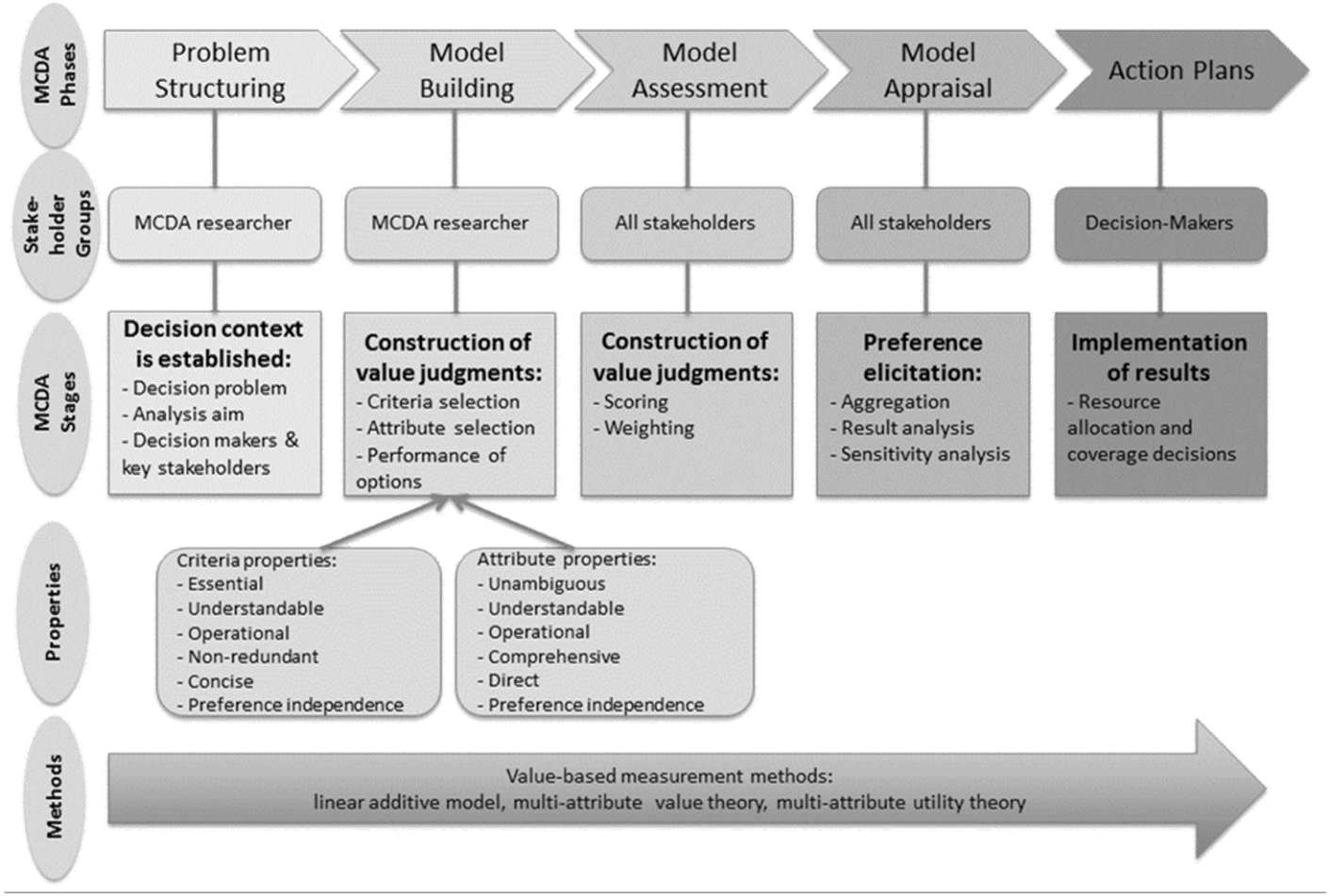
Decision Making body	Huntingdonshire Primary care Trust
Application	PCT spend of growth money
Criteria	Effectiveness (QALYs) Burden of disease Equity/fairness between social groups Deliverability and speed of implementation Engagement of public and professionals demand management Acceptability to public and profession Certainty/quality of evidence. Fit with national standard/targets Criteria chosen at independently facilitated workshop with PCT managers + GPs
Weights	Effectiveness 23.67%; burden of disease 16.67%; equity 13.67%; deliverability 13.67%; engagement 13.00%; acceptability 7.33%M; certainty 7.00%M; national standards 5.00%. Weight selected by workshop participants working in three groups, with one round of challenge and reweighting, and final weight= mean of group´ weight.
Use in decision making	Pilot scheme to test applicability to ranking priorities of incremental claims on PCT´s budget. Diagrammatic comparison to benefits points and cost per patient to inform decision, but not to make the decision.

Source: Devlin N et al 2015 (10), Incorporating multiple criteria in HTA. Office of Health Economics (11)

Some guides and handbooks to help in the process of MCDA can be found in the scientific literature. Some recommended handbooks Office of Health Economics (10) and Department for Communities and Local Government (11). A number of studies are also recommended (2,5,12).

Although there are different multi-criteria decision analysis approaches, all of them follow a general structure, as shown in Figure 1.

Figure 1. An overview of Multi-criteria decision analysis



Source: Angelis et al 2015 (13)

There are different MCDA methods, which are described in a number of published studies (14-17). The methods depend on the specific problem and user demands. The main difference between the approaches is the way in which this aggregation is done. A brief description of the three most commonly used methods are described below (14):

I. Value measurement models: models the intervention based on an overall benefit score estimated as the weight average of the criteria. Methods in this category include: simple linear additive model (SLAM), ordinal weighting methods, direct weighting, methods based on multi-attribute utility theory (MAUT) or on multi-attribute value theory (17) and the Analytic Hierarchy Process (AHP) (18). In the literature reviewed, this model is the most recommended due to its usefulness, simplicity and practicality (19).
II. Outranking models are based on a general concept of dominance. Alternative pairs are compared, initially for each criterion to determine the preference extent for one over another. The preference information across all criteria is aggregated to determine the strength of evidence for one selection over another. Methods in this family include ELECTRE I to IV, ELECTRE IS, ELECTRE TRI and PROMETHEE.
III. Goal, aspiration, or reference-level models involves derivation of alternatives, which most closely match a pre-defined satisfactory level of achievement for each criterion.

The key steps to perform a Multi-criteria Decision Analysis could be summarized into a number of stages (Figure 2), as follows (17):

Establish the decision context (or decision tree) - What is to be decided, by whom and identify criteria and attributes for assessing the value of each health technology (20).

In this step, it is necessary to establish the objective and define the decision problem, identify the key issues, define the alternatives or health treatments, select the stakeholders for the MCDA and their evaluation criteria. Different social, economic and environmental values and interests are represented, and the different scores and uncertainties can be discussed among participating stakeholders and consider the relevant trade-offs.

Define criteria and select attributes: Both quantitative and qualitative data can be incorporated to understand the relative value placed on different dimensions of decision options. The criteria must be defined through a process of literature review and stakeholder discussion and/or validation. Care should be exercised so that criteria are essential (all critical values should be included), understandable (so that all participants in the decision-making process should have a clear understanding of the criteria and their implications), operational (so that the performance of the options against the criteria need to be measurable), non-redundant (no double counting or overlap), and

concise (only the smallest number of criteria that can adequately capture the decision problem should be used) (11,22). The attributes should be clearly defined and based on generally accepted principles and evidence. Consequently, the definition of the criteria and values emerges in the value tree.

MCDA provides a systematic process for clarifying what is being taken into account, ie the criteria. Each criterion is to be scored and weighted according to importance (23). As described in the literature, MDCA related papers use an average of 8.2 (range 3-19) criteria to assess interventions (5). This can be a weakness since there may be a need for debate and consensus between the different options or that some criteria interact/overlap with others.

Assign weights to the attributes to indicate their relative importance for the decision. Score the expected performance of each treatment option against the attributes. Elicit weights for the different attributes to indicate their relative importance in the problem under investigation. Subsequently, scores and weights need to be combined. Once this has taken place, the evidence needs to be aggregated to indicate overall value.

Assigning the relative weight of each criterion is necessary. After scoring the criteria a multicriteria evaluation is performed. The results can be presented per individual or aggregated in different groups.

Assimilating evidence on the topic is essential to assign a weight to each criterion. Several information sources are used in the assessment process for MCDA. If there is a lack of data, this hinders the search for relevant studies and makes performance measurement more challenging. When evidence is sparse, such as for long-term economic impact, implementation feasibility and acceptability expert opinion can be of help. A discussion process with the different stakeholders increases their awareness of the existing shortcomings in management effectiveness, trade-offs and of how conflicts may be avoided. The challenge is to make a consensus with all the people involved in MCDA about which criteria matter and their weight.

In evidence identification there are some potential sources of bias, such as selection bias or lack of comparability. Furthermore, it is necessary to translate the relative effects to an absolute scale using an estimate of the absolute effect for suitably selected baseline treatment (see network meta-analysis in Chapter: III.2. Systematic Review).

With regards to weight-assessment, in the majority of papers identified in the literature, an analytical hierarchy process is conducted. Two difficulties were identified in the literature: variation in weight results of dominance of a particular point of view, and, the difficulty in achieving a representativeness of the population.

A value index is calculated by combining the scores and weights. Afterwards, the different weighted scores are calculated by the combination of the individual criteria scores with their respective weights. Finally, the overall value scores of each treatment or comparison item is obtained by the sum up of the weighted score. It could be done in a single operation or hierarchically (14).

Consider the implications of the results and test their sensitivity to reasonable variations in weights and scores.

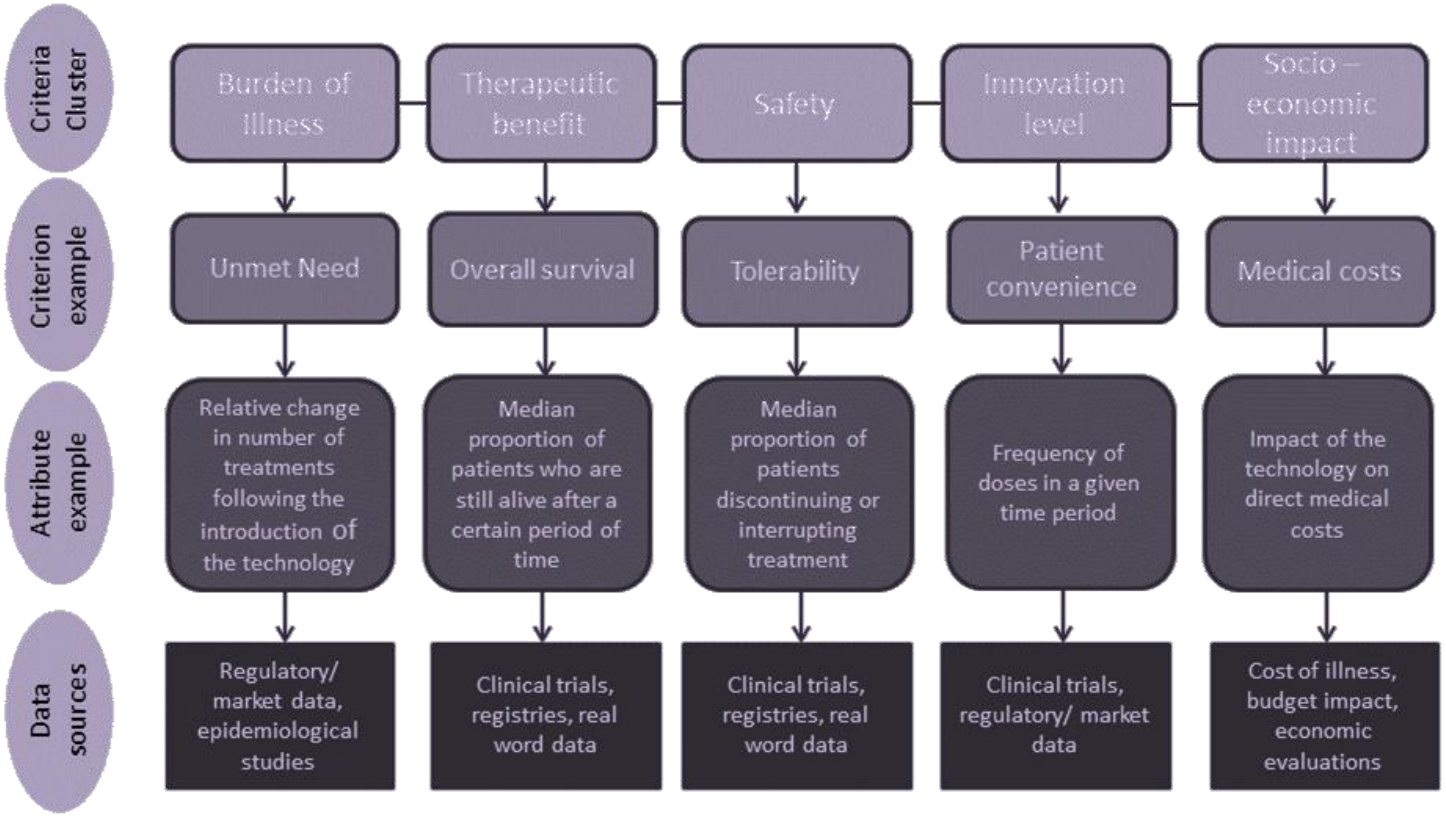
The sensitivity analysis is performed in three proposed steps:

I. Identify the sources of uncertainty.
II. Perform an assessment of the uncertainty.
III. Evaluate whether uncertainty will eventually lead to a different decision.

The approaches to manage the uncertainty are: deterministic sensitivity analyses, probabilistic sensitivity analyses, Bayesian frameworks, fuzzy set theory, and grey theory. According to the literature overviewed, the majority of the papers used probabilistic sensitivity analysis; see also a study recommended for this purpose (24).

Based on the above review, a model that captures different dimensions of value and also includes examples of criteria and attributes is shown on Figure 3. Altogether, there are 5 criteria clusters, notably burden of disease, therapeutic impact, safety profile, innovation level & potential and socio-economic impact.

Figure 2. Value tree hierarchies and data sources



Source: Angelis et al 2015 (13)

MCDA and the debate of how MCDA can be applied in health care decision-making is about 10 years old. It can be argued that MCDA needs time to mature before an accurate assessment of its contribution can be made. Nevertheless, the number of publications and experiences on MCDA has increased, and is shown to be a promising tool. Several examples of Multi-criteria decision analysis may be found in the peer review literature (7, 11).

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V. Implementation of the decisions

1. Evidence Informed Practice Guidelines

Many organizations recognize the importance of accurate diagnosis and management of patients suffering from several diseases and conditions. In order to provide the appropriate and best care, evidence-based guidelines are developed with specific recommendations for the treatment of each disease and/or condition. Some criteria should be observed when developing guidelines like (1):

- High prevalence of the condition and burden of disease
- High frequency of the medical procedure
- High associated cost
- Effects on premature mortality and avoidable morbidity
- Evidence that medical care can make a difference in outcomes
- Awareness of current variations in clinical practice

> *"A WHO guideline is any document developed by the World Health Organization containing recommendations for clinical practice or public health policy. A recommendation tells the intended end-user of the guideline what he or she can or should do in specific situations to achieve the best health outcomes possible, individually or collectively. It offers a choice among different interventions or measures having an anticipated positive impact on health and implications for the use of resources" (2).*

Methodological aspects for the development of guides

The World Health Organization (WHO) has developed the Handbook for Guideline Development, a complete guide that aims to provide advice and support through evidence-based guidance using the GRADE approach. The document comprises recommendations on equity, human rights, gender and social determinants and has an entire chapter about adaptation, implementation and evaluation of guidelines. The main standards and procedures proposed by WHO in its handbook are (2):

- Purpose and Target audience**:** a clearly defined purpose must be identified in the guideline, and the recommendations need to be tailored to the target audience(2).
- Establishing groups involved in the guideline development: the group committed to the development of the guidelines should be multidisciplinary and balanced, comprising a variety of methodological experts, clinicians and individuals who are likely to be affected by the clinical practice guideline. Patient and public involvement should also be facilitated (1,2).

Example

WHO suggests that an economist can be an important contributor to the guideline when resource related issues are at play in the formulation of recommendations. Also, depending on the topic, an expert in matters of equity, gender and human rights can contribute to the analysis and interpretation of evidence and determine how the intervention could affect specific populations. An expert in guideline development processes and methods should be involved in the development of WHO guidelines.

- Incorporate equity, human rights, gender and social aspects into guidelines: these issues should be considered early and throughout the guideline development process. By incorporating these aspects, it is possible to monitor how the recommendations will affect them, and whether the relevant subpopulations have been considered in the key research questions.
- Conflict of Interest Disclosure**:** individuals considered for participation in the development of the guideline should declare all **conflicts of interest** by written disclosure, to those convening the guideline development group (1).
- Formulating questions and selecting outcomes: crucially, the questions formulated determine the evidence search and base the recommendations of the guideline (2).
- Evidences**:** recommendations must be based on the best available evidence and systematic reviews should be used for guideline strengthening (1-7).
- Developing Recommendations**:** users of guidelines need to know how much confidence they can place in the evidence and recommendations (8). For each recommendation, a clear description of benefits and harms should be provided, together with a summary of relevant evidence available. A description and explanation of any differences of opinion regarding the recommendation also shall be provided in the document (1,2,9-11).
- Formal Consensus**:** occasionally, the main clinical authors can write a summary of the key evidence and draft initial recommendations and qualifying statements to be incorporated into the systematic reviews findings (10).
- External experts review**:** the guidelines ought to be reviewed by external experts for feedback. External reviewers should reflect the various levels of care comprising all relevant stakeholders, including scientific and clinical experts, organizations such as health care, specialty societies, federal government, patients, and representatives of the public (2,5,9,10).
- Publishing and updating**:** practice guidelines should be updated whenever new evidence suggests the need for modification of clinically important recommendations. For this, literature reviews should be carried out continuously. It is also important to provide the decision maker with date of the last systematic review conducted to base the guideline upon (9,10,12).

Adaptation of guidelines

Developing a guideline requires many resources, mainly time and human, and thus the adaptation of an existing guideline can be an efficient option. However, adapting a guideline involves selecting the appropriate recommendations and transferring them into a new local context. Any modifications to an existing guideline should follow the same principles and rules used as of the original guideline development and should not ignore the best evidence available. If recommendations are changed, the reasons should be provided (13). It is always important to indicate the document from which the adapted version originated.

A tool is provided by the international working group ADAPTE. The ADAPTE process (14) is an instrument to aid the adaptation of guidelines produced in one setting for use in a different cultural and organizational context (15-17). It has some limitations that countries have had to precisely modify and for this reason, PAHO has been working to establish a repository of guidelines using the GRADE approach and establishing mechanisms for facilitating the adaptation of guidelines at the national and local level.

Many organizations have developed grading systems to assess the quality of evidence and recommendations. A very widely used and known system is the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE). Currently many national and international guideline development groups, including WHO and PAHO, use the GRADE approach. The GRADE system can be applied across a wide range of interventions and contexts, and enables more consistent judgments, and communication of such judgments to support better-informed choices in healthcare (2,8).

Checklist for identifying guidelines requiring adaptation

The table below was proposed based on a study that evaluated some organizations responsible for developing guidelines. After analyzing several guidelines, the authors defined five questions that to identify guidelines that require adaptation to local circumstances (18).

Table 1. Checklist for identifying guidelines requiring adaptation

Factors influencing the applicability or transferability of guidelines across different settings	**Response** (positive answers increase the likelihood that recommendations should be flagged as requiring adaptation)
1. Is there important variation in need (prevalence, baseline risk or health status) that might lead to different decisions?	☐ Yes ☐ Unclear ☐ No
2. Is there important variation in the availability of resources that might lead to different decisions?	☐ Yes ☐ Unclear ☐ No
3. Is there important variation in costs (e.g. of drugs or human resources) that might lead to different decisions?	☐ Yes ☐ Unclear ☐ No
4. Is there important variation in the presence of factors that could modify the expected effects (e.g. resistance patterns of microbiological pathogens), which might lead to different decisions?	☐ Yes ☐ Unclear ☐ No
5 Is there important variation in the relative values of the main benefits and downsides that might lead to different decisions?	☐ Yes ☐ Unclear ☐ No

Source: Schünemann et al 2006 (16)

Guidelines in the Americas

Many countries have formally established national guideline programs for producing evidence-based recommendations. These programs aim to make higher-quality healthcare more accessible, equitable, and affordable, while ensuring that the evidence is adequately translated and used. The Pan American Health Organization has been working with Member States to strengthen their health systems and promote the use of evidence-based programs for public health and practice. The Knowledge Management, Bioethics and Research Department, Knowledge Translation and Evidence program, provides technical cooperation for strengthening national guideline programs and facilitates the implementation of standards and procedures for guideline development within the Organization, as well as providing regional support to the WHO Guideline Review Committee (GRC) (17).

Developing guidelines and making them available to healthcare professionals does not ensure their use. The purpose of a guideline is to improve the health and well-being of individuals and populations. To accomplish that, guidelines need to be disseminated, adopted, and their recommendations implemented (2,5).

WHO and PAHO Guidelines Repositories:

Most recent guidelines approved by the Guideline Review Committee are listed in the link below:

http://www.who.int/publications/guidelines/en/

The Pan American Health Organization also provides a Repository of guidelines in the link below. Information regarding its Member States and other jurisdictions can also be found at:

http://www.paho.org/hq/index.php?option=com_content&view=article&id=9756&Itemid=41052&lang=en

2. Disinvestment/ Reinvestment Decisions & Countries Examples

Health technologies have been incorporated to health systems as an additional and not substitutive feature. Thus, a significant portion of the health technologies currently in use has never been assessed, and therefore their cost-effectiveness remains unknown and they become obsolete (19,20,21). The use of obsolete technology can be harmful, ineffective and non-cost-effective and therefore identifying these and properly evaluation them is crucial (22). The effectiveness and safety of health care is one of the main problems of health systems. It is estimated that the use of new technology and abuse of existing technology is the cause for over 50% of the increase in healthcare costs (23). Disinvestment are processes by which a health system or service removes technologies that are considered unsafe, ineffective and/or inefficient, without necessarily replacing them (24,25). Therefore, the re-evaluation of existing technologies and services included in the healthcare system, applying criteria and standards of effectiveness, safety and cost-effectiveness is essential.

It relates to the processes of (partially or completely) withdrawing resources from any existing health care practices, procedures, technologies or pharmaceuticals that are deemed to deliver little or no health gain for their cost, and thus are not efficient health resource allocations (26) .

England, Spain, Australia, Brazil, Scotland and Canada are countries with disinvestment systems already in place. Disinvestment initiatives were identified in Denmark, France, Italy and Sweden (22,27).

Countries examples

England

The first recommendations that mention “disinvestment” date from 2007 and were evidence-based decisions. In its Guideline for Behavior change: The principles for effective interventions, NICE recommends “disinvest in interventions or programs if there is good evidence to suggest they are not effective” and “disinvest in approaches that lack supporting evidence”. According to NICE’s guide for developing service guidance, the Committee that evaluates the technologies should identify potential areas for disinvestment and follow the same evidence-based process used when the technology was firstly incorporated. The impact of the technology on the health of a population must also be considered (22).

Resources of interest:

NICE "do not do" recommendations database 2007 (24)

"Disinvestment" opportunities highlighted by Cochrane reviews (25)

Scotland

The Scottish Health Technologies Group aims to develop a method to investigate the potential disinvestment opportunities for the Scottish healthcare system based on "cost-saving" recommendations done by NICE.

Spain

A law issued in 2004 in the Basque Region stated that "managers of healthcare services should inform the Basque Health Service Director about all technologies that are no longer being used". In 2006, a national law (Real Decreto 1030/2006, de 15 de Septiembre) recognized the withdrawal of health technologies when "(i) There is evidence of a lack of efficacy, effectiveness or efficiency or an unfavorable risk-benefit ratio; (ii) There is no interest in a technology as a consequence of the technological and scientific development or when its usefulness has not been proven and (iii) It no longer fulfills the criteria established in the current legislation" (22,28).

The Basque Office for HTA (Osteba) launched a **Guideline for disinvestment** (28) that intends to enable a systematic process to assess the potential for disinvestment in non-assessed health technologies or in some of their indications (28).

Also, the Ministry of Economy and Competitiveness of Spain published a Health Technology Assessment Report to identify specific healthcare practices and technologies of uncertain effectiveness, safety and efficiency for disinvestment: Identifying opportunities for health care disinvestment (29).

Galician agency Avalia-t developed a document called "Identification, prioritization and assessment of obsolete health technologies: A methodological guide", which is a methodological manual for identification, prioritization and obsolete health technology assessment. In order to prioritize potentially obsolete health technologies for subsequent assessment, Avalia-t offers an online, open access prioritization tool (PriTec tool) that consists of three domains (population/end-users, risk/benefit, and costs, organization and other implications) with a total of ten criteria.

PriTec is an automatically executable web application that has been developed to facilitate the prioritization of technologies susceptible to post-introduction observation and the prioritization of potentially obsolete health technologies. It can compare up to 50 technologies simultaneously

and generate a report that includes the main results in the format of tables or charts.

Canada

In their Guideline for the Economic Evaluation of Health Technologies (30), CADTH recommends using stratified analysis or sensitivity analysis to evaluate the cost-effectiveness of technologies that are currently funded for potential changes in reimbursement status, such as delisting. In the Policy on the obsolescence of health technologies (31), CADTH shows explicit commitment to disinvestment political agenda.

The Ontario Health Technology Advisory Committee makes recommendations about health technologies to the Ontario Ministry of Health and the healthcare system and, among its tasks, is to determine whether the technologies meet best practice and expected investment or disinvestment across the province. However, neither process nor methodology is clearly shown in its website (32,33).

Resources of interest:

- Reassessment of Health Technologies: Obsolescente and Waste. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2009.

  This report promotes discussion about health technology obsolescence, considers related practical and policy issues, and proposes a framework for advancing the reassessment and decommissioning of health technologies in Canada.

- Policy perspectives on the obsolescence of Health Technologies in Canada. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2009.

  In this document we conclude a regulatory framework for disinvestment decision-making, additional resources… regulatory support provided for health technology assessment recommendations for (a) removing or (b) reducing reimbursement or (c) restricting use of a technology or practice, and a centralized process to systematically and transparently identify existing, potentially ineffective practices on which to prioritize candidates for assessment.

Australia

The first article considering disinvestment in healthcare in Australia was published in 2009 (28). HTA Policy in Australia includes disinvestment, and it is a routine task by MSAC. However, the way in which it is accomplished could not be identified (see the Medical Services Advisory Committee website). The Pharmaceutical Benefits Advisory Committee (PBAC) has responsibility for assessment of pharmaceutical products and vaccines for inclusion on the National Immunisation Program and it has developed explicit criteria for removing a drug from the Pharmaceutical Benefits Scheme (PBS). Thus, it has the capacity to implement its own reviews of drugs or classes of drugs, which could result in disinvestment. This review capacity has existed since 2006, but as of yet has not been used in such a way as explicitly lead to disinvestment decisions (34).

Brazil

A national law issued in 2011 states that all technology to be invested or disinvested in the Brazilian healthcare system has to be evaluated. The deliberations of CONITEC (HTA agency) were analyzed and no standard methodology was found for disinvestment recommendations (35-40). In only one case, the disinvestment was evidence-based.

Examples

1. The Department of Specialized Care of the Secretariat for Healthcare of the Ministry of Health requested the delisting of biological therapy (adalimumab, certolizumab pegol, etanercept, infliximab, golimumab, rituximab, abatacept and tocilizumab) for rheumatoid lung disease and rheumatoid vasculitis due to adverse events. Brazilian HTA body proceeded with the PubMed/Medline search – which is available in the dossier – and, based on the evidence found, recommended the delisting of these drugs for those particular therapies (36).
2. The Department of Specialized Care of the Secretariat for Healthcare of the Ministry of Health requested the exclusion of cyclosporine for Feltry Syndrome (ICD M050), rheumatoid arthritis with involvement of other organs and systems (M053), sero-negative rheumatoid arthritis (M060) and other specified rheumatoid arthritis (M068), as this medicine only registered in the country rheumatoid lung disease (M051), rheumatoid vasculitis (M052) and juvenile rheumatoid arthritis (M08.0) (38).

Colombia

Colombia has a national list of technologies not covered nor reimbursed by the Ministry of Health. This list is updated every two years, however, no methodology was found for the delisting process (40). The Colombian Law

issued in 2015 states that technologies that meet the following criteria will be explicitly excluded according to a technical-scientific, public, collective, participatory and transparent procedure. Neither the exclusion list nor the procedures are public so far.

Table 1. Criteria for technologies delisting in Colombia

Criteria for technologies delisting in Colombia
Cosmetics not related to the recovery or maintenance of functional capacity or life of the patient;
No scientific evidence of safety, clinical efficacy nor clinical effectiveness;
Technologies under trial

Source: Ley Estatutaria 1751/2015. Colombia

The HTAi Interest Sub-Group on Disinvestment of Obsolete or Low Added Value Health Technologies (DSIG) has over 100 members working in a wide variety of capacities to support decision-making on disinvestment, and promote initiatives or programs in their agencies, organizations and countries. It aims to be a key international centre for sharing knowledge and expertise, both in methods for prioritizing and assessing obsolete or low-added value technologies, and in the practical application of disinvestment for health systems.

The purpose of this group is to:

- Formalize a forum of discussion on this topic in HTAi.
- Develop a repository of current experiences and methodological approaches to dis-investment.
- Establish criteria on common approaches to the topic.
- Propose methodological approaches.
- Give advice to members of HTAi and other agencies working in this area.

The resources available on the web for the DSIG included a Survey of Disinvestment Activities, with the aim to share and discuss the results, and reference bibliography. Other resources of interest related to disinvestment are:

- Reducing the use of ineffective health care interventions (Center for Health Economics Research and Evaluation).
- Identification, prioritization and assessment of obsolete technologies. A methodological guideline.
- GuNFT - Guideline for Not Funding existing Technologies.
- Using HTAs to support disinvestment - the case of sleep apnea in Norway.
- Methods of no value must be abandoned (background paper).

3. Monitoring and Evaluation

Monitoring can be defined as routine tracking and reporting of priority information about a policy, program and/or project, and provides information on where these products are at any given time. On the other hand, evaluation is a systematic collection of information about these products (policy/program/project). An evaluation provides information on whether or not those products are working and why objectives are not being achieved. In healthcare, M&E is strategically used to make the correct decisions in order to achieve the desired results of a policy, a program and/or a project (41).

A good way to start an M&E plan is by building a clear framework of the program that explains how it is supposed to work, by identifying the components of the initiative and the actions needed achieve the desired goal. This is a continuous process of M&E (41).

One of the methodologies used in the process of M&E is the "theory of change". This is a pathway that includes research-supported assumptions for decision-makers use to explain the process of change (42). An initiative that relies on this theory has been identified: the international Decision Support Initiative (iDSI), launched by NICE International, aims to support low and middle-income governments in making resource allocation decisions for healthcare. Further information at:

- International Decision Support Initiative. NICE.
- The International Decision Support Initiative

One of the key principles of HTA relies on M&E; The implementation of HTA findings needs to be monitored, both to ensure the original HTAs is valuable and to ensure that findings are being implemented in a fair and correct manner (43).

Knowing that HTA reports can impact a healthcare system in several ways (table below), M&E becomes a valuable tool for providing decision-makers with specific information on objective achievement (44).

Impacts of HTA findings have been reported on through technology adoption, disinvestment, reimbursement, and other policies and practices (44,45) however, M&E strategy is not mentioned in these cases.

How the HTA report can impact a healthcare system:

- Regulatory
- Third-party payment policy (coverage, pricing, reimbursement)
- Rate of use of a HT
- Clinical Practice Guidelines
- Stakeholders awareness and behavior
- Acquisition, adoption, or diffusion of a HT
- Organization/ delivery of healthcare
- R&D priorities and associated spending levels
- Allocation of resources
- Investment decisions

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