



**HEALTH
TECHNOLOGY
ASSESSMENT IN THE
EUROPEAN UNION**
STATE OF ART AND
FUTURE SCENARIOS

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EXECUTIVE SUMMARY

Health Technology Assessment (HTA) is defined as a multidisciplinary field of policy analysis and, as such, it studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology. A major purpose of HTA is to inform policy decision located at different levels in order to shape both investment/disinvestment choices and/or coverage and reimbursement decisions. Nowadays we are witness to a dramatic heterogeneity of HTA methodologies and regulatory and decision making frameworks among European Member States.

The aim of this paper is twofold. On the one hand describes the state of the art in Europe and at comparing HTA methodologies, functions, governance, and role in policy making among representative EU countries. On the other hand it underlines the need to achieve a greater degree of harmonization, by tracking similarities and differences among Member States to highlight shortcomings and to hypothesise future developments. The paper is divided into four chapters.

Chapter 1 defines Health Technology Assessment and describes its origins and its rationale, with a focus on aspects frequently considered and problems faced when selecting components of an assessment (paragraph 1.1). Emphasis is usually put more on safety, clinical effectiveness, economic and budgetary considerations, while acceptability to health care providers and patients, equity issues, ethical issues and feasibility considerations

are not considered as often. In particular, equity and ethical issues are the most debated among those eligible for inclusion.

In 2014, EU aggregate health care expenditure, comprehensive of government schemes and compulsory contributory health care financing schemes, covered an amount of 1.095 billion €. EU countries taken into consideration for the purpose of this paper spend an average of 2.706 € per capita on health care and more than 307 € per head for medical goods: in some Member States (like Germany, France, Spain and Italy) this item represent more than 14% of government and compulsory contributory health care schemes expenditure. This is one of the reasons why it is important to define HTA as a tool to inform decision makers (paragraph 1.2). Even if international networks and good practices for conducting HTA exist, decisions on how to implement health technology assessments are the prerogative of national governments, thus creating inequalities among countries in HTA inclusion within national regulatory frameworks.

Chapter 2 describes the development of HTA in Europe, starting from the creation of the European network for HTA (EUnetHTA) in 2006 (paragraph 2.1) and arriving at the main objectives reached in latest years (paragraph 2.2). Particular attention is given to the domains of the so-called “core model” – which represents the framework for HTA reports – and on their classification

into categories to distinguish between “rapid REA” and “full HTA”. Most HTA agencies agree that activities within the domains of technology use, safety, effectiveness, economic evaluation and organisational aspects are the most easily applicable and adaptable across countries and different policy settings. The chapter ends with a description of HTA in the EU framework programme for research and innovation, from FP7 projects to Horizon 2020 (paragraph 2.3).

Chapter 3 shows a cross-country comparison of HTA among European Member States (paragraph 3.1). Since the late 1970s, many European countries have established HTA systems to inform coverage and pricing decisions. Today, almost all EU countries have some kind of national HTA agency that coordinates and disseminates assessment reports for informational and scientific purposes, but for the most part, this function is not directly involved in coverage and pricing decisions. Many differences exist also among countries where HTA bodies are provided by law to participate in national decision making process.

Chapter 4 describes main challenges to HTA harmonisation in Europe, evaluating the possibility to create a centralised European HTA agency that would reduce the risk of costly repetitions and duplication of efforts in their separate filings for national bodies. In contrast to what happened with the creation of the EMA, there are a number of factors which present significant resistance to the delegation of full HTA decision powers to a EU agency (paragraphs 4.1 and 4.2). However, a progressive harmonisation of the type of

evidence pharmaceutical companies must provide, and the development of a mutual recognition process of a partially joint HTA report could potentially have a positive impact on market access. To this purpose, the European Commission recently opened a consultation to consider the views of a number of different stakeholders on the future of HTA across EU, with some of the responses reported in this paper (paragraph 4.3).

The first step of the HTA harmonisation could be cooperation in the development of joint Rapid Relative Effectiveness Assessments (REA) reports between EU countries and regions within countries, since processes and value dossier format requirements seem to bear more similarities than economic assessments. This would not affect national pricing and reimbursement decisions, and areas of price-setting and reimbursement should clearly remain a national responsibility (paragraphs 4.4 and 4.5). Extending cooperation to the clinical/medical components of impact assessment would improve the cost efficiency of national bodies’ resources, by allowing them to save time in order to generate more reports and further improve the average quality of HTAs in terms of management, relevance and transparency. Joint assessments would also reduce costs and the administrative burden on the industry, by reducing the number of submissions to be performed and a greater harmonisation in data requirements.

At the end of the paper, policy conclusions and implications are drawn.



PART



**WHAT IS HEALTH
TECHNOLOGY
ASSESSMENT?**

WHAT IS HEALTH TECHNOLOGY ASSESSMENT?

1.1. DEFINITION AND ORIGINS OF HEALTH TECHNOLOGY ASSESSMENT

Over the last five decades, technological innovation has yielded truly remarkable advances in health care delivery and patient outcomes. However, the proliferation of health care technology and its expanding uses have contributed to burgeoning health care costs. The development, adoption, and diffusion of technology has been, and continues to be, influenced by an expanding group of health sector policymakers and stakeholders. This is both a reflection of the growing demand for information (given the critical role of technology in modern society), its potential and the existing need for efficiency gain. Increasingly, Health Technology Assessment (HTA) is being utilised, primarily to provide input into decision making.

HTA is generally defined as the systematic evaluation of properties, effects, and/or impacts of health technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. The evidence derived through an HTA should address aspects of a medical or health technology such as safety, efficacy, effectiveness, cost, and cost-effectiveness, ethical and legal implications, both in absolute terms and in comparison with other competing technologies. To date, the most well known

applications have been in the field of pharmaceuticals, and have focused on cost-effectiveness. However, HTA has grown remarkably over the last decade, and should have much wider application in the coming years.

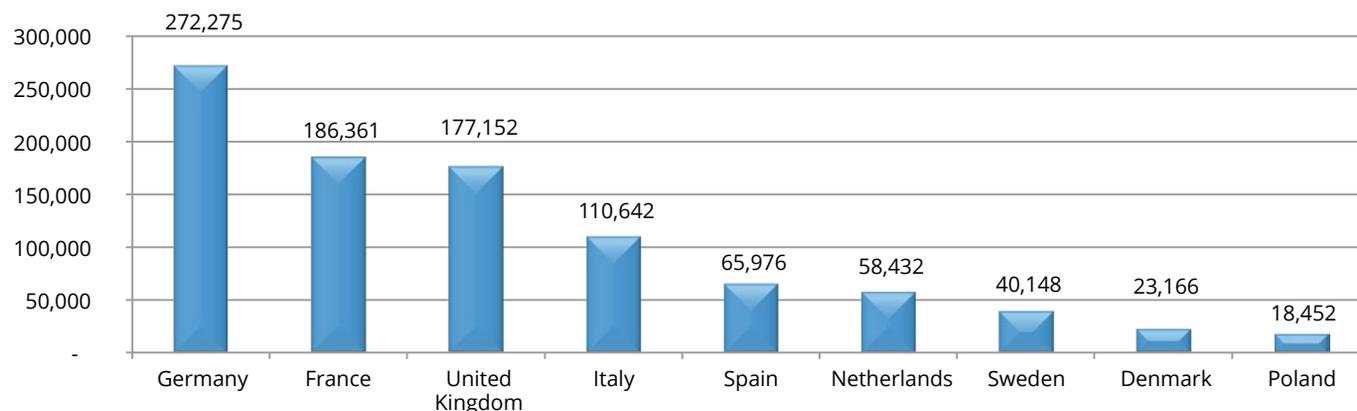
HTA dates back to around 1975 (when the Office of Technology Assessment in the US established its health program) and, in its early years of development, aimed at synthesising available evidence dealing with efficacy and cost-effectiveness of health care interventions in order to be helpful to health policy-makers. Since the early 1980s, HTA has sought more effective links with these policy-makers, particularly in Europe, where at present the main scope has been to influence administrators and clinicians with more effective dissemination and implementation of activity and results.

Early on, assessments tended to focus on large, expensive, machine-based technologies; however, later, the scope of HTA widened to include both smaller and softer technologies (such as counselling, organizational and management processes and so on). First HTA practitioners recognized that partial assessments might be preferable in circumstances where selected impacts are of particular interest or necessary because of financial constraints and, in practice, relatively few assessments have encompassed the full range of possible technological impact.

In recent years, the scope of HTA reports has diversified, taking into account broader issues: is a specific technology effective? Is it safe? Has a health improvement been witnessed and can it be quantified? Since the

Fig 1.1 Current public health care expenditure in million € (2014)

Source: Eurostat, data including government and compulsory contributory health care financing schemes



2008 financial crisis, the economic aspect of evaluation has become more important, with the sustainability of public finances becoming of primary interest for central governments and as such, policy makers must determine whether they can sustainably afford to add a specific medical technology to the set of interventions already included within a national health system.

HTA may have a significant impact on health expenditure and public coverage, enhancing access to care for a growing population, reducing inequalities and acting as a means to improve efficiency in allocating public resources. In 2014, EU aggregate health care expenditure¹ reached almost € 1,095 billion (Eurostat), distributed

¹ It includes government schemes and compulsory contributory health care financing schemes (from now on “public health care expenditure”). Our scope is to define coverage other than private insurance or out-of-pocket expenditure, that is compulsorily provided by governments.

among different European countries depending both on country dimension and macroeconomic characteristics, different policies and health care systems design. Figure 1.1 reports public health care expenditure in the EU countries taken into consideration later in the paper for mapping differences in HTA across representative EU countries².

Pharmaceuticals and medical devices not only represent a high share of public health care expenditure but also are highly innovative sectors, able to improve population health status and to cover unmet patients’ needs. For both reasons “medical goods” is, at present, the category most interested in HTA evaluation: it is made up of “pharmaceuticals and other medical non-durable goods” (that is pharmaceutical products and

² See chapter 3

non-durable medical goods intended for use in the diagnosis, cure, mitigation or treatment of disease, including prescribed medicines and over-the-counter drugs) and “therapeutic appliances and other medical” (that is medical durable goods including orthotic devices that support or correct deformities and/or abnormalities of the human body, orthopaedic appliances, prostheses or artificial extensions that replace a missing body part, and other prosthetic devices including implants which replace or supplement the functionality of a missing biological structure and medico-technical devices). The share of medical goods on government and compulsory health care financing schemes expenditure is very high in some countries while rather low in others, reflecting existing differences in healthcare systems and coverage amongst Europe.

According to Eurostat classification, public health expenditure for medical goods represents in Germany the 18% of public health expenditure. This share is quite high also in France (16,2%), Spain (16%) and Italy (14,5%), while it is lower than the mean of considered countries in Poland, United Kingdom, Netherlands, Sweden and Denmark (Figure 1.2).

A high per capita current public health expenditure is not always associated with a likewise high per capita expenditure for medical goods. Germany, France and Netherlands spend more than € 2,706 per capita on health care and more than € 307 per capita for medical goods (which are the means of the group of countries considered), while United Kingdom, Sweden and Denmark show a higher than the mean per capita public health expenditure but a lower than the mean per capita

Fig 1.2 Medical goods as a share of current public health expenditure (2014)

Source: I-Com elaboration on Eurostat data, including government and compulsory contributory health care financing schemes

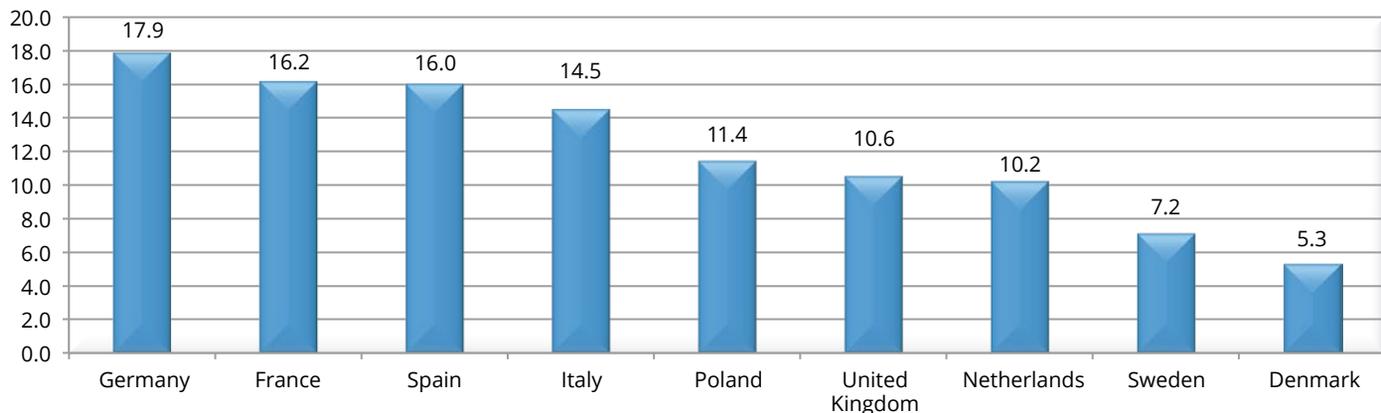
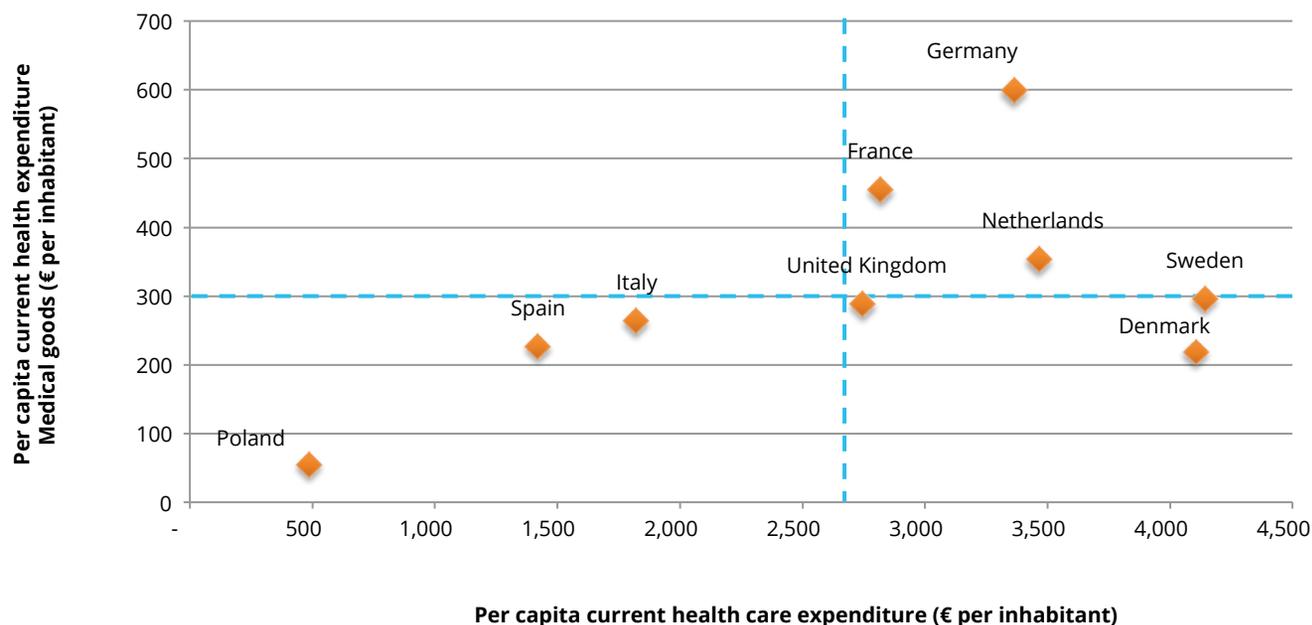


Fig 1.3 Per capita current health care and medical goods expenditure (2014)

Source: I-Com elaboration on Eurostat data, including government and compulsory contributory health care financing schemes



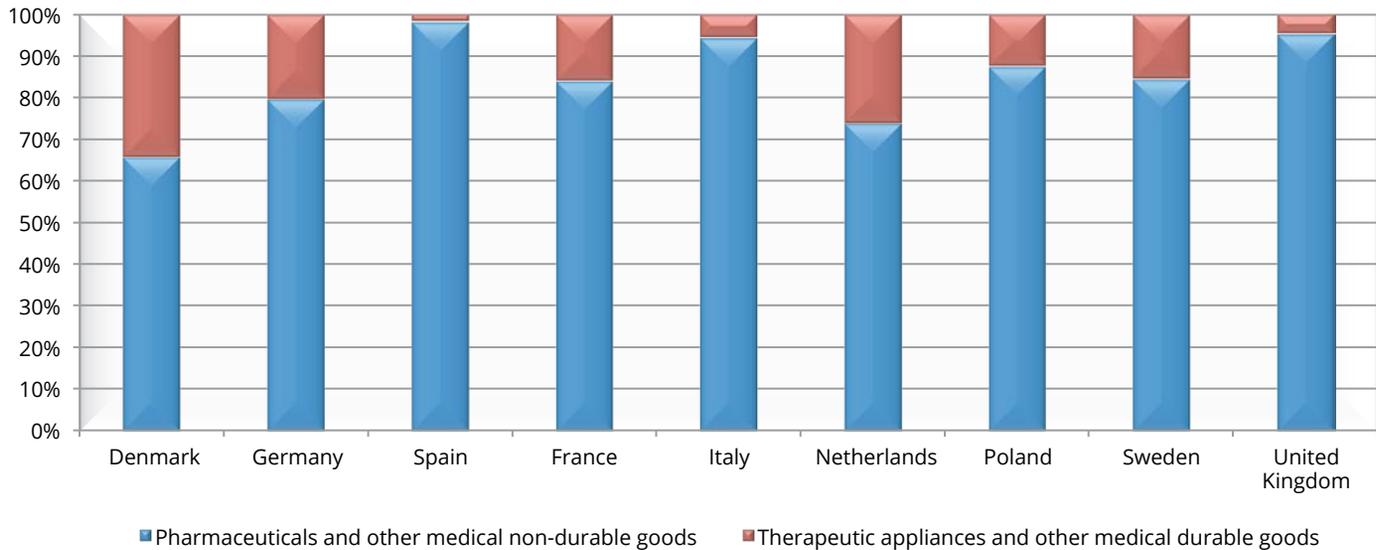
public expenditure for medical goods. Italy, Spain and Poland are below the mean for both indicators (Figure 1.3).

Under the Eurostat definition, current public expenditure in medical goods is mainly made of spending for “pharmaceuticals and other medical non-durable goods” in all countries. The latter represents 98% of the expenditure for medical goods in Spain, followed by United Kingdom (95%) and Italy (94%) (Figure 1.4). The economic dimension of this item of expenditure is significant, as such as differences among Member

States. HTA could have a direct impact on this sector. HTA could indeed bring to a relevant decrease in inequalities among covered expenditure for medical goods in Europe, overtaking differences in the design of health care systems, granting equal access to health care for patients irrespective of the subject providing the coverage and avoiding inefficiencies in the allocation of financing given the different health care needs of national population.

Fig 1.4 Allocation of current public expenditure for medical goods (2014)

Source: I-Com elaboration on Eurostat data, including government and compulsory contributory health care financing schemes



1.1.1. HTA main orientations and impact assessment

To better understand the nature of HTA, it is useful to clarify what a “health technology” is, and the different ways in which assessment reports can be used to inform policy decisions. Health technology is a technology (or process) whose application can improve patient care and population health in general. A health technology can be described by its physical nature (drugs, biologics, devices, medical procedures, public health programs), purpose (prevention, screening, diagnosis, treatment) and stage of diffusion (experimental, established, obsolete). A single health technology may fit in more than one category – consider technologies that combine

characteristics of drugs, devices or other major categories – and often a technology can be assessed in a report for certain indications and characteristics rather than for others. HTAs can differ both in terms of technologies assessed, and in aspects considered in the assessment. Usually, the evidence for assessing the properties and effects of a health technology, both in absolute terms and in comparison with other competing technologies, concern safety, efficacy, effectiveness, cost, cost-effectiveness, ethical and legal implications. Table 1.1 reports the main categories of health technologies assessed in WHO countries, together with the different aspects that can be considered in HTA.

Table 1.1 Aspects considered in HTA for different health technologies

Source: WHO Global Survey on HTA 2015

Types of health technologies	Aspects considered
Medicines	Safety
Vaccines	Clinical effectiveness
Medical devices	Economic consideration
Surgical interventions	Budget impact analysis
Service delivery models	Organization impact
Public health interventions	Equity issue
Clinical interventions	Ethical issue
	Feasibility considerations
	Acceptability to health care providers
	Acceptability to patients

The survey conducted in 2015 by the WHO reports that emphasis is usually more on safety, clinical effectiveness, economic and budgetary considerations than on other potential aspects that could be included. Acceptability to health care providers and patients, equity issues, ethical issues and feasibility considerations are not considered as often. Equity and ethical issues are the most debated among those eligible for inclusion. The absence (in the majority of cases) of ethical analysis in HTA reports has persisted, despite calls for more ethical analysis occurring throughout the history of technology assessment, and despite the fact that ethics is included in the HTA domain. Indeed, some academics argue that information derived from safety, clinical effectiveness and economic and budget impact analysis may not be sufficient to decide whether to disseminate a new intervention: economic

analysis is typically insensitive to distributive issues, that is, it is independent of the intervention recipient and any issues of systemic inequality.

However, the ethical issues involved in these questions fall short of quantitative methods to be assessed, since they are subjective by nature and there may be disagreement about ethical issues related to specific technologies. For this reason, some suggest that HTA should focus only on a limited range of questions for which quantitative methods are available, and let policy makers address other issues. On the other hand, it has also been argued that HTA should be as useful as it can be, and it is therefore necessary to consider how it can include these additional issues.

Above all, HTA is not merely a matter of collecting the facts about a healthcare technology. It is about collecting

facts about a healthcare technology that need to be considered plausible, relevant, and manageable to be inquired.

To begin to tackle this issue, three questions may be asked. The first regards contributing factors – what are the major contributory causes of a health problem, and what interventions are likely to solve it? The second question regards relevance, and it depends on values: what is considered important in terms of how healthcare is being delivered, and in terms of outcomes and their distribution? The third question, concerning amenability to inquiry, finally, depends on methodological and epistemological considerations: what sort of things can knowledge be acquired of, and what sort of methods can provide knowledge that is reliable?

In summary, two main problem areas can be identified. The first is data validity: data from trials may be inconclusive, conflicting, or susceptible to all sorts of bias. Therefore, it is necessary to look at the data carefully and ask what conclusions may confidently be drawn from them. Validity, moreover, can have different aspects and whether it involves experimental or non-experimental design, studies vary in their ability to produce significant findings. A validity measure is what allows comparison of pros and cons of different studies on the same theme. The second regards the value that a health technology can yield for relevant stakeholders (including ethical issues). In this case, different types and sources of data are needed, coming from stakeholders involved in the process generated by the use of a particular technology (i.e. public administrations, patients, families, citizens and so on).

1.1.2. A tool to inform decision makers

The efficient use of resources is crucial for the sustainability of a health system, particularly if the final goal is universal health coverage. In recent years, there has been significant increases in access to essential medicines, including generic medicines, medical devices and procedures, and to other health care interventions for promotion, prevention, diagnosis and treatment, rehabilitation and palliative care. Moreover, the last WHO World Health Report indicates that as much as 40% of spending on health is being wasted, and that there is an urgent need to find systematic and effective solutions to reduce inefficiencies and enhance the rational use of health technology.

To address this issue, both clinicians and policy makers have expressed greater interest in “evidence based medicine” (EBM), “comparative effectiveness research” (CER), and “health technology assessment” (HTA).

Evidence-based medicine constitutes the integration of the best available research evidence with clinical judgment as applied to the care of individual patients. It is conventionally defined as *“the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”* (Sackett et al, 1996, p. 71)”. It considers evidence deriving from well-controlled randomized clinical trials, essential to demonstrate a causal relationship between an intervention and an outcome and RCTs conducted in routine practice settings to address broader questions to assess external effectiveness. In summary, for a given healthcare intervention, EBM tries to both answer the

questions of “can it work?” (efficacy) and “does it work?” (effectiveness). EBM was born with the aim of applying scientific results to individual patient’s cases, and was later extended to health policy planning and delivery of services programs – now known as Evidence Based Health Care (EBHC).

Comparative effectiveness research is somewhat similar: it includes, and sometimes refers uniquely to, head-to-head clinical trials. However, it has also been referred to as the comparison of alternative health care interventions using already available clinical and administrative data. While EBM places emphasis on the processes by which clinicians gain knowledge of the most recent and relevant clinical research to determine whether medical interventions alter the disease course and/or improve the length or quality of life, the origins of HTA lie in the escalating costs of pharmaceuticals across the globe and the need to find transparent, fair and scientifically robust ways of determining whether new drugs are effective and cost effective (Sorensen et al, 2010).

As previously noted, health technology assessment is a method that considers evidence regarding clinical effectiveness, safety, cost-effectiveness and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies. However, the precise balance of these inputs depends on the purpose of each individual HTA. A major use of HTA is in informing reimbursement and coverage decisions answering for a given health care technology to the question “is it worth it?” HTA should then include cost-benefit assessment

and economic evaluation. HTA goes beyond the mere evaluation of therapeutic interventions of EBM, thus creating a direct link between research outcomes and concrete health policy choices. It appears how HTA and EBM complement each other and they are both direct consequences of market failure theory: markets alone are not optimally allocating resources in health care.

Both efficacy and effectiveness assessments depend on evidence accumulation deriving from the exponential growth in medical knowledge, and the degree of accuracy about the phenomenon being observed depends on the number of observations available for it. Theoretically, the greater the number of observations, the greater the chance to eliminate uncertainty, but questions of uncertainty have several dimensions and model design can differ depending on the preferred statistical method to assess the validity of the model.

Moreover, health outcome variables that are used to measure safety, efficacy and effectiveness of health care technologies differ, meaning that comparison among different assessment results can be complex. The main categories of health outcomes are: mortality, morbidity, adverse health effects, quality of life, functional status, and patient satisfaction. Besides, health outcomes can be indexed by different measures, which can also be generic, or disease specific³.

Methods employed in HTA to evaluate economic convenience, in order to provide useful information for reimbursement and coverage decisions, also differ from

3 Cfr Clifford S. Goodman (2014), Introduction to health technology assessment, Fundamental Concepts II-13

one another (see the BOX at the end of this chapter). Notwithstanding the variety of impact assessed, outcome variables, statistical methods and economic evaluation methods, the objective of HTA is unique: it must be a tool to support universal health coverage, as recognised by WHO during the 67th World Health Assembly in May 2014. The document strongly invites States to establish national systems of health intervention and technology assessment, in support of universal health coverage to inform policy decisions and, above all, to strengthen the link between health technology assessment and regulation and management, as appropriate.

1.2. GOVERNANCE: EVIDENCE IS GLOBAL, DECISION IS LOCAL

The core theme is straightforward: if international networks and good practices for conducting HTA exist, decisions on how to implement health technology assessments are the prerogative of national governments. As evidenced, health care decision making requires a great amount of (right) evidence and every day there are new health technologies available that can improve patient outcomes and refine health system efficiency. For this reason, a number of transnational HTA agencies exist. The common mission of these networks is to support and promote the development, communication, understanding and use of HTA around the world as a scientifically-based and multidisciplinary means of informing decision making on the use of

effective technologies and the efficient use of resources in health care. International HTA networks usually involve national HTA agencies or academic/scientific institutions that produce HTAs. They are developed as international discussion platforms for stakeholders engaged both in production and use of HTAs in decision making.

INAHTA was one of the first HTA networks. It was established in 1993 and at present involves 52 HTA agencies that support health system management. The aim of the network is to connect these agencies together to cooperate and share information about producing and disseminating HTA reports for evidence based decision making.

However, the global scientific and professional society for all those who produce, use, or encounter HTA Assessment is HTAi which gathers members from over 65 countries and embraces all stakeholders, including researchers, agencies, policy makers, industry, academia, health service providers, and patients/consumers. HTAi is a neutral forum that was officially launched in June 2003 at an international HTA conference in Canmore, Canada. The forum also provides access to a variety of resources for the public and stakeholders (such as The International Journal of Technology Assessment in Health Care).

In Europe, the WHO Regional Office for Europe coordinates HEN (Health Evidence Network): an information service for public health decision-makers in the WHO European Region, active since 2003. The aim of the latter is to support public health authorities to use the best available evidence in their own activities, to ensure greater links

Table 1.2 15 guiding principles for HTA linked to resource allocation decisions

Source: Drummond et Al. (2008)

- | | | | |
|----|--|-----|---|
| 1. | The goal and scope of HTA should be explicit and relevant to its use | 9. | HTAs should consider and address issues of generalizability and transferability |
| 2. | The HTA should be an unbiased and transparent exercise | 10. | Those conducting HTAs should actively engage all key stakeholder group |
| 3. | The HTA should include all relevant technologies | 11. | Those undertaking HTAs should actively seek all available data |
| 4. | A clear system for setting priorities for HTA should exist | 12. | The implementation of HTA findings needs to be monitored |
| 5. | The HTA should consider a wide range of evidence and outcomes | 13. | HTAs should be conducted in a timely manner |
| 6. | HTAs should consider a wide range of evidence and outcomes | 14. | HTA findings need to be communicated appropriately to different decision-makers |
| 7. | A full societal perspective should be considered with undertaking HTAs | 15. | The link between HTA findings and decision-making processes needs to be transparent and clearly defined |
| 8. | HTAs should explicitly characterize uncertainty surroundings estimates | | |

between evidence and health policies. HEN produces a synthesis report series, which is a useful tool for summarizing what is known about a specific policy issue, the gaps in the evidence, and the areas of debate.

As shown in greater detail in the next chapter, EU Member States cooperate on HTA in EUnetHTA: a network that coordinate the efforts of 29 European countries, including 25 Member States of the European Union in evaluating health technology in Europe (set up in 2013). The aim of transnational HTA network is to collect, systematise and provide international available evidence and, if it is the case, to propose policy options, but not to emanate recommendations: national governments are free to

define the role of HTAs in their national context as long as its design and implementation. The responsibility for implementing any recommendations does not belong normally to the body conducting the HTA, unless the organization is itself a decision maker.

In any case, HTA is rapidly evolving and it currently embraces different types of assessments. A set of fifteen principles, collected in Table 1.2, was crafted in order to assess existing or establish new HTA activities (Drummond et al.⁴).

⁴ Drummond M. et Al. (2008), "Key principles for the improved conduct of health technology assessments for resource allocation decisions"

BOX Summary of pharmacoeconomic methodologies

Source: I - Com

	Description	Application
COI	Estimates the cost of a disease on a defined population	Used to provide baseline to compare prevention/ treatment options against
CMA	Finds the least expensive cost alternative	Used when benefits are the same
CBA	Measures costs and benefits in monetary units and computes a net gain	Can compare programs with different objectives
CEA	Compares alternatives with therapeutic effects measured in physical units; computes a cost-effectiveness ratio	Can compare drugs/programs that differ in clinical outcomes and use the same unit of benefit
CUA	Physical, social, andmotional aspects of patient's well-being that are relevant and important to the patient	Used to compare drugs/programs that are life extending with serious side effects or those producing reductions in morbidity
QOL	Physical, social, andmotional aspects of patient's well-being that are relevant and important to the patient	Drug effects are assessed in areas not covered by laboratory or physiologic measurements



PART

**HEALTH
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IN EUROPE**

HEALTH TECHNOLOGY ASSESSMENT IN EUROPE

Since the establishment of the first national HTA agency in Sweden in the 1980s, the number of institutions involved in the assessment of health technologies has multiplied in Europe, and European countries are still increasingly creating formal systems to translate HTA into policy and reimbursement processes. However, many differences still exist both among methodologies used and regulatory and legislative frameworks.

HTA in Europe has developed through a combination of scientific, political and practical steps thanks to integration among EU Member States. The European network for HTA (EUnetHTA) was set up in 2006 with the objectives to promote more effective use of financial resources, to increase HTA input in decision making, to strengthen the link between HTA and policy making, and to support countries with less experience in HTA. An important outcome from European cooperation through EUnetHTA is the HTA Core Model, which aims at enabling national, and transnational production and sharing of HTA results in a common format and at representing a wide range of perspectives. Other outputs were a handbook on HTA capacity building, a toolkit for adapting existing HTA reports to other settings, and two databases of on-going projects and additional data collection on new technologies.

2.1. EU COOPERATION ON HTA: HOW DID WE GET THERE?

In 2004, the European Council concluded that the exchange of expertise and information through HTA may be enhanced through systematic EU cooperation in order to assist the Members States to plan, deliver and monitor health services, thanks to the best available evidence on the implications of health technology. Following a recommendation by the High Level Group on Health Services and Medical Care, and a call for proposals in the work programme of the European Commission Health and Consumer Protection Directorate General (DG SANCO), the European network for HTA (EUnetHTA) was developed and then supported by the European Commission, which defined Health Technology Assessment as a political priority. In 2005, a Commission call was answered by a group of 35 organisations throughout Europe, and the activities of the EUnetHTA Project were led by the Danish Centre for HTA (DACEHTA) in Copenhagen. The consequent activities of the European network for Health Technology Assessment were organised through the establishment of the EUnetHTA Collaboration 2009, the EUnetHTA Joint Action 2010-2012, EUnetHTA Joint Action 2 2012-2015 and EUnetHTA Joint Action 3 2016-2020.

The EUnetHTA Joint Action (2010-2012) refined the collaboration structure and tools with attention to global developments in the field. EUnetHTA Joint Action 2 (2012-2015) extended this by strengthening the practical application of tools and approaches to cross-border HTA

Fig 2.1 European cooperation on HTA

Source: European Commission



collaboration, further supporting and defining a system of collaboration on HTA. These two Joint Actions have proven the ability of national HTA organisations to work together and produce valuable products. EUnetHTA Joint Action 3 (2016-2020) will now proceed with the final step of establishing a permanent network on HTA in Europe. Joint Actions represent the scientific and financial

framework under which EUnetHTA mission has been implemented. In general, Joint Actions focus on developing common methodologies, on piloting joint REA and full HTA reports, and on developing and maintaining common IT tools, with the understanding that cooperation at EU level shall not interfere with areas of Member States' competence: individual States are free

to decide at which level they are willing to participate in cooperation efforts.

2.1.1. EUnetHTA, from the project to the Network

The legislative framework at the basis of the EUnetHTA project is the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. The Article 15 of the latter i.e. "Cooperation on health technology assessment" explicitly provides that the European Union shall *"support and facilitate cooperation and the exchange of scientific information among Member States within a voluntary network connecting national authorities or bodies responsible for health technology assessment designated by the Member States"*, and that *"the members of such a health technology assessment network shall participate in, and contribute to, the network's activities in accordance with the legislation of the Member State where they are established"*. According to the document, such a network should operate on the basis of the principle of good governance including transparency, objectivity, independence of expertise, fairness of procedure and appropriate stakeholder consultations.

The rules for the establishment, management and functioning of the Network of national authorities or bodies responsible for health technology assessment are then provided by the Commission Implementing Decision of 26 June 2013, while the rules of procedure of the health technology assessment network were adopted at the first HTA network meeting in October 2013.

As defined by the Directive, the objectives of the HTA network shall be to support cooperation between national authorities or bodies and to broadly support Member States in the provision of comparable and transferable information. The final goal is to avoid duplication of efforts and assessments and, above all, to enable Member States to develop and share methodologies. To reach these objectives, the first Joint Action (JA 1) developed the methodology for joint HTA assessments while JA 2 developed ten pilots to follow for the testing methodology and procedure of joint assessments. The latest JA 3 will increase the use, quality and efficiency of joint work at a European level and support re-use of transnational HTA reports and activities in regional and national contexts. In synthesis JA 3 seems to go towards a better integration of tools and methods in national settings. One of the objectives of this Joint Action is to decentralise the collaborative production of structured HTA core information and rapid HTA's. Methodologies and production-related information and communication technology infrastructure will be finalised as stand-alone support network from 2020 onwards. That is also because the activities of EUnetHTA are being held with the financial support of the European Commission only until 2020.

2.2. MAIN PROJECT RESULTS AND POTENTIAL CHALLENGES

Since it began, the objectives of EUnetHTA have been progressively adjusted in order to reflect the changing healthcare systems environment, experience, needs and mid-term results from work performed, Strategic objectives have been defined in order to lead to the development of a set of practical tools. For this reason each work package has been expected to produce specific deliverables (concrete outputs) connected with specific objectives.

The deliverables are structured to allow the application of the methodological guidance on HTA in a transnational context and therefore to facilitate sharing of information and coordination of HTA activities among countries.

To date, the main outputs of the joint work include: a Core HTA model, which represents a framework for HTA reports; a database to share planned, on-going or recently published projects conducted by individual agencies (POP database); an evidence database to store information either on reimbursement/coverage and assessment status of promising technologies or on requests for additional studies arising from HTA (EVIDENT); an adaptation toolkit developed as an aid to HTA agencies in the adaptation of reports from one setting into another.

The Core HTA model was developed on the basis of the nine 'domains' (Table 2.1). Within each domain, different topics are defined, each topic is then associated with different issues that, in turn, should be translated into research questions. For example, the

Table 2.1 Domains of the HTA Core Model, differences between rapid REA and Full HTA

Note: * REA stands for Relative Effectiveness Assessment

HTA Core Models DOMAINS	
Rapid REA*	1. Health problems and current use of technology
	2. Description and technical characteristics
Comprehensive / Full HTA	3. Safety
	4. Clinical Effectiveness
	5. Costs and economic evaluation
	6. Ethical analysis
	7. Organisational aspects
	8. Patients and social aspects
	9. Legal aspects

domain n.4, “clinical effectiveness” may address the topic of quality of life by one or more questions such as “What is the effect of the technology on quality of life?”. An issue, in a specific topic, in a specific domain is defined as an “assessment element”. The same issue could be addressed in different domains, which is why the assessment element is the base unit for the Core HTA model. The whole set of HTA Core model domains define a full/comprehensive HTA since they also address economic, ethical, organizational, social and legal aspects of assessment, while the first four domains, which only concern clinical characteristics and testing, are defined as rapid REA (Relative Effectiveness Assessment). Assessment elements can help, for example, to use an existing Core HTA report as the basis for a national assessment to be enriched with local circumstances, values, epidemiology etc. in order to deliver recommendations about the use of a specific technology more rapidly. An HTA Adaptation Toolkit has been developed to facilitate better use of existing reports, together with the Core model. The toolkit aims to recognise reports (or parts of them) that could be adapted to inform policies in other countries or contexts. In practice, the Adaptation Toolkit consists of a series of checklists that should be answered to determine the policy relevance, the reliability and transferability of data and information contained in an existing assessment report.

The two databases are instrumental in sharing assessments, either in whole or part, and new information. The POP database includes planned,

on-going or recently published projects conducted by individual agencies, while the EVIDENT database stores information either on reimbursement/coverage and assessment status of promising technologies or on requests for additional studies arising from HTA. However, only a very small number of reports can be adopted in different national context without adapting (at least) information and data to the specific context: the direct transnational application of existing HTA is still not possible. Potential challenges to the uptake of the HTA Core Model in national settings include: 1) in national assessments methodologies may not be applied as strictly as in assessments produced through the Core model; 2) the use of less/more advanced methodology may render comparisons difficult; 3) there may be diverse resources available to adapt the Model's outcomes to the national procedure among countries; 4) implementation may lead to longer timelines; 5) implementation may lead to loss of autonomy in deciding on REA outcomes; 6) legal restrictions may hinder the use of the Core model; 7) there may be variance in the interpretation of the methods. Most HTA agencies agree that that activities within the domains of technology use, safety, effectiveness, economic evaluation and organisational aspects are the most easily applicable and adaptable across countries and different policy settings. The first three of the latter pertain to rapid REA (domains 1, 3 and 4 of Table 2.1) while economic evaluation and organisational aspects are part of comprehensive HTA. As a consequence, it may seem that rapid REA should be more easily applicable across countries. In the Inception

Impact Assessment provided for information purposes in September 2016 by the Directorate General for health and food safety of the EC (i.e. DG Sante)⁵, cooperation on production of joint REA reports and their uptake (cooperation on clinical/medical matters) is one of the options mapped for the future of European cooperation on HTA. According to this option, Member States shall jointly produce REAs that would be available to all users and stakeholders through a database, accompanied by measures outlined for the uptake of the joint assessments in national contexts.

The assessment of non-clinical domains (number 5 to 9 of Table 2.1) would remain under the exclusive responsibility of Member States. An academic survey published on the “Health Policy” Journal in 2015⁶ shows that the respondents (eight European HTA organisations involved in the assessment of drugs for coverage decision making) agreed that Member States should first focus on collaboration in the field of relative effectiveness, before addressing health economic issues. Several respondents indicated that they think there are less differences in REAs between EU countries and regions within countries, if compared with economic assessments.

5 EC Inception Impact Assessment, September 2016, “Strengthening of the EU cooperation on Health Technology Assessment (HTA)”.

6 S. Kleijnen, W. Toenders, F.de Groot, M. Huic, E. George, B. Wieselerg, M. Pavlovich, A. Bucscsi, P. D. Sivieroe, M. van der Graaffa, R. Rdzanyk, F. Børlum KristensenI, W. Goettscha, “European collaboration on relative effectiveness assessments: What is needed to be successful?” Health Policy 119 (2015) 569–576.

2.3. HTA IN THE EU FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION

Of course EU financial support will only be useful if Member States cooperate in the development and advancement of a sustainable model once the Health Programme funding ends in 2020. Indeed, under EU Financial Regulations, the Health Programme cannot fund recurring activities. For this reason other financial sources to support scientific and technical cooperation after 2020 must be sought.

One international funding option could come from the European Union’s Research and Innovation funding programme – which was “FP7” for the period 2007-2013, while the current programme is called Horizon 2020. Three projects funded under FP7 have already dealt with HTA on different levels (AdHopHTA, Advance_HTA and Integrate-HTA) and have some links to EUnetHTA. AdHopHTA was an EU-funded research project that aimed at improving the practice of hospital-based HTA and developed tools tailored for hospitals (for managerial decisions) to perform HTA activities.

The main objective of Advance_HTA was the methodological advancement of HTA across a range of settings in Europe, North and Latin Americas achieved by involving the stakeholder community in the debate surrounding decision-making and resource allocation. It also aimed to improve HTA methods, which can be taken further by competent authorities nationally supplementing the work of international entities such as EUnetHTA.

Integrate-HTA, aimed to adapt and develop concepts and methods for HTA to enable an integrated assessment of issues of complex technologies as, for example, palliative care, that was indeed used as a case study to test the methodology developed within the project framework. The new EU funding programme for research and innovation, Horizon 2020, opened the call for proposals on personalized medicine in October 2015 as part of

the “societal challenges programme” which include the chapter “Health, demographic change and wellbeing”. In this context, pricing and reimbursement, health economy, HTA and models of healthcare organisation are recognised as main challenges for the uptake of healthcare coming from research and development efforts, and are therefore included in the themes available to be considered for financing.



PART

3

**A CROSS-COUNTRY
COMPARISON OF HTA
AMONG EUROPEAN
MEMBER STATES**

A CROSS-COUNTRY COMPARISON OF HTA AMONG EUROPEAN MEMBER STATES

Many European countries have established HTA systems to inform coverage and pricing decisions since the late 1970s. The first national HTA agency was established in Sweden in the 1980s; since then, the number of institutions involved in health technology assessment has multiplied. Some European Member States have established formal HTA programmes, while others are still evaluating the feasibility of establishing HTA bodies to inform health policy-making.

Over the years, a large number of publications have focused on analysing the use of health technology assessment and on understanding why different HTA agencies across countries give different recommendations for the same molecules. The aim of these publications have been to develop “best practice principles” to represent the best framework for conducting counterfactual analysis and for establishing a summary score that takes into account the various dimension of comparison conducted in HTA⁷.

Relevant methodological difficulties lay behind such an exercise and therefore, despite guidelines and best

practices that have been developed, thus far a specific methodology has not been identified.

As a consequence, a twofold policy issue is evident: on the one hand, international and European existing methodological guidelines are not compulsory – given the voluntary participation of different countries in HTA networks (there is no supranational HTA body in Europe nor globally) – on the other hand, national HTA bodies can have advisory or regulatory functions and may or may not be formally provided by law.

Besides, they can be involved at different levels in the decision making process, influencing different steps of the latter, from the beginning (market access) to pricing and coverage of health technologies (or none of them at all). Broadly speaking, market access is the process to ensure that all appropriate patients who would benefit from the introduction of a health technology (drugs, medical devices etc.), get rapid and maintained access to it, at the right price.

In the next paragraphs we are going to distinguish between “market access”, defined as the phase in which health technologies receive the authorisation to be commercialised on the market, and “pricing and reimbursement”, the phase in which the price at which health technologies are going to be sold is negotiated and decision about coverage and reimbursement for patients (or particular subgroup of population) is taken. The entire decision making process is usually carried on by what is called a “regulatory body” i.e. an institution which have the remit to make decision about market access and / or pricing and reimbursement. Not always the two functions

7 “A comparative analysis of the role and impact of Health Technology Assessment”, CRA Charles River Associates, Prepared For: PhRMA and EFPIA, 2013; “A Comparative analysis of the role and impact of Health Technology Assessment”, prepared for EFPIA, PhRMA, Medicines Australia and EuropaBio. This is referred to as the initial Comparison report.

are performed by the same regulatory body. The way in which the decision making process is structured depends on national systems. When health technology assessment takes part – to some extent – to the decision making process, it can have a regulatory function (i.e. it is provided by law to be a part of the decision making process and the regulatory body is thus obliged to take into consideration the assessment to take the final decision) or an advisory function (HTA recommendation to government authorities are made, but government is not compelled to take it into consideration in order to take the final decision). From now on, we will refer to “HTA bodies” as entity which conduct assessments, independently on the role fulfilled by HTA in national setting.

In the latter case, the assessment process is usually overseen by the Ministry of Health and sometimes external organizations are involved. England’s National Institute for Health and Clinical Excellence (NICE), for example, coordinates independent reviews by academic research centres.

Anyway, almost all EU countries have some kind of national HTA body that coordinates and disseminates assessment reports for informational and scientific purpose, but in the majority of cases, it is not part of coverage and pricing decision making process. Next paragraph will examine the main differences among representative EU Member States (Sweden, Netherlands, Denmark, Germany, United Kingdom, France, Italy, Spain, Poland) both in terms of governance and application of HTA principles, as a foundation for later discussion on further development and harmonization of HTA in Europe.

3.1. MAPPING DIFFERENCES AND SIMILARITIES ACROSS REPRESENTATIVE EU COUNTRIES

The practice of HTA varies considerably across national settings in Europe. HTA informs policy and decision-making in specific political, economic and institutional contexts but it provides only one input for decision making and it is usually not the only source taken into consideration, nor is it always the most important. HTA bodies use a variety of criteria deriving from the appraisal of evidence to inform pricing and coverage decisions, but the extent to which they are able to effectively lead decision making depends on the role of the HTA and its link to the regulatory body responsible for health policy making.

The following two tables (Tables 3.1a and 3.1b) describe bodies responsible for HTA, national authorities responsible for pricing and coverage decision, the link between the latter two and the general approach used for assessment among different EU countries, including differences in the economic evaluation component of the assessments when it is performed.

3.1.1. A comparison among avant-garde examples

In some countries, namely Sweden, France, Netherlands, Spain and Poland, it is possible to find HTA bodies which perform what we defined a “regulatory” function (cf. supra). In fact, even if health technology assessments are usually produced with the participation of an HTA body which does not coincide with the regulatory body, the conduction of HTA is mandatory and it represents a formal step in the decision making process, provided

by law. It means that it is not possible to complete the process without having an HTA recommendation which, although not binding for final coverage and decision making process, is usually followed by regulatory bodies. Differences also exist among these countries.

Sweden has the longest HTA history in Europe: the Swedish Council on Technology Assessment in Health Care (SBU) is one of the oldest HTA bodies in Europe. It was established in 1987 and in 1992 it became a governmental agency. It is headed by a Board of Directors, representing key organizations in the Swedish healthcare system and in social services, and by a Scientific Advisory Committee, which provides specialist expertise. The key regulatory body is, instead, the Dental and Pharmaceutical Benefits Board (TLV), which does not negotiate on the price of drug: a pharmaceutical company who wants to apply for reimbursement should do this at a proposed price.

For drugs, a TLV assessment is usually initiated by the manufacturer. Assessment is directly conducted by TLV after a submission by the manufacturer is made. The content of the submission is detailed in a set of general guidelines published by TLV. Cost-effectiveness evidence should be provided in a health economic model which is then reviewed by TLV and adapted, if necessary. The assessment takes a wide societal perspective considering all costs and revenues for treatment and ill health including factors such as lost productivity, work loss and time loss for the patient and their relatives. At the same time SBU conducts its own research, but no submission from the manufacturer is required and its publications

have no direct mandate for influencing reimbursement of a drug, or its use in practice. The assessment deserving an official influence over pricing and reimbursement decision is the one conducted by TLV. Since there are no negotiations on price in Sweden, reimbursement is rejected if the price is deemed too high with respect to its potential benefits, and the company can re-apply with a lower price. Principal methods used in the assessment are relative effectiveness, cost effectiveness and cost per quality adjusted life years (QALY). Currently, there is no corresponding managed introduction of medical devices in county councils, but an initiative has been taken to explore the possibilities of this: in April 2012, TLV received a Government commission to conduct economic evaluations of medical devices and this mandate was subsequently extended annually.

Also if SBU has no direct mandate for deciding about reimbursement of drugs or its use, in practice it has a government remit to comprehensively assess healthcare technology from medical, economic, ethical, and social standpoints. It means that its activity is supported by law. The regulatory context is similar in France, although more steps are needed to complete the decision making process. The Social Security Funding Law (2012) introduced the Economic and Public Health Assessment Committee (Commission Evaluation Economique et de Santé Publique, or CEESP) in the Social Security Code as a specialised committee affiliated with the Haute Autorité de Santé (HAS) in charge of providing recommendations and health economic opinions. HTA in France is part of the pricing and reimbursement process but, differently

from the case of Sweden, it has influence both on access to the market and on setting of price and reimbursement. As part of the HTA process, products are assigned a score based on the improvement they provide in medical value (ASMR score), which is then used to inform pricing decisions. The part of HTA inherent to the improvement of medical benefit (ASMR) and of clinical benefit (SMR) are conducted by the Transparency Committee (CT), under the HAS guidance, whose opinion is considered for establishing the reimbursement rate, while CEESP, as well as under the HAS guidance, is responsible for the medico-economic assessment of data supplied by manufacturers at the moment of application. The final decision about pricing and level of co-payment is taken by the Ministry of Health (MoH). However, few relevant stakeholders are involved in the HTA process.

In the Netherlands, the National Health Care Institute (ZINL) is the body responsible for HTA and it is an independent body established in 2014. It advises the Ministry of Health, Welfare and Sport, which serves as the regulatory body, on what should be included in the basic health insurance package. ZINL forms an advice based on four criteria: necessity, effectiveness, cost-effectiveness and feasibility. The assessment is performed only after regulatory approval of a medical technology for market access and in collaboration with the Scientific Advisory Body and the Advisory Committee Package. The Ministry of Health Welfare and Sports is in turn responsible for the final decision about pricing and reimbursement.

The Spanish system is different again. Central

government maintains the responsibility related to pharmaceutical pricing and reimbursement, while decisions related to the content of the national catalogue of services are responsibility of the Inter-territorial Council, and decisions related to regional additions to the national catalogue of services and management of the regional health services are responsibility of regional governments. HTA is required when incorporating new techniques, technologies or procedures, or when excluding those already provided, in the national common benefit package. Thus in Spain two different HTA levels are in place: the national level for common benefit package (including pharmaceuticals) and the regional level. The evaluation is undertaken by the Ministry of Health through the ISCIII (Instituto de Salud Carlos III, an autonomous institution attached to the Ministry of Health) in collaboration with the regional HTA agencies, but a proposal of inclusion of new technologies that could significantly increase health expenditures also requires to be approved by the Fiscal and Financial Policy Council. Health Care Service Coverage Regulation (2006) states that *"the new techniques, technologies and procedures have to go through an evaluation process before their introduction to the National Health System. This evaluation has to be performed by the Spanish Agency for Health Technology Assessment in collaboration with the agencies from regional governments."* Therefore, HTA in Spain directly influences market access, while public coverage is then informed by HTA and it has to respect the following criteria: to show an effective contribution to the prevention, diagnosis, treatment of diseases, to

maintain or improve life expectancy, to promote self-autonomy or to eliminate or decrease pain and suffering; to show an improvement in safety, efficacy, effectiveness, efficiency, or utility compared with currently available alternatives and to comply with the current legislation if drugs or medical devices are used in the process of care. Finally, in Poland HTA plays a role both in access to the

market and in pricing decisions, while only partially in reimbursement evaluation of health technologies. The Agency for Polish Health Technology Assessment (former AHTAPoI, now AOTM) was established in 2005 and an official statement issued by the Minister of Health sets out the minimum requirements for HTA reports supporting reimbursement applications, the establishment of the

Table 3.1a Cross country comparison of HTA bodies and functions

Source: I-Com literature and academic review.

Abbreviations: CEA - Cost effectiveness analysis, CMA - Cost minimization analysis, CUA - Cost utility analysis, CBA - Cost benefit assessment

EU Member States	Decision making process (Review, pricing and coverage)	HTA authority	Function of HTA authority	General approach	Principal outcome measures	Health economic component
Sweden	Pharmaceutical Benefits Board (LFN / TLV)	Pharmaceutical Benefits Board (TLV)/ Swedish Council on Technology Assessment in Health Care (SBU)	Regulatory / Coordination	Systematic review and analyses of clinical and economic studies. Assessment before market entry.	Mortality, morbidity, quality of life, willingness to pay	CEA, CMA
Netherlands	Minister of Health, Welfare and Sport	National Health Insurance Board/ Committee for Pharmaceutical Aid/ Health Council	Regulatory/ Advisory	Health economic information. Evidence from manufacturer dossier is required. Assessment before market entry.	Mortality, morbidity, quality of life	CEA, CUA
Denmark	Danish Medicine Agency (use of free pricing)	Until 2012 Danish Centre for Evaluation and HTA After 2012 decentralized at regional level	Advisory	Health economic information recommended but not required	N/A	N/A
Germany	Federal Association of Sickness Funds / Ministry of Health (use of free pricing)	G-BA/Institute for Quality and Efficiency in Health Care (IQWiG)	Advisory	Two step process. Clinical evidence (randomized controlled trials or RCT's) followed by CBA	Mortality, morbidity, quality of life	Health economic modeling
UK	Department of Health (use of free pricing)	NICE/National Coordinating Centre for Health Technology Assessment (NCCHTA)	Advisory/ Coordination	Clinical evidence (RCT, advanced statistical approaches, probabilistic sensitivity analysis	Mortality, morbidity, quality of life	CEA, CUA with explicit cost effectiveness threshold

Table 3.1b Cross country comparison of HTA bodies and functions

Source: I-Com literature and academic review

Abbreviations: CEA - Cost effectiveness analysis, CMA - Cost minimization analysis, CUA - Cost utility analysis, CBA - Cost benefit assessment

EU Member States	Decision making process (Review, pricing and coverage)	HTA authority	Function of HTA authority	General approach	Principal outcome measures	Health economic component
France	Ministry of Health/ Economic and Public Health Assessment Committee (CEESP)	National Health Authority (HAS)/ Transparency Commission	Regulatory	Evidence required from manufacturer dossier. Clinical and economics literature review recommended. Assessment before market entry.	Mortality, morbidity, length of life, health related quality of life	CEA, CUA
Italy	AIFA	Since Fall 2014 RIHTA network coordinated by AGENAS (Regions, Autonomous Provinces and Regional Agencies)	Advisory	No guidelines. Generally considered for market entry / coverage and reimbursements : clinical effectiveness, disease relevance	N/A	N/A
Spain	Ministry of Health, National Health System inter - territorial Council	Instituto de Salud Carlos III – Spanish Agency for Health Technology Assessment (AETS) – Regional agencies	Regulatory, Coordination	Systematic reviews of existing evidence, evidence based clinical guidelines, cost efficacy, efficiency and effectiveness analyses	Mortality, morbidity, length of life, health related quality of life	CEA (no explicit threshold, on a voluntary basis)
Poland	Economic Commission (EC), Ministry of Health	Health Technology Assessment Agency (AOTM)	Regulatory, Coordination	Systematic review of clinical findings, economic evaluation, and budget impact analysis	Mortality, cases or recoveries, health - related quality of life, adverse effects and/or medical events	CEA with explicit cost effectiveness threshold

official price or increases to the official price of a drug, special purpose dietary supplement or a medical device. It seems that Poland has an edge over other countries, in fact not only AOTM assesses drugs and devices, but also all medical technologies and services that claim public funding. An important issue is the cost-effectiveness threshold of 3 x GDP per capita/QALY introduced by

law for all medical technologies claiming public funding. The Ministry of Health is responsible for deciding which medicines will be reimbursed and how they will be priced: the recommendation delivered by the Agency for HTA is explicitly considered when it comes to decide about pricing and it is mandatory, while for reimbursement decisions medicines are chosen to be

reimbursed based on the product's efficacy in treating disease and its cost. From January 2015 a Council for pricing has been instituted to work in parallel to the HTA Agency to recommend the tariff and standards of costing, the methodology of tariff benefits, tariff benefits and its changes.⁸

3.1.2. When HTA authority performs advisory tasks

Countries described in the latter paragraph represent special cases in the European landscape. Most countries have HTA advisory bodies rather than bodies which participate in the regulatory process for access, pricing and reimbursement decision making. Advisory bodies supply recommendations to government authorities but their participation into the regulatory process is not formally defined and provided by law. They are usually national agencies that coordinate and disseminate assessment reports on health technologies and other interventions but, occasionally, external organizations are also involved in assessments.

England's National Institute for Health and Clinical Excellence (NICE) is an excellent case among this group of agencies. In terms of economic evaluation, NICE is the only organisation that has developed its own cost-effectiveness framework and the scope of the programme includes not only drugs but all health-care technology. Moreover NICE guidance combines

⁸ For updated infographics on health policy decision making processes involving HTA see: N. Mason, M. Schurer, A. Marie Chapman, R. Akehurst (2016): European HTA, pricing and reimbursement roadmaps: Revisited 2016, BresMed.

two forms of analysis: third party and manufacturer base cost-effectiveness assessment. However, it occurs separately to the decision making process and it influences (if it is the case) only the access to market, with no relationship existing between HTA and pricing and reimbursement. It means that in theory products can be prescribed and reimbursed prior to review by NICE but, in practice, local decision makers usually restrict usage until a recommendation has been issued. However, HTA is conducted separately from market authorisation and it is possible that health technologies go directly into pricing without passing through an assessment. In the UK, it is rare for health technologies not to go through HTA although, they are free to avoid it.

In Denmark the situation is reversed. Here, HTA is decentralized, in line with the national strategy for HTA, which states that HTA should be performed at all levels of health services, as a systematic process in planning and operational policy. Before 2012, HTA was performed at a national level by the former Danish Health and Medicines Authority, but since 2012 HTA has mainly been conducted at a regional level. There is no regulatory mechanism in the Danish health service requiring the use of HTA in policy decisions, planning, or administrative procedures and, although a number of comprehensive assessments of health technology has formed the basis for health policy decisions, the conclusions of HTA are often disregarded due to political or health priorities.

A further example is in Germany, where HTA is instead separate from the decision about access: access to the

market is immediate, with a free price negotiation, while HTA evaluation is conducted before fixing pricing and reimbursement. The Federal Joint Committee (G – BA), under the supervision of the Ministry of Health, requests to the Institute for Quality and Efficiency in Health Care (IQWiG) to perform HTA in order to inform its final decision about pricing and reimbursement. Assessments conducted by another HTA body, the German Agency for Health Technology Assessment (DAHTA), are independent and used only in case further indications are needed. This system was introduced in 2011 under the AMNOG reform and, since then, technology assessments have focussed on added therapeutic value rather than on economic evaluation of health technology. The latter is indeed performed by the Federal Joint Committee when proceeding with pricing and reimbursement decisions. Italy, as well as Denmark and Spain, has a regionalized health system but no HTA formally informs the decision making process, even if a network of bodies performing HTA do exist. AIFA is the national authority responsible for drugs regulation in Italy. New drugs must first be registered on the national pharmaceutical formulary, then further reimbursement decisions can be made. When the extent of the therapeutic benefit of a new treatment is considered, AIFA uses three classifications for clinical endpoints (which are not defined as HTA): reduction mortality and/or morbidity, benefit on the disease and benefit on some aspects of the disease. HTA is instead usually performed at a regional or even local level. In 2009 a network (RIHTA – Rete Italiana HTA) was created with the aim of creating and developing

initiatives, projects and actions to support systematic health technology assessments among Regional Health Services. However, HTAs are performed on a voluntary basis and do not directly influence health technologies' access to the market or pricing and reimbursement decisions. Since fall 2014, RIHTA network has been coordinated by AGENAS (Regions, Autonomous Provinces and Regional Agencies).

3.1.3. Most common methodologies used in health technology assessment

A key issue is transparency. Some countries have HTA guidelines, and the assessment process is highly transparent. Such is the case in England, Poland, Germany, Netherlands and France. Other countries lack transparency in the assessment process and do not seem to have national guidelines to follow when conducting an health technology assessment, leaving freedom on what outcomes have to be considered and with which methodology.

However, irrespective of the body who conducts HTA in different countries and of the role/function that HTA bodies have in national settings, it is possible to track, even if by and large, most common methodologies used to perform assessments in the sample of countries we have considered. A survey conducted by Stephen et al. in 2012⁹ reported that the starting point and

⁹ Stephen et al (2012), "International survey of methods used in health technology assessment (HTA): does practice meet the principles proposed for good research?", Comparative Effectiveness Research 2012:2 29-44, Dove Medical Press Ltd.

Table 3.2 Most common methodologies used in HTA

Source: I-Com on Stephen et Al. (2012)

	Sweden	Netherlands	Denmark	Germany	United Kingdom	France	Italy	Spain	Poland
Clinical Trial	✓	✓	✓	✓	✓	✓	✓	✓	✓
EPI and observational analyses	✓	✓			✓	✓	✓	✓	✓
Cost and economic analyses	✓	✓	✓	✓	✓	✓	✓	✓	✓
Comparative analyses	✓	✓	✓	✓	✓	✓	✓	✓	✓
Post - marketing surveillance	✓	✓				✓	✓	✓	
Modelling	✓	✓	✓	✓					
Expert - opinion	✓	✓			✓	✓	✓	✓	✓
Group judgement		✓			✓	✓	✓	✓	✓
Systematic review	✓		✓	✓	✓	✓	✓	✓	✓
Meta - analyses	✓		✓	✓	✓	✓	✓	✓	

primary methodologies used for synthesis of evidence is either systematic review or meta-analysis and, besides, meta-analyses and comparative analyses are the most common methodologies used for drug therapies. Among the respondents of the countries considered, only Netherlands doesn't report systematic review as a common methodology when performing HTA, while both Netherlands and Poland do not report meta-analyses. Among epidemiological studies, clinical trials are the most commonly used (all the European countries in the survey report using this kind of analyses) while EPI and observational analyses are performed

by all the respondents except for Denmark and Germany. For bodies that consider cost and economic analyses, the most common analyses seem to be cost-effectiveness also if they are more often considered only for conformance with economic evaluation or pharmacoeconomic guidelines (when present). Table 3.2 shows for each methodology countries that recognize it as a methodology which is commonly used to conduct health technology assessments.

Without clear, unambiguous and shared guidelines on how to perform rapid REA and full HTA, it is difficult to contemplate harmonized rules to define the policy

function of HTA bodies in national settings. However, the extent to which the harmonization of evidence requirements in HTA can generate benefits is related to the contextual nature of the evidence. HTA is used to inform decisions in the context of local healthcare systems, and different inputs to HTA may be more or less context-specific: the evidence from international clinical studies, or systematic literature reviews of clinical

studies, might be considered largely context-free, and applicable in multiple jurisdictions. On the other hand, data on healthcare resource use, associated with a technology, may be very specific to a particular health system. The first challenge is the identification of HTA inputs we are interested in sharing and applying directly in national settings.

PART

4

**CHALLENGES
TO HTA
HARMONISATION
IN EUROPE**

CHALLENGES TO HTA HARMONISATION IN EUROPE

4.1. THE SUCCESSFUL REFERENCE CASE OF CENTRALISED REGULATORY APPROVAL PROCESS

Regulatory bodies, which are responsible for issuing marketing authorisation to medicines at Member State level, delegated part of their powers to a centralised body, the European Medicines Agency (EMA), which evaluates efficacy and safety of pharmaceutical products seeking approval in the EU through a centralised procedure.

Under this centralised authorisation procedure, pharmaceutical companies submit a single marketing-authorisation application to the EMA, and the Committee for Medicinal products for Human Use (CHMP) carries out a scientific assessment of the application and makes a recommendation on whether the medicine should be marketed or not. This allows the marketing-authorisation holder to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorisation. Thus, medicines are simultaneously authorised for all EU citizens and product information is available in all EU languages at the same time.

Furthermore, the EMA plays a key role in providing developers regulatory tools, such as scientific advice, protocol assistance procedure, adaptive pathways scheme and accelerated assessment, in order to speed up availability of new products.

While harmonised regulatory approval processes at EU level have created synergies that decrease the workload of European payers and institutional stakeholders, there is no EU agency empowered with HTA responsibilities at present, and we refer to a 'network' and "not to an 'agency'" when HTA is discussed at European level. Indeed, HTA powers remain concentrated at national or regional level.

4.2. A CENTRALISED EUROPEAN HTA: REALITY OR CHIMERA?

The current EU HTA network allows for increased European collaboration and synergies for the production of shared HTA information but the uptake of joint work at EU level into national decision-making processes remains low, leading to duplication of work by national and regional HTA authorities.

The creation of a centralised European HTA agency would reduce the risk of costly repetitions and duplication of efforts in their separate filings for national bodies. Furthermore, it could be very important for smaller countries with limited resources or countries that have recently implemented HTA.

In the HTA harmonisation process, an agreement on methods and evidences such as common standards for surrogate outcome measures could be easily reached at EU level. Indeed, the definition of surrogate endpoint is based on scientific knowledge and principles that are expected to be the same across Europe.

On the contrary, the selection of the comparators is one of the examples which can pose serious difficulties at transnational level, as standards of care can vary significantly among EU healthcare systems.

The creation of a fully-fledged HTA agency in the EU would potentially face a number of obstacles and barriers. The main concerns revolve around the fact that member states apply different assessment models, limiting opportunities for HTA harmonisation. Furthermore, the role and usefulness of HTA in decision making, priority setting and its final impact on healthcare could be very different between Member States. Without high-quality evidence, there is a risk that the uptake and diffusion of technologies may be influenced by social, financial and institutional factors that may not generate optimum health outcomes and an efficient use of limited resources.

Moreover, the definition of healthcare budget remains a national responsibility and HTA evaluations have a direct impact on the management of healthcare resources at national or regional level. Thus, Member States could be unwilling to relinquish the HTA authority and its impact on healthcare spending. Lastly, local and regional systems, which in some countries feature a high degree of administrative independence, may further prevent the HTA harmonisation in Europe.

Therefore, in contrast to what happened with the creation of the EMA, there are a number of factors which present significant resistance to the delegation of full HTA decision powers to a EU agency. However, a progressive harmonisation of the type of evidence

pharmaceutical companies must provide European payers and the development of a mutual recognition process of a partially joint HTA report could potentially have a positive impact on market access.

To this purpose, the European Commission recently opened a consultation to consider the views of a number of different stakeholders on the future of HTA across the EU member states. Speaking at the EC-EUnetHTA Forum in Brussels in October 2016, the EU Commissioner for Health and Food Safety, Vytenis Andriukaitis, said: *"The Commission has supported voluntary cooperation on HTA for more than 20 years, and through several HTA Joint Actions, we have built a solid knowledge based on methodologies and information exchange. Now it is time to take the next step: to build a permanent, sustainable mechanism for EU cooperation on HTA so that all Member States can benefit from the added value created by pooling resources, exchanging expertise and avoiding duplication in the assessment of the same product or intervention."*

4.3. POTENTIAL FUTURE EVOLUTION OF HTA COOPERATION AT THE EU LEVEL

As previously mentioned, in September 2016, the European Commission launched a public stakeholder consultation to explore how HTA cooperation at EU level could be carried out in a sustainable way as well as support EU Member States in their HTA activities. Looking at the current prospective and potential future evolution of HTA harmonisation, the European

Commission's Inception Impact Assessment ¹⁰ suggested the five initiatives described below, envisaging five possible scenarios:

OPTION 1: The status quo with Joint Action until 2020. In this scenario, HTA is regulated and organised at national/regional level. The Commission and the Member States set up a voluntary cooperation mechanism through the current Joint Action and the HTA Network until 2020.

OPTION 2: Long-term voluntary cooperation, financed by the EU beyond 2020. This option foresees the continuation of the current cooperation model, but on a longer-term basis.

OPTION 3: Cooperation on collection, sharing and use of common tools and data. This option foresees the introduction of a legal framework for HTA cooperation, enabling the efforts by national bodies to be compatible, shared and used. This will facilitate cooperation of Member States, and ultimately allow for the production of joint REA reports on a voluntary basis.

OPTION 4. Cooperation on production of joint Relative Effectiveness Assessments (REA) reports and their uptake. This option consists of a mutual recognition of HTA assessment opinions applying joint REAs at national level, by establishing a permanent central structure in charge of managing the preparation, coordination and follow-up of the reports. Member States would jointly produce REA reports on the relative effectiveness in terms of clinical/medical benefits of the technology,

covering the first four domains of HTA Core Model. The REA reports, which only concern clinical characteristics and testing, would then be available to all through a shared repository, with measures for the uptake of the joint work at national level. A successful reference case for the mutual recognition of HTA assessment opinions across Europe already exists in the form of the centralised regulatory approval process used by the European Medicines Agency (EMA). Therefore, the chances of this happening and working are likely very high, given the political momentum being initiated at EU level.

OPTION 5. Cooperation on production of joint Full HTA reports and their uptake. This option foresees the joint production of Full HTA reports, comprising not only the assessment of clinical/medical domains (as already provided in the REA reports), but also the assessment of economic, ethical, legal and organisational domains. This means that the joint work will cover all the nine Core Model domains, and include a substantial amount of context-specific information and parameters.

The key issues inherent to the options mentioned above try to answer the question of "What should we harmonise in the HTA at European level?".

Some of the answers given to the European Commission consultation questionnaire by participants have already been individually published by respondents.

Diverse stakeholders seem to agree upon the existence of differences between HTA procedures and HTA methodologies for the economic assessment among EU

¹⁰ EC Inception Impact Assessment, September 2016, "Strengthening of the EU cooperation on Health Technology Assessment (HTA)".

Member States. Namely, EFPIA (European Federation of Pharmaceutical Industries and Associations), EPHA (European Public Health Assurance – a member-led organisation made up of public health NGOs, patient groups, health professionals and disease groups, that works to improve health and strengthen the voice of public health in Europe), CPME (Standing Committee of European Doctors – representing national medical associations across Europe), BEUC (The European Consumer Organisation) and ECPC (European Cancer Patient Coalition) agree on the latter point of view. However, CPME and EFPIA report less significant, though existing, differences in HTA methodologies for clinical assessment (REA) among Member States.

If similarities and differences between HTA methodologies for clinical assessment amongst EU countries do exist, EFPIA underlines that companies present data in different ways, because HTA agencies adopt different approaches to interpreting the same clinical data. This might apply to trial design, relevant endpoints, appropriateness of defined patient subgroups and treatment comparators. For companies, this means duplicative administrative work; for agencies, this means sometimes inability to conclude on the basis of the evidence provided, because the evidence was generated for other purposes and does not fit national requirements; for patients this means unnecessary trials, potential delays, and access restrictions because of methodological misalignment. EFPIA considers that more alignment on relative efficacy assessment at time of launch would streamline processes and lead to better decision-making

in the interest of patients in the European Union. For this reason the first four domains should be able to cover patient-specific aspects while it is not possible to align on full HTA as this covers context-specific elements which are best dealt with at the national level.

CPME doesn't explicitly give examples of differences among Member States and on their adverse effect but comments on the potential advantage and disadvantages of an EU initiative on HTA. CPME considers that a EU initiative on HTA which would provide clinical and/ or full assessment of new medicines and technologies, would enhance evidence based decisions, taken at both decision – makers and physicians level.

EPHA believes, instead, that differences in HTA procedures are to be expected as they are closely related to national contexts with a diverse set of objectives and priorities. Moreover, EPHA recognises that HTA key objective is not to act as a cost-containment mechanism neither for the industry nor for the public, but rather to improve the quality of health care in national settings. The notions of value and benefit in the context of the assessment of medicinal products should then by no means be used to justify high prices for medical products. When talking about the need to continue EU cooperation on HTA after 2020, EPHA supports a EU initiative that upholds high standards best if financed through EU budget and Member States participation instead of industry fees. Indeed keeping in mind the sensitive nature of HTA and the ties with pricing and reimbursement decisions, fees from the pharmaceutical industry should be limited and, if it is the case, exposed to checks and balances in order

to prevent conflicts of interest which would undermine and distort the nature and credibility of HTA evaluations. EFPIA agrees about the latter financing system (both EU and Member States finance support) but also states that EFPIA members are open to continue the current practice of paying a fee to receive scientific advice, provided the system to be set up is fit for purpose and responds to industry needs. CPME doesn't agree on industry fees. The Committee feels that a European framework on HTA requires a political commitment and should be based on a EU budget.

BEUC perceives differences among European countries mainly in the publicity and transparency of assessments. Some HTA bodies make the assessments publicly available, directly or upon request, while some others consider them confidential. Moreover, observational studies to assess the value of a drug are accepted by some HTA bodies but rejected by others. This is important since, as BEUC reports, existing literature shows that these data are less robust than those provided by randomized trials and efficacy profiles of medicines. Although these differences do not directly affect the work of BEUC, they may contribute to duplication of work and high costs to Member States. Thus, it is relevant to raise consumers' awareness of the importance of HTA and bring patients' and end-users' contribution. Last but not least, the organisation feels that although joint full HTA, could be very useful, it should adapt to national healthcare contexts. Moreover, also if early dialogues can be beneficial, it is crucial that individuals involved in these do not contribute to the final evaluation of the

product/medical device: for this reason independent audits have to be carried out.

ECPC seems to have a similar point of view. Its response to the EC consultation focuses both on the lack of transparency of HTA procedures and publications and on existing regulatory and methodological differences between Member States: not all EU countries perform HTA, or do perform it in ways comparable to other countries. For a patient organisation it is very difficult to check the legality of such diverse procedures in legislation and regulations and in so many languages. Above all, ECPC feels that non-binding reports undermine the principle of evidence-based policymaking. The risk could be that economic factors impact decisions on pricing and reimbursement more than health-related factors. To change this, ECPC proposes HTA to be legally binding at a national level, but with a variable value depending on the specific set up of each healthcare system. An important warning concerns the involvement of patients in the HTA process. This is considered to be patchy and insufficient. During a recent survey among the participants to the ECPC Annual General Meeting (June 2016), none of the participants declared to be involved in HTA at the national level. All of this contribute to unacceptable delays in access to innovative treatments and differences in the time frame for access to treatments across EU countries. ECPC recognises overall achievements of EUnetHTA, but it underlines the necessity to fix them in reliable EU regulatory framework. Again, there is general agreement that Member States should have the prerogative to decide about pricing and reimbursement

of healthcare services. However, options 3 and 4 proposed by the European Commission seem to be the only able to provide real added value at the EU level. The impact assessment should take into consideration how to harmonise patients' involvement in HTA.

4.4. THE IMPORTANCE OF REACHING AN AGREEMENT ON HEALTH ECONOMICS AND OUTCOME RESEARCH MODELLING

Health Technology Assessment and Health Economics and Outcomes Research (HEOR) modelling will continue to spread in order to achieve a more comprehensive clinical decision-making and potential cost savings, in particular for countries struggling with tight budgets. HEOR has a dual function: Health economics (HE) specifically deals with the allocation of resources to improve healthcare, whilst Outcomes Research (OR) models humanistic, economic, and clinical outcomes in order to evaluate the effect of healthcare interventions on patient health status.

Outcomes Research activities focus on generating evidence to optimise and maximise product value, through meta-analysis and systematic review to understand clinical pathways, unmet needs, burden-of-illness, disease area and treatment options, and develop a network of trial evidence to inform the treatment effect of various interventions using Bayesian Statistics methods.

Health Economic (HE) modelling is an essential part of

demonstrating product value and it is determined by answering two key questions 1. Is it cost-effective? 2. How much does it cost? HE studies consist of assessing the drug price and its cost-effectiveness, considering direct costs of medical expenditures, indirect costs associated with work loss and disability, the impact of treatments, diseases, and conditions on patients' health and well-being.

As mentioned before, alignment at EU level of HTA methodology, HEOR modelling, assessment criteria, and data requirements will improve consistency and sharing of results, reducing some duplication and the relative costs for national bodies and industry. It is fundamental to reach an agreement regarding the collection and interpretation of evidence, HTA recommendations and their transposition into policymaking.

Therefore, it is essential to harmonise the research procedures with regard to data and evidence collection, in order to generate coherent evaluations in Europe. Furthermore, clear guidelines with regards to Health Economics evaluations are necessary to align the economic assessment in different European countries.

Concerning the evidence used in the Core Model to assess the properties and effects of health technology work, the domains of technology use, safety and clinical effectiveness (Rapid REA) and the procedures to evaluate the target population should be harmonised. On the contrary, costs and economic evaluation, cost of pathology, target population definition, and organisational aspects (comprehensive/full HTA) are intrinsically linked to

the national landscape. For this reason, drug pricing should be defined at national level as it should take into account all the aspects inherent to the local context.

4.5. MUTUAL RECOGNITION PROCESS OF RAPID RELATIVE EFFECTIVENESS ASSESSMENT (REA) REPORTS

The first step of the HTA harmonisation could be the cooperation on the production of joint Rapid Relative Effectiveness Assessments (REA) reports between EU countries and regions within countries, since processes and value dossier format requirements seem to bear more similarities than economic assessments. Member States shall cooperate on clinical and medical evidence and jointly generate REAs (number 1 to 4 domains of the Core Model), with a single database collecting evaluations on technology use, efficacy and safety. Therefore, what is considered acceptable evidence by different payers in Europe should be shared on a transnational level.

The most frequently debated issue for the production of joint REAs is the choice of the comparator. For example, some countries include drugs used off-label or best supportive care as a comparator while other territories do not, and also the process for choosing the right comparator may be based on the proposal of the manufacturer or on the input from a national physician organization. The most important assessment at transnational level is the analysis of data derived

from randomised clinical trials. However, it would be necessary to create an ex-ante agreement on how the trials should be designed and how the evidence should be drawn from such trials, in order to avoid inconclusive, conflicting and potentially biased information.

In conclusion, it is fundamental to reduce differences between national HTA approaches with regards to procedures and methodologies, and make it easier for national HTA bodies to share results produced by them individually or jointly.

Moreover, extending the cooperation to joint assessments of the clinical/medical part of HTA (Option 4 in the Inception Impact Assessment) would improve the cost efficiency of national bodies' resources, by allowing them to save time in order to generate more reports and further improve the average quality of HTAs in terms of management, relevance, transparency. Joint assessments would also reduce costs and administrative burden for the industry, due to the reduction in the number of submissions to be performed and a greater harmonisation in data requirements.

However, at present some national barriers, preventing the adoption of joint reports on European relative efficacy assessments, do exist. EFPIA asked Charles River Associates (CRA) to analyse them and discuss solutions to foster the acceptance of joint reports at the national level¹¹. Five potential barriers are identified in the document: inconsistency between the EU REA

¹¹ Wilsdon T., Pistollato M., Lieu Rea L. (2017): " A discussion of barriers for adoption and possible actions to overcome them", prepared for EFPIA by Charles River Associate

and national HTA timelines and incorporation of joint reports in national processes, changes required in national laws and regulations, differences between EU REA and national HTA methodology, regionalisation of the HTA decisions and position of relevant stakeholders. The consistency of the EU REA timeline and the national timeline are recognised as the main issues. Addressing these barriers is possible, but it will certainly require different stakeholders to work together and the benefits of EU REA to be clear to all stakeholders in the Member States.

On the other side, cost-effectiveness analysis is infrequently applicable to all EU member states because the cost of technology across Europe differs considerably. The assessment of non-clinical domains such as price assessment, target population definition, costs and economic evaluation, organisational aspects (number 5 to 9 of Core Model) should remain under the responsibility of each National Member States due to the heterogeneous socioeconomic perspectives and heritage of the European countries. The costs of pathology are influenced by the national context, thus the drug pricing and reimbursement decisions should be defined at local level, allowing the use of differential pricing.

Differential pricing (DP) is the strategy of selling the same product to different customers at different prices and can be related to the concept of “willingness-to-pay”. Value-based differential pricing shows that the use by payers of an incremental cost-effectiveness ratio (ICER) threshold based on their covered populations “willingness-to-pay” for health gain will lead to price

levels and use within each payer system and price differentials between countries that are consistent with second-best static and dynamic efficiency¹². In alternative, DP can be due to the concepts of “ability-to-pay” because low-income countries can have the “willingness-to-pay” for medicines but cannot afford it because of their limited “ability-to-pay”. Differential pricing has been considered extensively for its potential to increase access to medicines in low- and middle-income countries and to improve economic efficiency. A differential pricing system applied within an economic union comprising high-income and middle-income countries would also increase access and provide stronger incentives to invest in the R&D of innovative medicines.

In conclusion, HTA harmonisation on REA approach should be chosen but it will not affect national pricing and reimbursement decision, and areas of price-setting and reimbursement should clearly remain national responsibility. Mutual recognition process of these joint Rapid REAs may help to use an existing Core HTA report as the basis for a national assessment to be enriched with local circumstances, values, epidemiology etc. in order to deliver recommendations about the use of a specific technology more rapidly. Therefore, potential benefits from cross-border REAs would include shorter ‘to market’ timeframes and a reduction in manufacturers’ expenditure for submission files, thanks

12 Danzon P, Towse A, Mestre-Ferrandiz J. Value-based differential pricing: Efficient prices for drugs in a global context. *Health Econ.* 2015;24:294-301.

to the reduced duplication of disposable information. ECORYS final report for the Executive Agency for Health and Consumers estimates €152 million of net cumulative benefits deriving in 2022 from the implementation of a cooperation model based on the production of joint assessments in Europe. Above all, since performing HTA requires cross-functional collaboration throughout the entire assessment process, main benefits deriving from cross-border REAs would be a reduction of complexity of evidence generation and of clinical trial design with

a presumable increase of investment in innovation, thanks to more predictable results from assessment. All of this would, of course, reduce the time needed for the assessment process, improving patient access to care. A Full-HTA harmonisation may be very difficult to reach because some of the non-clinical domains of the HTA Core Model are context-specific, whilst it seems that cooperation on production of joint Rapid REAs would be the most effective strategy for efficient and quicker HTA decisions across countries.



POLICY CONCLUSIONS

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Evidence is global, decision is local. Rethinking the future of HTA and harmonizing REA for a more rapid and equal access to innovation in Europe

In recent years, there have been significant increases in access to essential medicine. The proliferation of health care technology and its expanding uses have contributed to burgeoning health care costs. The efficient use of resources is crucial for the sustainability of a health system, particularly if ultimate goal is universal health coverage.

The economic aspect of evaluation has become more important, with the sustainability of public finances becoming of primary interest for central governments: and as such, policy makers must determine whether they can sustainably afford to add a specific medical technology to the set of interventions already included within a national health system.

In this scenario, HTA has been an essential tool to inform decision makers and helps Member States allocate national resources to make health interventions more effective.

HTA is a key instrument to ensure the accessibility, quality and sustainability of health care. HTA assesses the added value of a given health technology over and above existing ones. In other words, it establishes the relative effectiveness of the new technology, compared to the existing ones.

Therefore, HTA has grown remarkably over the last decade, and should have much wider application in the coming years.

Health technology assessment must be a tool to support universal health coverage, aimed at synthesising available evidence dealing with efficacy and cost-effectiveness of health care interventions in order to be helpful to health policy-makers.

It is a method that considers evidence regarding clinical effectiveness, safety, cost-effectiveness and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies.

EU Member States cooperate on HTA in EUnetHTA, a network which coordinates the efforts of 29 European countries, including 25 Member States of the European Union, in evaluating health technology in Europe.

The common mission of these networks is to support and promote the development, communication, understanding and use of HTA around the world as a scientifically-based and multidisciplinary means of informing decision making on the use of effective technologies and the efficient use of resources in health care. Therefore, the aim of transnational HTA network is to collect, systematise and provide international available evidence and, if it is the case, to propose policy options, but not to emanate recommendations: national governments are free to define the role of HTAs in their national context as long as its design and implementation.

The EUnetHTA Joint Actions focus on developing common methodologies, piloting joint REA and Full HTA

reports, and developing and maintaining common IT tools, with the understanding that cooperation at EU level shall not interfere with areas of Member States' competence: individual States are free to decide at which level they are willing to participate in cooperation efforts.

An important outcome from European cooperation through EUnetHTA is the HTA Core Model, which aims at enabling national, and transnational production and sharing of HTA results in a common format and at representing a wide range of perspectives.

The whole set of HTA Core model domains define a full/comprehensive HTA since they also address economic, ethical, organizational, social and legal aspects of assessment, while the first four domains, which only concern clinical characteristics and testing, are defined as rapid REA (Relative Effectiveness Assessment).

If international networks and good practices for conducting HTA exist, decisions on how to implement health technology assessments are the prerogative of national governments. Some European Member States have established formal HTA programmes, while others are still evaluating the feasibility of establishing HTA bodies to inform health policy-making.

The practice of HTA varies considerably across national settings in Europe. HTA agencies use a variety of criteria deriving from the appraisal of evidence to inform pricing and coverage decisions. Some countries have HTA guidelines, and the assessment process is highly transparent. Other countries lack transparency in the assessment process and do not seem to have

national guidelines to follow when conducting an health technology assessment, leaving freedom on what outcomes have to be considered and with which methodology.

The wide variety of HTA processes also has a significant influence on the increasing gap between pricing and reimbursement of medical therapies, creating an additional burden cost for healthcare systems in Europe. The variety and variability of European healthcare systems and HTA have created a challenging environment and a need for much greater harmonisation.

Synergies regarding the regulatory approval processes managed to decrease the workload of European payers and institutional stakeholders, whereas the same may not be said with regard to health technology assessment (HTA). Public reimbursement stakeholders have produced a diverse range of national and local HTA processes and cost-benefit perspectives on new drug entrants and a great need exists for HTA harmonisation across most European healthcare systems.

All EU member states can take advantage from shared processes in the collection and evaluation of evidence, generating synergies with regard to resources and expertise with the objective of avoiding duplication and maximising the local potential in health technology assessment.

HTA is used to inform decisions in the context of local healthcare systems, and different inputs to HTA may be more or less context-specific: the evidence from international clinical studies, or systematic literature

reviews of clinical studies, might be considered largely context-free, and applicable in multiple jurisdictions. On the other hand, data on healthcare resource use, associated with a technology, may be very specific to a particular health system. The first challenge is the identification of HTA inputs we are interested in sharing and applying directly in national settings.

An effective strategy for efficient and quicker HTA decisions could be harmonising joint Rapid Relative Effectiveness Assessments (REAs) reports. This could have a tangible impact on the decisions taken at national or regional level, and on the time required to bring a new drug to market, leading to a more equal access to innovation in Europe. On the contrary, the assessment of non-clinical domains, pricing and economic evaluation should remain under the responsibility of each Member State and decisions on how to implement this part of the HTA as a prerogative of national governments.

Most HTA agencies agree that activities within the domains of technology use, safety, effectiveness, economic evaluation and organisational aspects are the most easily applicable and adaptable across countries and different policy settings. The first three of the latter pertain to rapid REA (domains 1, 3 and 4 of Table 2.1) while economic evaluation and organisational aspects are part of comprehensive HTA. Therefore, it may seem that rapid REA should be more easily applicable across countries, and the present year seems the right time to envisage an institutionalized HTA body at EU level, boosting collaborations on Health Technology Assessment in Europe according to the principle that

evidence is global and decision is local.

However, in the light of the existing differences in HTA regulation among EU countries we have shown up to this point, some more stringent policy conclusions could also be drawn. The assessment of non-clinical domains, pricing and economic evaluation shall remain under the responsibility of each Member State, with a compulsory, even if not binding, HTA process.

In other words, Member States should have the mandatory assignment to design a national body, different from the regulatory body charged with deciding about pricing and reimbursement, responsible for conducting HTA. The assessment findings of the HTA body shall not be binding on the regulatory body, but have to be considered in the pricing regulatory process. In this way, rapid REAs could be assessed jointly at a European level, thus allowing a uniform definition of efficacy and safety, as well as the level of innovation, as already is happening with the orphan drug designation, for example.

At this stage, with a more comprehensive understanding of the value of HTA and with the wish of a stronger cooperation among members states in HTA processes, it is time to re-draw the European pharmaceutical governance, starting from a more clear definition of European and National competences in the evaluation process of pharmaceutical innovation.

The impact will encompass the entire system of access to innovative drugs and technologies through Europe, reducing duplications in the evaluation steps at National level, decreasing and leveling time to market across

Member States, improving evaluation system and allowing national authorities to regulate pharmaceutical pricing and reimbursement scheme, considering the national context and the even more problematic issue of economic sustainability. Last but not least, a stronger role of EMA in REA with the same scheme of assessment/regulation of innovative drugs in all Member States (in stronger cooperation among them) will contribute to reduce the phenomenon of differential access to innovation for European patients living in different countries.

Harmonising joint REAs and leaving the assessment of non-clinical domains, pricing and economic evaluation under the responsibility of each Member State – free to choose if and how to implement this part of the

HTA – could be an efficient strategy. It is probable that this option would allow a common definition of health technology innovation and support the industry in the phase of submission of a clinical dossier for access to the market; however, it would likely leave the current situation unchanged when it comes to differences and lack of transparency in national decision making processes. These results may thus be considered as a first step towards a more radical intervention; otherwise there would be a concrete risk that Member States will continue to consider different inputs, evaluate different outcomes and use different methodologies to influence the decision making process, just in case they decide HTA to be part of the latter.



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