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*Health Technology Assessment in Europe  
Current Status and Main Challenges*

Monografia realizada no âmbito da unidade Estágio Curricular do Mestrado Integrado em Ciências Farmacêuticas, orientada pelo Professor António Augusto Miranda Lemos Romão Donato e apresentada à Faculdade de Farmácia da Universidade de Coimbra

Março 2015



UNIVERSIDADE DE COIMBRA

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(Steve Estêvão Cordeiro)

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## List of Abbreviations

**ACE** – Angiotensin Converting Enzyme

**DACETHA** - Danish Health and Medicines Authority

**EC** – European Commission

**EMA** – European Medicines Agency

**EUnetHTA** – European Network for Health Technology Assessment

**EPAR** - European Public Assessment Report

**EU** – European Union

**EVIDENT** - Evidence database on new technologies

**HTA** – Health Technology Assessment

**HTAi** - Health Technology Assessment international

**IMIS** - Information Management Infrastructure and Services

**JA** – Joint Action

**MWP** - Multiannual Work Programme

**PA** – Plenary Assembly

**POP** - Planned and On-going Projects

**QALY** - Quality Adjusted Life Year

**RCT** - Randomized Controlled Trial

**REA** – Relative Effectiveness Assessment

**WP** – Work Package

## **Abstract**

Every single European citizen deserves equal opportunities to access medicines. In the last years the introduction of new technologies has exponentially increased the ability to manage some diseases, but despite of that fact, some citizens didn't have access to these treatments. Nowadays, to choose efficiently the best options provided to citizens, a range of new health technologies' evaluations are performed, however patients' access throughout Europe is still different.

The aim of this dissertation is to demonstrate the current status and main challenges of HTA in Europe, in order to know the European mechanisms to struggle inequality.

**Keywords:** HTA; EUnetHTA; HTA Network; European Union; Health Technologies; Equality; Transparency.

## **Resumo**

Todo o cidadão europeu merece ter as mesmas oportunidades no acesso a medicamentos. Nos últimos anos a introdução de novas tecnologias tem aumentado exponencialmente a capacidade de lidar com algumas doenças, mas, apesar desse fato, alguns cidadãos não tiveram acesso a esses tratamentos. Hoje em dia, para escolher de forma eficiente as melhores opções providenciadas aos cidadãos, são efectuadas uma série de avaliações de novas tecnologias da saúde, no entanto, o acesso dos doentes em toda a Europa ainda é diferente.

O objetivo deste trabalho é demonstrar o estado atual e os principais desafios da Avaliação de Tecnologia de Saúde na Europa, a fim de conhecer os mecanismos europeus para lutar a desigualdade.

**Palavras-Chave:** HTA; EUnetHTA; HTA Network; União Europeia; Tecnologias de Saúde; Igualdade; Transparência.

## **I - Introduction**

Over the past decades, the introduction of new technologies has exponentially increased the ability of health care systems to provide treatment for an increasingly wide range of diseases. Demand for care also has increased, partly in response to this. The resulting rise in health care costs has put considerable strain on health care systems' finite resources, a situation that has worsened in the face of the current global economic slowdown. Facing this scenario, decision makers are obliged, more than never, to know how much they should spend on health care and how to ensure it is spent efficiently.

The recent situation regarding the delay on treatment of hepatitis C in Portugal with sofosbuvir, when comparing to other European countries, it's the very best example of it. This issue allied with the controversy surrounding the high costs on research and development, that supposedly are the reason for these technologies being so expensive, served as a compass on a search for answers.

In a matter of fact, the last health technologies haven't been that innovative, despite their high price. Around 85 per cent of new drugs have been little or no better than existing ones (Light, 2011). In light of these facts some questions are raised. What kind of approaches are being developed to help address these important questions of efficiency? What kind of approaches are being developed to grant to all European citizens equal opportunities on the access of medicines? Presently, a multidisciplinary process named Health Technology Assessment (HTA) is broadly used to assess the innovation, thus providing information to decision makers whether it should be used at health care systems or not.

On a conquest to better understand what is being done at the European Level to struggle these unequal access' issues, a search on the current status and challenges of HTA in Europe was performed.

## **2-HTA in Europe – Current Status**

According to the HTA Glossary, HTA is a *systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision-making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods* (EUnetHTA, 2011).

In the early years of the European Union (EU) the definition of HTA was yet to be drawn. Its usage beginning can be dated back to the late 1970s, when interest in the economic aspects of health technologies started to grow, and the first scientific activities in

the evaluation of health interventions in terms of HTA can be identified. By that time, with the biomedical advances, governments started to have some concerns while dealing with issues of balancing pressures on public spending and providing coherent, solidarity-based health and social systems. In the 1980s started to appear the first institutions or organizational units dedicated to the evaluation of health care technologies, initially in France and Spain. The late 1980s and the 1990s can be described as the era of institutionalization of HTA in Europe, having the Swedish Council on Technology Assessment in Health Care, Sweden in 1987, as the first national agency for HTA. Since then, in almost all countries of the EU, programmes for HTA have been established through either the foundation of new agencies or institutes, or the establishment of HTA departments in universities or in other existing governmental and non-governmental bodies (Banta *et al.*, 2009; Williams *et al.*, 2013). On *Annex I* are described the precise years of their foundation.

Additionally, the European Commission (EC), the executive branch of the EU, supported four major projects in HTA, from 1993 to 2008. The first in these series of formal collaboration was the EUR-ASSESS project, from 1994 to 1997. That project was immediately followed from 1997 to 1998, by a EC-sponsored activity named HTA-Europe and in 2000, a third major project named The European Collaboration for Assessment of Health Interventions and Technology was involving all member states of the EU and observers from eight other countries. In 2005, the EC co-founded yet another huge HTA project at the European level, which defined itself to be a practical project to make European Collaboration sustainable. The EUnetHTA Project was then created (Banta *et al.*, 2009).

Today, up to 2015, the Joint Action (JA) EUnetHTA supports cooperation between national and regional HTA bodies and to further strengthen the cooperation between Member States on HTA, the EC, in line with provision of article 15 of the Directive on Cross border care (2011/24/EU), established the HTA Network (Council of the European Union, 2011).

## **2.1 - EUnetHTA**

The EUnetHTA was planned in response to a need for a sustainable network for HTA, expressed in 2004 by the EC and Council of Ministers, being firstly established as the EUnetHTA Project. In 2005, the Danish and Finnish HTA agencies had the initiative to respond a Commission call for a network. They were supported by other thirty-three organisations throughout Europe, giving rise to the EUnetHTA Project from 2006 to 2008 and having DACETHA as main partner. During 2006 to 2008, EUnetHTA Project strategic

objectives were to reduce duplication of effort to promote more effective use of resources, increase HTA input to decision making in Member States and the EU to increase the impact of HTA, strengthen the link between HTA and healthcare policy making in the EU and its Member States, and support countries with limited experience in HTA (Kristensen *et al.*, 2009). By the end of 2008, a representative of the EC stated that further funding could not be considered before 2010, despite all work done by the EUnetHTA Project and HTA being a high priority subject for Europe and the EC. After this, the leaders of the project announced that a permanent EUnetHTA collaboration had been created with the support and funding of twenty-five initial partners, keeping EUnetHTA alive during 2009. However, the Work plan for 2009 of the EU Health Strategy 2008–13 called for a JA on HTA between Member States and the Commission, and consequently EUnetHTA was asked to develop a proposal for a JA to start in 2010 (Banta *et al.*, 2009). EUnetHTA JA was supported and funded by the EU Health Programme between 2010 and 2012 continuing into another JA from 2012 until 2015. At the end, it is expected from this network the development and implementation of practical tools that could provide reliable, timely, transparent, and transferable information to HTA bodies in EU Member States and EEA countries (Kristensen, 2012).

### **2.1.1-EUnetHTA Mission, Vision & Values**

As mentioned on the document *EUnetHTA Strategy 2012 and beyond* (EUnetHTA, 2012a), EUnetHTA is a preferred facilitator of high-quality HTA collaboration in Europe. It is part of their mission to support collaboration between European HTA organisations that brings added value to healthcare systems at the European, national and regional level. Moreover, EUnetHTA's role delivers an access point for communication with stakeholders, provides an independent and science-based platform to efficient production and use of HTA, by also exchanging and developing HTA information and methodology, and allies with contributing fields of research to support a stronger and broader evidence base use.

In the same way as the EU, EUnetHTA believes that is crucial to recognise and facilitate solutions to overcome barriers caused by language, variations in terminology, and culture. The EU values for health systems (universality, access to good quality care, equity and solidarity); The Principle of subsidiarity of the EU; Efficiency in HTA production; Sustainability of healthcare systems and the use of best evidence, common methodological standards, trust and transparency, are the values that support the network mission and vision, serving as a compass for actions and describing how they act in Europe.

### 2.1.2-EUnetHTA Governance Structure

To be able to understand the network, it's essential to know how it is organised and what are their governance bodies. There are four governance bodies: the Plenary Assembly (PA); the Executive Committee; the Secretariat; the Stakeholder Forum. The PA has the purpose of being the principal policy setting body and is comprised of a Head from each partner organisation. Evidently, this body takes a strategic overview of the work of EUnetHTA including roles such as: admitting new partners / exclusion of partners; advising on future developments; approving strategy, work plans, an annual report, budgets; monitoring / supervising the progress of the network and performance of the Executive Committee and the Secretariat; deciding on the Work Packages (WP) and their Lead Partners. Regarding the strategic leadership, confined to the Executive Committee, it's composed of representatives from the WP Lead Partner's organisations, the secretariat, three elected Partner organisations and chair of the PA. The Executive Committee is responsible for: being accountable for the performance of EUnetHTA to the PA; reviewing finances; information exchange with the Stakeholder Forum and other identified strategic external parties; preparing work plans and monitoring outcomes; supervising the Secretariat in implementing the work plan; developing strategy for approval by the PA.

The operational leadership is confined to the Secretariat that is comprised of a director, a manager and staff members. The Secretariat supports partners in conducting the routine EUnetHTA management affairs and is responsible for the: coordination function; communication; financial management; development of strategy in coordination with the Executive Committee; preparation of Work Plan; organisation of the PA and the Executive Committee meetings. Lastly, the Stakeholder Forum is composed of representatives from groups of Payers, Industry, Providers and Patients/Consumers. Providing advice to overarching governance questions to the Executive Committee and delivering their perspective and knowledge to EUnetHTA WPs, through the Stakeholder Advisory Groups, are essentially their responsibilities towards EUnetHTA (EUnetHTA, 2012b).

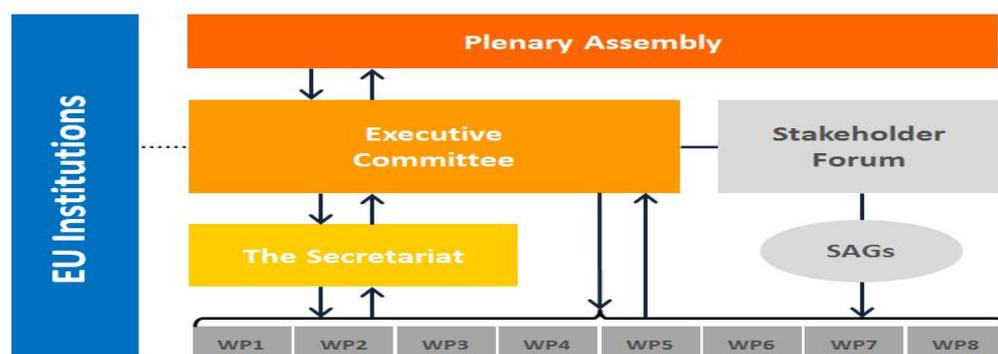


Figure 1 - EUnetHTA Governance Structure (EUnetHTA, 2012b)

### 2.1.3-EUnetHTA JA 2 (2012-2015)

As described before, EUnetHTA it's at the second JA, after a previous one, the 2009 Collaboration and the 2006-2008 Project. Contemplating figure 2, on what has been done since the beginning, for the JA 2, the main objective is to strengthen the practical application of tools and approaches achieved until now.



Figure 2- EUnetHTA's Pathway (EUnetHTA, 2015)

Eight Work Packages compose the EUnetHTA Joint Action 2 work plan, each one led by one partner organisation (EUnetHTA, 2013a).



Figure 3- EUnetHTA's WPs (EUnetHTA, 2015)

#### 2.1.3.1-WP1 - Coordination and sustainable network implementation.

The Danish Health and Medicines Authority lead this WP. During this JA, WPI is responsible for the coordination of the activities in the WPs and assistance of the Secretariat with timely reporting and provision of information upon request. In other hand, they are analysing new data on the JA2 collaboration across WPs and cooperation with various relevant European and national bodies, and developing recommendations based on further testing and development of stakeholder involvement. It's expected to be delivered by the end of JA2 a recommendation on design of the permanent EU HTA cooperation produced and approved by the JA PA, and the final report to send to the EC.

#### 2.1.3.2-WP2 – Dissemination and capacity building

WP2 is lead by the Norwegian Knowledge Centre for the Health Services and co-lead by the Belgian Health care Knowledge Centre. During this JA, WP2 is responsible for providing training in EUnetHTA tools and methodologies to partners and stakeholders, notwithstanding also their duties to disseminate and communicate the knowledge and results

of the JA2. Until the end of the JA it's estimated to happen three face-to-face training workshops on EUnetHTA tools and methodology and three training courses in Core HTA Model online tool, culminating both on a report to be developed.

**2.1.3.3-WP3 – Evaluation of the joint action and data collection on costs and efficiency**

Lead by the Association of Austrian Social Insurance Institutions, this WP, together with WP4 and WP5, is accountable for testing the capacity of national HTA bodies to producing together core HTA information (full core/rapid HTAs) and applying it in national context, more specifically by performing an evaluation on costs and overall efficiency data collected. WP3 aim to verify if the project is being implemented as planned and reaches its objectives, by documenting and implementing on-going monitoring, evaluation, feedback and vigilance processes and systems. A report on evaluation of project completion including assessment of impact on secondary users of HTA information will be delivered.

**2.1.3.4-WP4 – Testing collaborative production of HTA information for national adaptation and reporting**

The *Agenzia Nazionale per I Servizi Sanitari Regionali* lead this WP. Besides the objective shared with the WP3 and WP5, WP4 provides guidance and testing in identifying and organising collaborations between partners, for setting up specific collaborations for production of assessments topics in core HTAs. This WP will have to ensure the production of at least three full core HTAs, to be used in a minimum of twenty national HTA reports in relation to applicability by partners. In addition to this deliverable, Methodological Standards and Procedures for partners' collaboration are going to be created.

**2.1.3.5-WP5 – Apply(ing) the HTA Core Model for Rapid Assessment for national adaptation and reporting**

This WP is lead by the Dutch National Health Care Institute and co-lead by the Ludwig Boltzmann Institute for Health Technology Assessment. Taking into account the objective shared with WP3 and WP4, the WP5 is more specified in rapid assessments. The capacity of national/local HTA bodies to jointly produce structured rapid core HTA information on pharmaceuticals and other health technologies, such as medical devices, surgical interventions or diagnostics, and also their application to national/local context are going to be tested. In particular, a total of fourteen pilot assessments (ten on drugs and four on other health technologies) and thirty national/local reports based on these pilots, are projected. The rapid HTA information, used on the assessments, is going to be based on structured core information from the HTA Core Model for Rapid Relative Effectiveness Assessment (REA).

### **2.1.3.6-WP6 – Information Management Infrastructure and Services (IMIS)**

Briefly, the IMIS is an infrastructure to support the piloting of collaborative production of HTAs by partner agencies, and assists the duties and team working of the other WPs. Lead by the Belgian Health care Knowledge Centre and co-lead by the German Institute for Medical Documentation and Information, this WP is responsible for the provision of the infrastructure above mentioned. It is also responsible for some activities such as the: implementation of the new website; implementation of the new intranet (including “work rooms”); implementation of the Newsletters diffusion tool; centralized authentication system (EUnetHTA ID); EUnetHTA Aggregator; EUnetHTA Toolbar; “e-learning” platform; “Aggregated” Newsletter; Planned and On-going Projects database operation (POP Database). IMIS’ implementation and its report are expected.

### **2.1.3.7-WP7 - Methodology development and evidence generation: guidelines and pilots production**

WP7 is lead by the French National Authority for Health and co-lead by the Institute for Quality and Efficiency in Healthcare. This WP is divided into four subgroups, as follows: SG1-Pilots and guidelines to improve quality and adequacy of initial evidence generation: Early Dialogue and Disease specific guidelines; SG2-Guidelines/position paper and pilots to improve quality and adequacy of additional evidence generation; SG3-Guidelines on methodological issues, all health technologies; SG4-Templates for manufacturers’ submissions to support production of core HTA information and rapid assessments. WP7 aim to develop and test a methodological basis for European cooperation on HTA, including guidelines for distinct methodological issues and quality improvement of evidence generation for HTA, and also, shared with WP4, Implement, pilot and further develop models and tools as well as production processes to support collaborative production of core HTA information. Until the end of the JA it is estimated the creation of guidelines and pilots to improve quality and adequacy of initial and additional evidence generation, as part of SG1 and SG2 work, and also methodological guidelines and templates to support the production on core HTA information and rapid assessments, as part of SG3 and SG4 work.

### **2.1.3.8-WP8 - Maintenance of HTA Core Model infrastructure to support shared production and sharing of HTA information**

The National Institute for Health and Welfare lead this WP with the purpose of develop and maintain a conceptual and technological infrastructure, that enables an effective use of the HTA Core Model for producing, storing, publishing, sharing and utilizing core HTA information. Updated instructions and applications of HTA Core Model online to allow assessment of medical and surgical interventions, diagnostics, screening and pharmaceuticals

are predicted, as result of WP8 duties. Also in the pipeline is an upgraded version of HTA Core Model application for pharmaceutical evaluation.

## **2.1.4-EUnetHTA Tools**

### **2.1.4.1-EUnetHTA Aggregator**

EUnetHTA Aggregator is a tool that aggregates RSS feeds from HTA agencies. When no feed is available, Feed43 service is used to transform news from webpage into RSS feeds that are then aggregated. With this tool we can get in one place all the news published on the EUnetHTA Partners' and Associates' own websites.

### **2.1.4.2-EUnetHTA Evidence database on new technologies (EVIDENT)**

As a tool, EVIDENT Database enables sharing early information on evidence gaps identified during the production of HTA reports, more precisely, it includes information on the related technology and about additional studies or any kind of Additional Evidence Generation following a HTA. Despite the purpose to reduce redundancy, promote generation of further evidence and facilitate European collaboration in the domain, it also contains information on reimbursement / coverage and assessment status of promising technologies in Europe. Presently, the database stores 23 projects from 6 EUnetHTA partners from 5 countries, and based on EUnetHTA's interim data, around 48% of the respondents use it (Huic, 2014)

### **2.1.4.3-EUnetHTA Planned and On-going Projects Database**

Established to facilitate collaboration among European HTA agencies and reduce duplication of work, the POP Database allows EUnetHTA Partners and Associates to share information on planned, on-going or recently published projects of participating agencies and identify similar projects through a matching system provided by the online database. This database currently has 1270 projects, where 16-20% are similar and 7-10% have the same topic. It is used by 73% of the partners and 35% of them have the search in POP as a standard procedure, leading to the fact that more than 11% hold on a project, waiting for another partner to publish a identical report (EUnetHTA, 2014a; Huic, 2014)

### **2.1.4.4-EUnetHTA Adaptation Glossary & Toolkit**

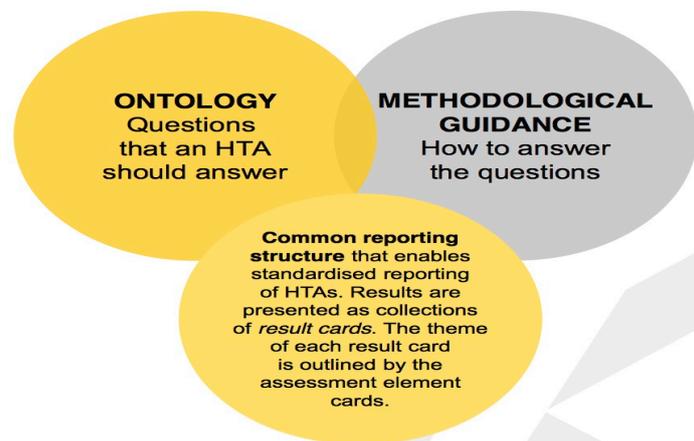
Comprised of a series of terms descriptions and containing examples of where the usage of these terms may differ, the Adaptation Glossary aim to identify and highlight key words and concepts that are easily misunderstood between countries with a view to aiding the adaptation of HTA reports between settings. Together with the Glossary, the Adaptation Toolkit allow an HTA agency in one setting to make use of an HTA report

produced elsewhere, thus saving time, money and ensuring a better use.

The Adaptation Toolkit aid in the adaptation of HTA reports that are a synthesis of evidence, by questioning and helping to assess the relevance, reliability and transferability of HTA reports. It is divided in two sections: Speedy sifting, a screening tool to measure the relevance of the report for adaptation and helping deciding whether the report might be suitable for use; Main Toolkit, a tool with questions on reliability and issues regarding transferability, in other words, this part it's more focused in the quality of the report and the guidance on issues when applying data to the target setting. There are currently five domains within the main part of the toolkit: The technology's use (Current state of the health technology and alternative technologies and the technology's background); Safety; Effectiveness (including efficacy); Economic evaluation (costs, cost-effectiveness, cost-utility and cost benefit analysis); Organisational elements (health service generally and within settings). Depending on their needs, one or more of these domains can be used to aid in adaptation (EUnetHTA, 2011).

#### **2.1.4.5-EUnetHTA HTA Core Model®**

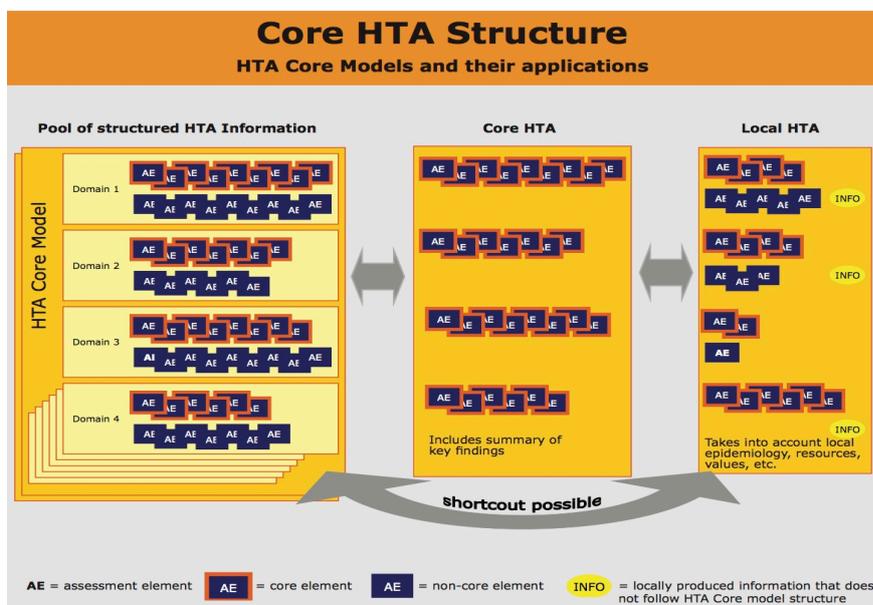
HTA Core Model is a methodological framework for shared production and sharing of HTA information, with three elements: list of generic questions to be answered in HTAs, methodological guidance to assist in finding the answers, common reporting structure that enables standardised reporting of HTAs.



**Figure 4- Structure of the HTA Core Model®** (EUnetHTA, 2015)

Utilization of the Core Models lead to production of structured HTA information (standardized pieces of information on a technology) that is further compiled into Core HTAs, standard-format reports that can be used as the foundation or building blocks of national HTA reports. The Information created through HTA Core Model is presented as assessment elements (basic unit of the model), whereas some elements are probable to be important to support European collaboration, defined as core elements and composing Core

HTAs. Any HTA information produced using the Model and published through the database within the HTA Core Model Online is referred to as core HTA information, and presently 50% of the partners use it to produce local HTA Reports (EUnetHTA, 2013b; Huic, 2014). On EUnetHTA's website, more precisely at 6 of March of 2015, was launched a *National Uptake* webpage, where is possible to find examples of the implementation of the HTA Core Model in local setting.



**Figure 5- Core HTA Structure** (EUnetHTA, 2008)

#### 2.1.4.5.1-Domains of an HTA

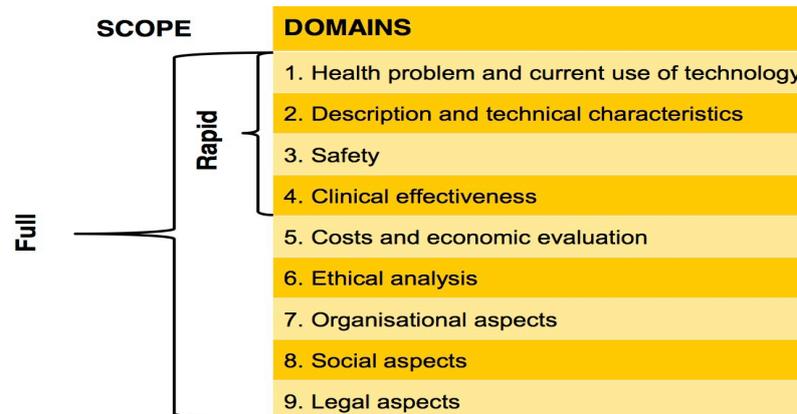
When assessing a technology with the HTA Core Model it is considered several domains, each of which provides a wide framework for the analysis. There are nine domains: Description and technical characteristics of technology; Health problem and current use of technology; Safety; Clinical effectiveness; Costs and economic evaluation; Ethical analysis; Organisational aspects; Social aspects; Legal aspects. Brief definitions of the domains are presented in the *HTA Core Model Handbook* (EUnetHTA, 2014b).

#### 2.1.4.5.2-Application of the HTA Core Model®

An application of the HTA Core Model is built for assessing a specific kind of health technology. Different applications all draw from the same pool of assessment elements, but not all elements are used in all applications. Currently applications exist for the following five types of technologies: medical and surgical interventions, diagnostic technologies, screening technologies, pharmaceuticals and rapid REA of pharmaceuticals.

In order to produce full core HTAs for medical and surgical interventions, diagnostic technologies, screening technologies and pharmaceuticals, their scope has to include all the nine domains, making the assessment more widespread. On the other hand to produce rapid REA of pharmaceuticals, it's used only four domains (Description and technical

characteristics of technology, Health problem and current use of technology, Safety and Clinical effectiveness).



**Figure 6-Scope's Differences between Full Core HTA and Rapid REA**(EUnetHTA, 2015)

The HTA Core Model® for Rapid REA of Pharmaceuticals is a specific application of the model towards the assess of relative effectiveness within a limited timeframe. Relative effectiveness is described as the extent to which an intervention does more good than harm compared with one or more alternative interventions for achieving the desired results, when provided under the usual circumstances of health care practice (EUnetHTA, 2013c).

## 2.1.5- External Collaborations of the EUnetHTA

### 2.1.5.1-EUnetHTA's & FP7 Projects' Collaboration

Collaboration established with the objective of identifying opportunities for developing alliances with contributing fields of research, in order to support a stronger and broader evidence base for HTA. EUnetHTA collaborates with the following projects cofounded by the EU under the seventh Research Framework Programme: AdHopHTA (Adopting Hospital Based HTA in EU); Advance-HTA (Advancing and strengthening the methodological tools and practices relating to the application and implementation of HTA); Integrate-HTA (Integrated HTA for evaluating complex technologies); MedTechHTA(Methods for HTA of Medical Devices: a European Perspective) (EUnetHTA, 2015).

### 2.1.5.2-EU Joint Actions PARENT and EUCERD

In order to facilitate a timely information flow and input between EUnetHTA and the current EU initiatives in the areas of patient registries and rare diseases, a liaison with PARENT and EUCERD was created. This joint actions are respectively, the Cross Border PATient REGistries iNiTiative and the European Union Committee of Experts on Rare Diseases (EUnetHTA, 2015).

### 2.1.5.3-EUnetHTA's & HTAi's Collaboration

The Collaboration with the Health Technology Assessment international (HTAi) is a

technical cooperation focused on ensuring that the latest developments and new / regional HTA terminology are reflected in the global efforts to streamline HTA glossaries. Also, with this connection it's provided a structured access to information of interest about HTA (EUnetHTA, 2015).

#### **2.1.5.4-EUnetHTA's & EMA's Collaboration.**

In 2008 a recommendation from the Pharmaceutical Forum provided a political mandate to initiate collaboration between the European Medicines Agency (EMA) and the EUnetHTA, with the aim of improving the availability and best use of data relevant to HTA (Pharmaceutical Forum, 2008).

The ensuing collaboration, focusing as a first step on the improvement of European public assessment report (EPAR), started in February 2010 and was performed over 2 years. An EPAR reflect the scientific conclusions reached by the EMA's Committee for Medicinal Products for Human Use at the end of the evaluation process, after deletion of commercially confidential information, and it's published for every medicine authorised through the centralised procedure in the EU. This step to consider how the information on the assessment of the risks and the benefits of a medicine contained in the EPARs can best be used in the assessment of the relative effectiveness of new medicines was the first to be initiated, since the REA are increasingly being used in the European Member States to help policy makers to identify the most valuable medicines (EMA, 2010). As a result, the templates for preparing EPARs were revised to better address the needs of HTA bodies (Berntgen *et al.*, 2014).

Presently, so as to identify opportunities for, and undertake specific steps to implement improvements to the efficiency of the process and conditions for patients' timely access to an effective medicine, a three-year work plan was generated. During 2013 to 2015, the collaboration will be focused on the following main areas: Scientific advice/early dialogue involving regulators and HTAs; Scientific and methodological guideline development; Post-licensing (post-authorisation) data generation; Availability of clinical study data; Orphan medicinal products (EMA and EUnetHTA, 2013).

## **2.2-The Health Technology Assessment Network**

The HTA Network aims at supporting cooperation between national authorities or bodies responsible for HTAs. It is a voluntary network, set up by Directive 2011/24 (article 15) and it gathers all Member States, Norway and Iceland. Stakeholders' representatives are also associated to the Network as observers. Cited in Article 15(2) of Directive 2011/24,

the objectives of the Network are to: Support cooperation between national authorities or bodies responsible for HTA; Support Member States in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy as well as on the short and long-term effectiveness, when applicable, of health technologies and to enable an effective exchange of this information between the national authorities or bodies; Support the analysis of the nature and type of information that can be exchanged; Avoid duplication of assessments (Council of the European Union, 2011).

### 2.2.1 -The HTA Network and the EUnetHTA

According to the implementing decision 2013/329/EU, Article 5(2), the HTA Network shall be supported by a scientific and technical cooperation and may initiate or participate in activities involving all or some of its Members, if such involvement contributes to the objectives of the HTA Network (European Commission, 2013a). During the meeting of the HTA Network on October 16, 2013 in Brussels, it was confirmed that EUnetHTA performs the function of the scientific and technical cooperation until the end of JA2, working alongside with the strategic layer (European Commission, 2013b).

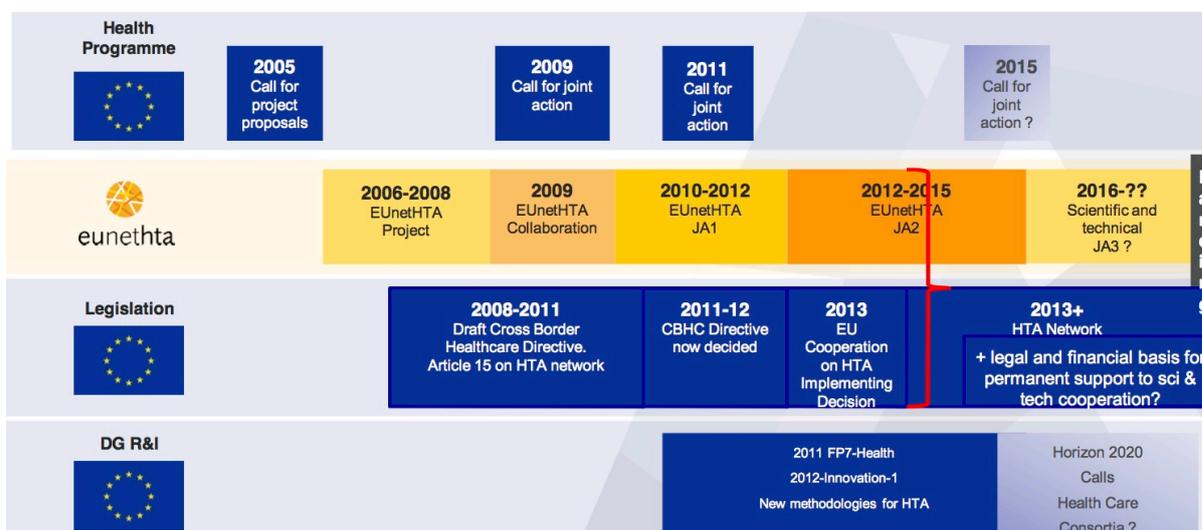


Figure 7-The Timeline of HTA Cooperation in Europe(Kristensen, 2014)

### 2.2.2-Multiannual Work Programme 2014-2015

As a result of the implementing decision 2013/329/EU, Article 5(1), the Network had to adopt a Multiannual Work Programme (MWP) for 2014-2015 (European Commission, 2013a). The overall aim of this programming period is to develop a vision on the long-term provisions for HTA cooperation in the EU. To put that into practice, the HTA network must notably agree on the scope of EU cooperation both on the technologies and the HTA domains, reflect on new ways of delivering existing and innovative health technologies and

health care services that contribute to value, and agree on how a permanent cooperation mechanism at EU level, consisting in both a strategic and scientific level, can be implemented, by also addressing its financial sustainability (European Commission, 2013c).

In order to fulfil this objective, three specific tasks were planned. The adoption of a position paper on long-term provisions of EU cooperation on HTA, the adoption of a reflection paper on the conditions to facilitate take up and re-use at national level of joint HTA production and the adoption of a reflection paper on the interaction between regulatory and HTA issues. At this moment the only task completed was the creation and adoption of a strategy paper for EU cooperation on HTA. Drafted by the Network, the objective of this paper is twofold. Basically, based on the outcome of the existing cooperation, EUnetHTA, and other relevant EU funded initiatives, it set out its strategic vision, including its long-term sustainability, and identifies priority areas to be addressed through the Network and to be potentially co-funded by the EU (HTA Network, 2014).

In line with Article 15(7) of Directive 2011/24, measures adopted to implement the HTA Network MWP shall aim at strengthening cooperation, shall not interfere with areas of Member States' competence in deciding on the implementation of HTA conclusions and shall not harmonise national laws or regulations of the Member States. Cooperation at EU level shall fully respect their responsibilities to organise and deliver health services and medical care. Individual Member States are free to decide the level at which they are willing to participate in cooperation efforts (Council of the European Union, 2011). Moreover, it is stated on the strategic paper that the Network aims at implementing a vision, which reflects that methodologies and evidence used to assess technologies are often global and can and should be shared, as appropriate, while decisions made on the basis of the assessments are local and within the responsibility of national and regional authorities.

### **2.3-Future Perspective**

The governance of the HTA cooperation in Europe is based on a two-layer system, one strategic (the HTA Network) and one scientific-technical. When EUnetHTA JA 2 ends in 2015, a new JA on HTA could support the activities, but until 2020, a suitable sustainable mechanism shall be identified to continue to support the scientific-technical cooperation.

Presently the EC is planning to propose to Member States a new (third) JA funded under the Health Programme 2014-2020, but still to have EU financial Support taken for granted, Member States will have to commit themselves to joint work, and agree on a proposal for a sustainable model for the next phase of cooperation, once the Health Programme funding ends, because according to the EU Financial Regulations, it can't fund

recurring activities. Its support will be limited in time and cannot be extended beyond 2020. After 2020 it is expected that national and regional HTA agencies or bodies will continue to carry out scientific activities necessary to deliver joint work. Administrative coordination and other supporting functions may be performed within suitable structures and possibly be supported by the EU budget (HTA Network, 2014).

At the *deliverable 1* from EUnetHTA JA2 (EUnetHTA, 2014c), is provided scientific and technical aspects of cooperation on HTA in Europe, aiming to contribute to the development of content and structure of a possible third JA on HTA. It is outlined two types of recommendations, organisational and technical.

There are seven organisational aspects to consider:

1-Define and attribute distinct tasks to the strategic level and the scientific/technical level in the European cooperation on HTA while ensuring synergy between the levels with a clear separation of their remits and mandates; 2-Continue to provide flexibility of participation in the scientific and technical cooperation in line with the decided degree of commitment and responsibility in activities – Introduction of three levels of engagement, corresponding to a defined level of access to the output, services and financial resources of the cooperation; 3-Focus on a transition from piloting of cooperation activities to routine implementation and uptake of the joint output in national/regional HTA production processes; 4-Adjust stakeholder involvement to match the remits and mandates of the two levels of activities in the European cooperation on HTA; 5-Develop approaches to overcome organisational barriers in the HTA organisations participating in the European cooperation on HTA; 6-Aim at the European Commission's and Member States' financial support to facilitate sustainability of the operations of the European cooperation on HTA; 7-Hosting of the overall coordination function – No later than 2016, the scientific and technical cooperation for HTA needs to clarify and layout specific organisational and governance criteria and conditions for a permanent European scientific and technical cooperation on HTA;

In regards to the technical part, there are nine aspects to consider:

1-Test and deliver a final workable business model for the permanent European cooperation on HTA (*Annex 2*); 2- Engage in a continuous dialogue with the executive management of partner organisations to facilitate “readiness to change” in their organisation's routine working processes; 3-Develop a robust evaluation of the use of joint assessments for national utility and impact of joint assessments; 4-Continue advancing collaboration with regulators through cooperation with the EMA, specifically in the area of early dialogue and post-authorisation studies; 5-Continue advancing engagement with

industry, specifically through the activities of early dialogue, submission requirements and application of the HTA Core Model®; 6-Explore concrete ways of multi-technology assessment and of contributing HTA information to the development of the clinical practice guidelines; 7-Focus on capacity-building activities that allow exchange of experts and internships between the HTA organisations participating in the European cooperation on HTA; 8- Continue updating and adapting as well as developing a formally agreed common methodological guidance in HTA while avoiding duplication of efforts with other international collaborative initiatives; 9- Develop more effective and strategic communication approaches;

Furthermore, The Consumers, Health and Food Executive Agency, former Executive Agency for Health and Consumers, also in a pursuit of the best option for a suitable sustainable mechanism to support the scientific-technical cooperation, commissioned a study entitled *European Cooperation on Health Technology Assessment, Economic and governance analysis of the establishment of a permanent secretariat* (Ecorys, 2013). This Study concluded that most realistic and preferred option for a suitable structure would be the hosting of a permanent HTA secretariat through outsourcing to an external body and within the HTA network. In terms of the selection within the HTA Network, a rotating secretariat is preferable to a permanent, yet it bears significant issues with regard to efficiency.

### **3-HTA in Europe – Main Challenges**

Despite all the improvements made in the last years regarding HTA cooperation in Europe, there are still some challenges to face in the upcoming future to grant to all European citizens equal opportunities to access medicines. In this point, it will be described some of the key issues that could affect HTA's effectiveness to assist decision-making processes on efficient and effective manner and also on promoting value-added healthcare.

#### **3.1-More Clinical Evidence and Expertise**

In order to keep-up with the opportunities and challenges created by new technologies, decision makers will need access to more high-quality synthesised evidence, therefore it remain some significant challenges that need to be overcome, if HTA is to fulfil its role in driving greater use of evidence in decision-making. Since clinical evaluative research and HTA account for very small proportions of total health-care spending, a secure and long-term investment is needed to ensure the development of analytical capacity and expertise, providing a culture of evidence-based medicine and policy to the European countries. Moreover, initiatives to increase capacity within academia are considered a

necessary step to provide opportunities to harmonise education in the field of HTA and creating expertise, by taking also in account that in terms of numbers of HTA professionals, the European capacity is considered too limited.

Given the limited evidence on the economic evaluation of public health interventions, more research should be funded to identify completed assessments of public health interventions, especially those focused on prevention. It is needed a further exploration of applying the principles and methods of economic evaluation to preventive measures in order to facilitate a more evidence-based approach to important population health issues, thus having a wide broad view of all options to delivery value-added healthcare. HTA's are only useful if they have the necessary data and resources, without this it's not helpful and may even delay access to new treatments (Ecorys, 2013; OECD, 2005; Drummond *et al.*, 2008)

### **3.2-Differences in HTA Bodies & Health Systems across Europe**

The production of HTA varies considerably among countries. HTA has evolved within the framework of specific country health-care systems and just as health-care systems differ, so does HTA. As we can see on *Annex 3*, there exist not only different HTA processes, but also different system coordination between HTA agencies, regulators and coverage bodies. The fact that regulatory, HTA, and coverage bodies have different goals and priorities and that they have different traditions, ways of working, and relations with stakeholders, lead to an insufficient understanding of their respective purposes, remits, and processes. Also, in order to establish synergies within the life cycle of health technologies to better serve patients' interests, by enabling quicker access to innovative effective technology, a continue dialogue to promote understanding and interaction is needed both upstream with regulatory bodies and downstream with HTA and coverage bodies (Allen *et al.*, 2013; Henshall *et al.*, 2011).

In the other hand, different HTA processes eventually lead to different outcomes. As reported (Context Matters, 2014; Nicod *et al.*, 2012), such significant inter-country variability in the HTA recommendations exists. This variability in assessments illustrates the nuance and complexity of the clinical and economic data presented to HTA bodies and the varying ways individual HTA organizations interpret data based on local culture, perspectives and goals, thus limiting opportunities for an HTA harmonisation. According to the former Executive Director of the EMA, Professor Guido Rasi, an agreement on common standards for surrogate outcome measures could be easily reached. The definition of surrogate endpoint is based on scientific knowledge and principles that are expected to be the same across Europe (Rasi, 2014). Conversely, the selection of the comparators also poses serious

difficulties, as standards of care vary significantly among EU healthcare systems and therefore cost-effectiveness analysis results are infrequently, if applicable to member states, as the cost of a technology across Europe differs considerably. Nevertheless, knowing that health technologies are tradable economic goods, their evaluation also tend to be inflated on their country of origin, posing serious difficulties to assess equal value. The delegation of full HTA decision powers to an EU agency would be a good solution to overcome this barrier, yet member states are in general unwilling to relinquish the authority over HTA and its resulting impact on healthcare resources. In the end it seems an unrealistic option for the near future.

Some projects were developed to face these differences across European Countries, more recently it was the EUnetHTA, as described before. In this network we can find small agencies with less capacity in terms of scope of analysis and resources that dominant larger agencies and those with established capacity or starting to become engaged professionally in this field. An increased harmonisation of approaches and enhanced cooperation among agencies will particularly lead to large benefits for smaller agencies with no or limited established capacity in the field of HTA, but costs in terms of capacity building, developing new approaches and the intellectual property lies primarily with the larger, established HTA agencies, which do not have an immediate interest in transferring resources and know-how to other countries. This skewed distribution of benefits and costs among member states in the short to medium term will decrease the willingness to pursue a common agenda and the speed with which such an agenda can be implemented. Additionally, due to country differences, it is reasonable to think that full collaboration and harmonisation should not be expected in the near future because the outputs are currently not “fitting” in each national system. These weaknesses are carrying some agencies to not include EUnetHTA activities in their work processes, seen sometimes as a threat to the national activities (Ecorys, 2013).

### **3.3-Standard Operating Procedures**

Usually agencies are more focused on assessments of new technologies. In order to support real innovation of technologies is also essential identifying topics for potential disinvestment, ensuring that ineffective and inefficient products and practices do not remain in the health-care system. Re-evaluation is a key component of the HTA process, maintaining the accuracy of assessments and warranting that the best products are on the market (Wilsdon, T *et al.*, 2014).

If we have a look now to the fast-track assessments of new technologies, generally the data used on them to confirm the cost- and clinical-effectiveness of a technology can only be truly ascertained after a practical application in the market. Systems should be

created to allow the introduction of new clinical and health-economic information during the assessment process and following market entry. Safeguards against inefficiency, resource burden and delayed access to treatments have to be considered for this kind of situations (Ecorys, 2013). Presently, taking into consideration these necessities, there is a lot of expectation on how these accelerated HTA processes interact with the on-going debate regarding adaptive pathways (EMA, 2014). The HTAi Policy Forum identified several key issues that must be addressed to understand, accept, and implement adaptive pathways at HTA level (Husereau *et al.*, 2014).

Data challenges appear to happen not only at these specific HTA processes, but also at the standard ones. Although head-to-head RCT's are considered the most objective type of evidence to demonstrate a product's relative benefit, they have limitations when ascertaining product value. There's a rising need to adopt a broader definition of value and product benefit by considering patient preferences, quality, equity and efficiency, instead of only including observational studies and other important evidence. It is important to consider non-quantifiable factors so as to address effectively the social implications and constraints of efficient and equitable health care. Including more frequently indirect benefits and costs could also help to give a broader societal perspective (OECD, 2005; Sorenson *et al.*, 2008; Wilsdon, T *et al.*, 2014).

Another obstacle is the choice of some comparators used on head-to-head RCT's, since choosing some of the best implies the off-label use of old molecules. This patent issue is not only a barrier to RCT's, but also to the generation of evidence, because presently it's not worth to invest on old molecules with a huge amount of generics.

Industry's stakeholders, facing all these issues, agree that moving towards the use of a centralized EU assessment of relative clinical efficacy could offer worthwhile efficiency gains for companies and governments. Nevertheless, if that happens, they stated that safeguards have to be put in place to ensure that any involvement of EMA in any centralized EU assessment of clinical efficacy does not compromise the existing separation between the marketing authorization process, with its clear criteria of quality, safety and efficacy, and the evolving HTA process (Lundbeck, 2013).

### **3.4-Challenges for economic evaluation in decision-making**

Economic evaluation, often a component of HTA, faces its own set of challenges. One of these challenges is the potential lack of transferability of evaluation studies from setting to setting. Empirical research has shown that the way most economic evaluations are reported makes it difficult for local decision makers to assess whether the study does bear

relevance to the local setting. Another point it's the study design, with its usual emphasis on measuring the effect of the intervention on an "average" population, which precludes policy makers from determining subgroups within a study that might benefit most from an intervention, thus affecting the economic values of the assessments (Sorenson *et al.*, 2008).

Another challenge is the fact that HTA agencies have to be sensible when measuring cost of medicines per Quality Adjusted Life Year (QALY) in treatments for brain disorders, since typically they relieve symptoms of disease, rather than providing a cure, and QALYs promotes products that prolong life (Lundbeck, 2013).

### **3.5-Health-related biotechnologies and rare diseases**

As more new health-related biotechnologies are coming on stream, decision makers will increasingly require more evidence on all aspects of medical innovations, not just the clinical and economic effect, but also ethical, social and macroeconomic characteristics. Moreover, a question lays whether HTA can or should adapt its methodologies to capture these issues, or whether such evidence should come from other sources. There is an increasing uncertainty for these innovators, specially when doesn't exist clear policy frameworks to deliver vital information to decision makers. A necessity for better dialogues over the right questions on technologies, and the right technical and political mechanisms for answering them, are being raised as result of new biomedical advances (OECD, 2005)

On the other hand, rare diseases patient's access to treatments on an equitable and timely manner remains an issue. Despite of some regulatory initiatives have stimulated the research, development, and authorization of orphan products, there is still a paucity of evidence available for HTA due to the low prevalence and heterogeneity of rare diseases. Currently registries can provide valuable information to help characterize disease progression, being considered as a good choice for this evidence issue (Kanarikas, 2014). Indeed, it is gaining more relevance with the recent thematic of the adaptive pathways concept. Another form of evidence that could be key for HTA of rare diseases is qualitative research of patients' and carers' perspectives, where patients can act as expert witnesses to explain the relevance of an effect.

In order to ensure consistent and transparent approaches to the HTA of rare diseases, an international agreement on the evidentiary requirements for clinical effectiveness assessments of rare diseases is indispensable (Facey *et al.*, 2014).

### **3.6-HTA's Real-World Impact.**

There is a lack of understanding and evidence about HTA's real-world impact on decision-making processes, health outcomes, care delivery, health-care costs and research

innovation. Has HTA produced better managed health-care budgets or a decrease in health-care costs? Has HTA appropriately and accurately identified interventions that have led to improved health outcomes? These are some of the questions that in some cases still need an answer due to lack of outcomes' data (Ecorys, 2013; OECD, 2005; Sorenson *et al.*, 2008). As we can see on *figure 8* there isn't a process for monitoring the impact of HTA in most of the markets (Wilsdon, Tim and Serota, 2011). It would also be interesting for the future to develop a statistical analysis to see if HTAs have any significant effect on delays of market entry or on the speed of uptake of innovative drugs (Wilsdon, T *et al.*, 2014).

Another important issue is the limited availability of relevant data on organisational costs and current and future costs of HTA assessments, notwithstanding that presently more information on the cost/budget of the HTA agencies is publicly available (Ecorys, 2013; Wilsdon, T *et al.*, 2014).

It is crucial to have the real perception of HTA's impact and costs in order to improve its profitability on assisting decision-makers and granting equal opportunities to the access of the best value-added healthcare. HTA is an assessment method that needs also to be assessed.

Country	There is a body with responsibility for overseeing impact	There is measurement of the value of HTA to the healthcare system	Effects of HTA decisions are monitored and data is collected to evaluate clinical impact over time	This information is used to modify/revise HTA process/methodology
Australia	●	○	●	●
Brazil	⚠	○	○	○
Canada	●	○	○	●
England	●	○	●	●
France	○	○	○	○
Germany	⚠	○	○	○
Italy	○	○	○	○
Netherlands	○	⚠	⚠	⚠
New Zealand	●	⚠	⚠	●
Poland	○	○	○	○
Scotland	●	○	●	●
South Korea	○	○	○	○
Spain	○	○	○	○
Sweden	○	●	○	○

**Figure 8-Monitoring of HTA's outcomes** (Wilsdon, Tim and Serota, 2011)

## 4-Conclusion

Health-care innovation has transformed the practice of medicine over the course of the last century. Technological innovations can bring substantial benefits in the prevention, diagnosis and treatment of disease, as well as access to care. At the same time, there is widespread variation in the use of health-care technologies across European countries, indicating that the most effective and efficient technologies may not always be the ones most often used. Encouraging the uptake of efficient and effective health-care technologies is still a significant policy challenge in many countries.

As we can see on *Annex 4*, there has been a big increase of profit rate for major U.S. pharmaceutical companies compared with that of major U.S. companies in other sectors. Taking this into account and knowing that in the previous years there weren't that many real innovative technologies, from where came all this profit? It's the money really being used on an efficient manner by the health-care systems? Are the costs on research and development really increasing? (Light, 2011) A new health technology is a cost or an investment? How much should we pay for incremental innovation? Where would we be if there hadn't been payments for some incremental innovations? A more recent ACE inhibitor is or isn't better than captopril? There are different opinions on answering these questions, but one thing is sure, performing assessments of new health technologies is becoming vital.

Improvements in Europe to address cooperation on HTA are being made. In the last years, as describe before, a European network for HTA was set up, and more recently the EC implemented the HTA Network. Europe is now trying to grant all European citizens equal opportunities to access medicines, yet there is a long way to go if they want to reach this seemingly utopic state, taking into account cultural, organisational and economical differences between countries. For example, in regards to economical differences, should the financing be indexed to the GDP of countries? In the summary of the national assessments of sofosbuvir, delivered by EUnetHTA to the HTA Network (EUnetHTA, 2014d), it's perfectly stated the level of inequality throughout Europe. In Portugal the report done wasn't a full one, probably an additional reason explaining the access' delay of more than one year after the market authorisation. In the end, what is the real impact of HTA on a peripheral country like Portugal?

In conclusion, besides of all the challenges that HTA could face in next years, Europe is now on the right course, by "teaming up for value". It is crucial to solve the challenges by making new developments, in order to always make the right option for the right price

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## 6-Attachments

### 6.1-Annex I

This Table shows the year of foundation of the first agencies, institutes or departments for HTA in Europe (Williams *et al.*, 2013).

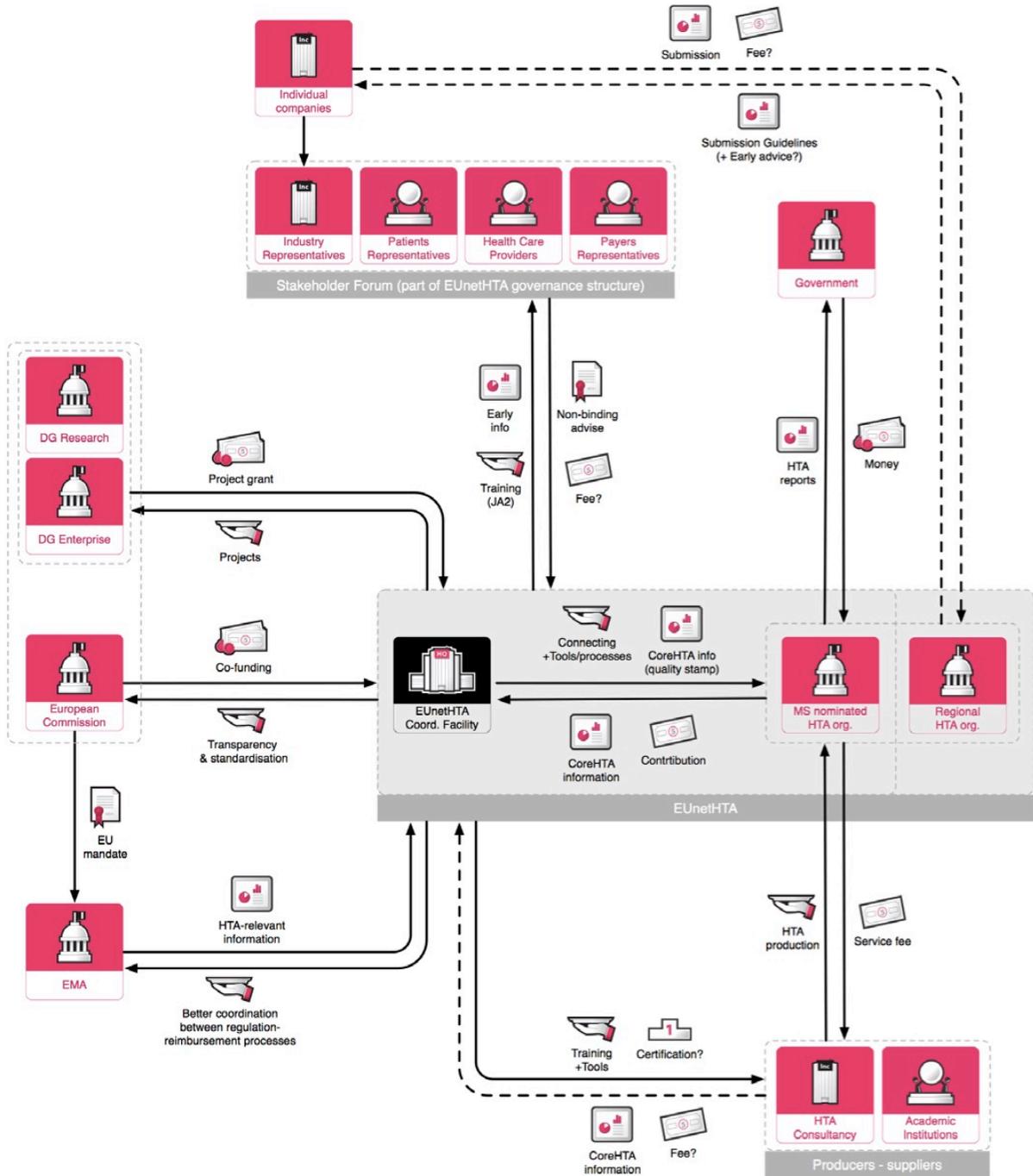
Year of establishment/ starting HTA activity	Organization	Country/ region
1982	CEDIT Comité d'Evaluation et de Diffusion des Innovations Technologiques Assistance Publique Hôpitaux de Paris	France
1984	CMT Center for Medical Technology Assessment	Sweden
1987	SBU Swedish Council on Health Technology Assessment in Health Care	Sweden
1987	TNO The Netherlands Organization for Applied Scientific Research	Netherlands
1988	– National Fund for HTA	Netherlands
1989	ANAES (formerly ANDEM)	France
1990	ITA Institute of Technology Assessment, Austrian Academy of Sciences	Austria
1991	CAHTA (formerly COHTA)	Spain
1992	OSTEBA Basque Office for Health Technology Assessment	Spain
1992	SFOPH Swiss Federal Office of Public Health	Switzerland
1992	TA-SWISS Swiss Science and Technology Council/Technology Assessment	Switzerland
1994	AETS Agencia de Evaluación de Tecnologías Sanitarias	Spain
1995	FinOHTA Finnish Office for Health Technology Assessment	Finland
1995	HSMTA Health Statistics and Medical Technology Agency	Latvia
1996	AETSA Andalusian Agency for Health Technology Assessment	Spain

Year of establishment/ starting HTA activity	Organization	Country/ region
1996	NCCHTA National Coordinating Centre for Health Technology Assessment	UK
1997	DACEHTA Danish Center for Evaluation and Health Technology Assessment (formerly DIHTA)	Denmark
1998	DSI Danish Institute for Health Services Research	Denmark
1998	NHSC National Horizon Scanning Centre	UK
1998	SMM Norwegian Center for Health Technology Assessment	Norway
1998	– Federal Committee of Physicians and Sickness Funds (since 2004: Federal Joint Committee)	Germany
1999	MTV- Aarhus Unit for Health Technology Assessment – Aarhus University Hospital	Denmark
1999	NICE National Institute for Clinical Excellence	UK
2000	DAHTA German Agency for Health Technology Assessment	Germany
2000	HTBS Health Technology Board for Scotland	UK
2001	HunHTA Unit of Health Economics and Health Technology Assessment	Hungary
2001	MTV- Odense Unit for Health Technology Assessment – Odense University Hospital	Denmark
2002	UETS Unit for Health Technology Assessment – Madrid Region	Spain
2003	FKG Federaal Kenniscentrum voor de Gezondheidszorg/Centre Fédéral d'Expertise des Soins de Santé	Belgium

*\*This overview is not intended to be exhaustive; it reflects developments up to 2004.*

## 6.2-Annex 2

Visual Business Map-EUnetHTA Business Model V1.1 (This Map is from the EUnetHTA's Business Model Report, May 2012)



### 6.3-Annex 3

This Annex shows a non-ranking method for classifying the diversity of European HTA agencies process and the organisational architecture of the national regulatory review to reimbursement systems (Allen *et al.*, 2013).

M: the regulatory, HTA and coverage body functions are performed by separate agencies.

S: the regulatory and HTA functions are performed by a single agency and the coverage body functions are independent.

P: the HTA and coverage body functions are performed by a single agency with the regulatory function performed independently.

F: the regulatory, HTA and coverage body functions are all performed within a single agency.

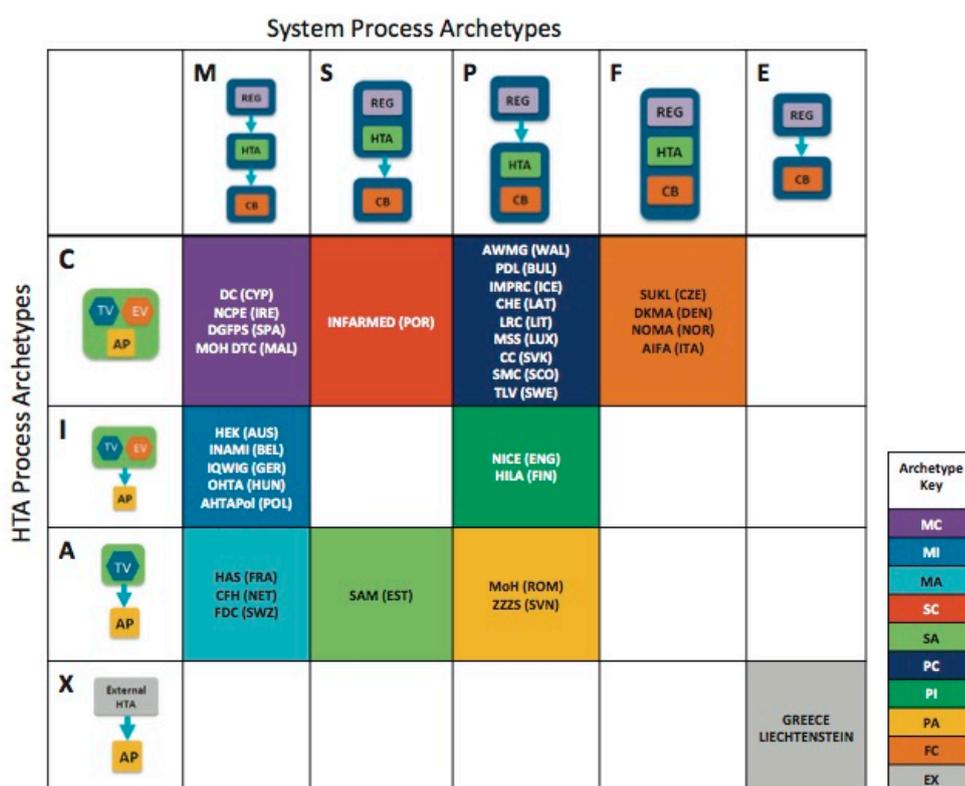
E: no HTA is performed within the national regulatory to reimbursement system.

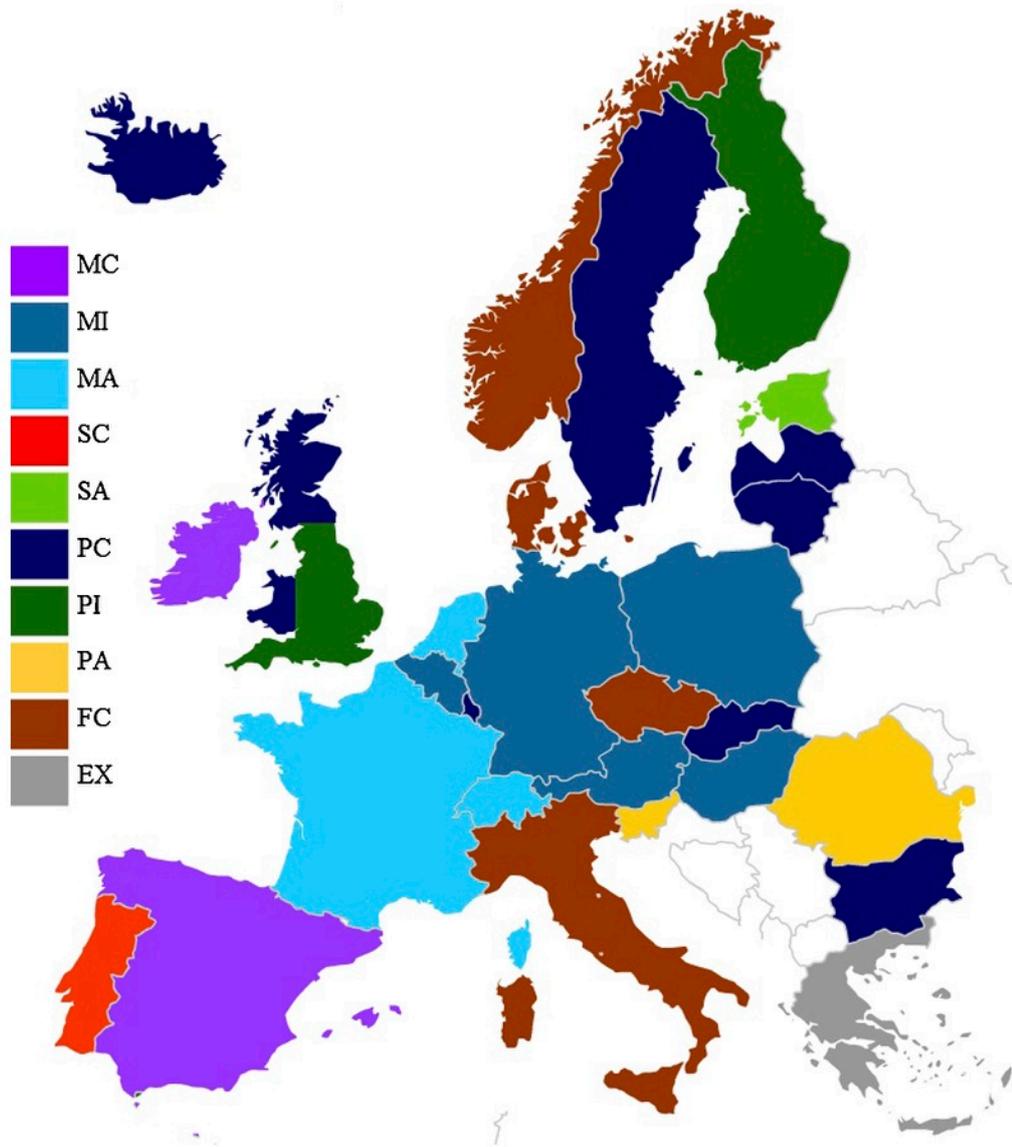
C: the therapeutic value is assessed prior to independent appraisal.

I: the therapeutic value assessment is conducted within the same agency as Economic evaluation but the appraisal is performed independently, usually by health professionals rather than civil servants.

A: the therapeutic value assessment, economic evaluation and appraisal are performed within the same agency.

X: the appraisal is conducted using information from an external HTA report or by considering the coverage decisions of reference countries.





### 6.4-Annex 4

This Annex shows a revenues' comparison between Pharmaceutical Companies with other companies (Gagnon, 2013).

