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Systematic Literature Review

Comparing Use of Health Technology Assessment in Pharmaceutical Policy among Earlier and More Recent Adopters in the European Union

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ABSTRACT

Objectives: To examine and compare the use of health technology assessment (HTA) for the reimbursement of new medicines in selected European Union member states with decades of experience in the use of HTA and in countries that have used it regularly since 2000. **Methods:** The selected countries were categorized into "earlier" adopters (group A: England, Germany, France, and Sweden) and more "recent" adopters (group B: Poland, Bulgaria, Hungary, and Romania). A systematic review of published literature was performed. The analysis and comparison of HTA procedures were done by using an analytical framework. **Results:** In all countries, the assessment criteria used include effectiveness, safety, relative effectiveness, and economic data. In group A countries, the main objectives are improving quality of care, ensuring equal access, and efficient use of resources. Group B countries have established HTA organizations with official guidelines but often seek the decisions of other developed countries. They place considerable emphasis on the budget impact of new therapies, and HTA is also used as a cost estimation tool for state budgets. **Conclusions:** HTA organizations have been developed dynamically not only in high-income countries but also in countries with limited resources. The experience and evolution of both can be used by countries that are in the dawn of creating an HTA organization.

Keywords: health policies, health technology assessment, pharmacoeconomics, reimbursement.

Introduction

Health technology assessment (HTA) is considered a key tool used for decision making in health care policy, which can support the efficient use of resources while rewarding innovation. A key purpose of HTA in decision making is to achieve greater value for the money spent [1]. Over the past 30 years, several European countries have established specific bodies and developed various programs for the implementation of HTA [2]. There are, however, considerable differences between national HTA agencies among European Union (EU) member states. The differing philosophy of these organizations is the result of political, social, and economic factors that have shaped European health systems [3].

A systematic comparison of HTA processes applied in decision making on the pricing and reimbursement (P&R) of medicines can identify similarities and differences that provide important information about the stages of development of this complex and multifactorial process. The aim of the present study was to compare how HTA is implemented in the procedures for reimbursement of medicines in selected countries at different levels of maturity in the application of HTA. The purpose of this exercise was to contribute to the evidence base that can be used in the process of planning and introducing an HTA system in a country, as in the case of Greece, which has a constricted health care budget and is in the process of institutionalizing HTA in decision making for the reimbursement of pharmaceutical products. We aimed to provide a snapshot of the selected HTA systems' organization, the procedures and evaluation criteria applied, and the role of HTA in the decision-making process; another question of interest was whether and in what way the characteristics of the HTA systems differ between countries that are at a different stage of HTA implementation. A detailed comparison of analytical methods

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and techniques applied during the HTA process as well as the actual result of the reimbursement decisions per se were out of the scope of the present analysis.

Methods

Criteria for the Selection of Countries

The first criterion was the countries' political-geographical position; the countries selected were members of the EU. Second, given that the Greek legislation provides for a centrally organized HTA organization, countries with regionally organized HTA procedures were excluded. To account for different levels of maturity in the application of HTA, the number of years of experience in HTA implementation (not limited to decision making on pharmaceuticals) was considered. Sweden, France, the United Kingdom, and Germany are considered leaders in the establishment of HTA in Europe and have also been very influential regarding the methods and tools applied in HTA and its use in policymaking [2]. Selected Central and Eastern European countries were included because they constitute "recent adopters" of HTA.

On the basis of the aforementioned criteria, the following countries and their respective HTA agencies were selected: France (*Haute Autorité de Santé* [French National Authority for Health]), Germany (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* [German Institute for Quality and Efficiency in Health Care]), the United Kingdom (National Institute for Health and Care Excellence [NICE]), Sweden (*Tandvårds- och läkemedelsförmånsverket* [TLV; Dental and Pharmaceutical Benefits Agency]), Bulgaria (National Centre of Public Health Analysis), Hungary (Technology Appraisal Head Department), Poland (*Agencja Oceny Technologii Medycznych i Taryfikacji* [Agency for Health Technology Assessment and Tariff System]), and Romania (HTA unit of the National Drug Agency). Two groups were formed: group A included the "earlier" adopters (France, Germany, the United Kingdom, and Sweden), whereas group B included the "recent" adopters (Bulgaria, Hungary, Poland, and Romania).

Collection of Information

Information was collected through a systematic literature review that applied modified guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. An extensive search using a structured search strategy was performed for peer-reviewed articles published in English during the last 15 years (from January 2000 to February 2015).

English terms including specific conditions (i.e., Medical Subject Headings terms) combined with free-text terms were used: the selected "country," with the phrases "health technology assessment" or "HTA," "health policy," "pharmaceutical policy," "pricing and reimbursement," "health reform," "pharmaceuticals reimbursement," "economic evaluation," and "impact on health budget" [4]. The first extensive search was done in PubMed, from which most of the included articles were recovered. An additional search was done in the following specialized journals: *International Journal of Technology Assessment in Health Care* and *Value in Health* (main and regional issues). Finally, manual search was performed by checking the list of references in the articles identified as satisfying all the inclusion criteria.

All recovered abstracts were reviewed independently and, subsequently, full-text articles were identified on the basis of specific inclusion and exclusion criteria. Articles were included if they 1) were in English, 2) were related to the implementation of HTA for decisions on medicine reimbursement, and 3) were published between January 2000 and February 2015. Articles were excluded if 1) articles presented results of economic evaluations of medicines and medical devices, 2) HTA implementation was in a hospital setting, and 3) full text was not accessible. The independent review was performed online by using Covidence, which is a tool for the organization and evaluation of information gathered in the context of a systematic literature review. When there were disagreements, the final decision was made after a discussion among all authors. A search for supplementary information was performed in HTA organizations' Web sites and guidelines (where available in English and in other cases with the use of Google Translate) and in the Web sites of the International Society for Pharmacoeconomics and Outcomes Research, the Organization for Economic Cooperation and Development, and the European Observatory on Health Systems and Policies.

Methods of Comparative Analysis

For the analysis and comparison of HTA processes in the selected countries, an adapted methodology developed by Hutton et al. [5] and modified by Franken et al. [6] was used. According to the Hutton framework, data are displayed in tables where the main characteristics of the HTA systems are depicted so as to facilitate comparison [5,6]. In this context, the organization of an HTA agency is split into two levels of analysis—the policy implementation level and the individual technology decision level. The policy implementation level concerns the way in which HTA is embedded in the broader political system, the HTA agency's legal status, and its relationships with other public sector bodies and stakeholders (such as industry and patient groups) and also provides information as to what the purpose of the HTA organization is, whom does it advise, and to whom it is accountable [5,6]. The technology decision level comprises the processes by which individual technologies are evaluated by the system, for example, assessment processes, how decisions are made, and how they are implemented [5,6]. Franken et al. [6] also differentiated between an assessment and an appraisal phase in the HTA process.

Results

A total of 1724 articles were identified for initial review. Of these, 309 were duplicates and thus excluded. By applying the inclusion and exclusion criteria, 1165 articles were excluded after the assessment of abstracts, resulting in 249 articles for full-text evaluation. Applying the same independent assessment process, 64 articles were found to fully satisfy the inclusion criteria. An additional nine articles were identified after checking the reference lists of included articles. Thus, finally 73 articles were used in the analysis. The collected information was analyzed and classified according to the two dimensions of the Hutton framework.

A schematic representation of the search and selection process is shown in Figure 1.

Policy Implementation Level

The main characteristics of the political implementation level for the countries of groups A and B are presented in Table 1.

In England, France, and Germany, the HTA bodies are public bodies that operate independently from the government, whereas in Sweden the TLV is a governmental agency. All four HTA bodies in group A countries were established by government bodies in the context of broader reforms toward evidence-based medicine, improvement of safety and quality of care, as well as promotion of equity and efficiency in the use of health care budgets [7–11]. HTA was seen as a tool toward achieving these goals while rewarding innovation and has an important role in the decision-making process [9,11–15]. This is reflected in the organizations' objectives and scope of activities, which are broader than the assessment of medicines. These organizations also place emphasis on operating with processes and procedures that are

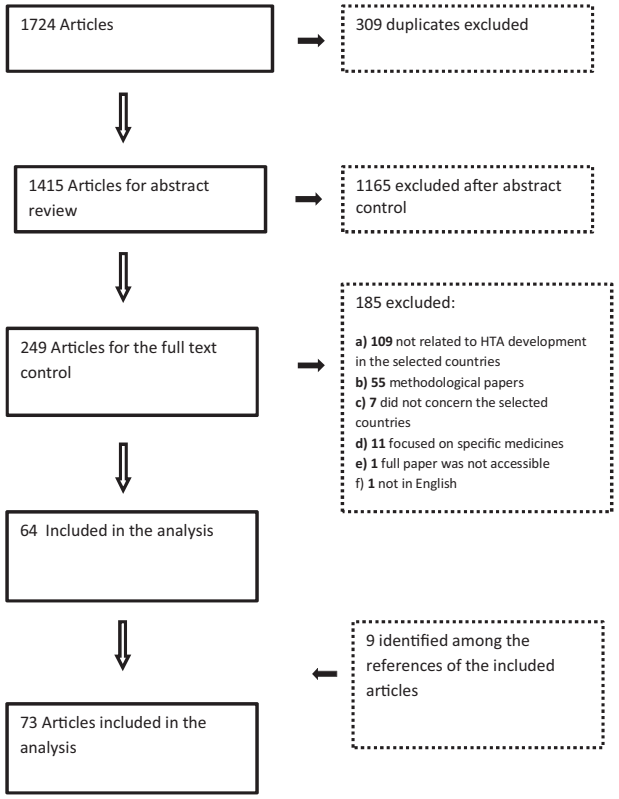

Fig. 1 – Schematic representation of the systematic review based on the PRISMA model. HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

considered best practice (e.g., independence, transparency, and openness) [2,4,6,14,16–19].

In group B countries, the HTA process was integrated into the health system through reforms of existing legislation and in the framework of system restructuring [20–23]. In Hungary and Poland, the HTA organizations were established as autonomous organizations under the Ministry of Health (MoH) in 2004 and 2005, respectively. In Bulgaria and Romania, the respective agencies were established in 2013 [24,25] and consist of a dependent unit or a division within the MoH. In all group B countries, the HTA process is centralized with no reassessment of the decision in other regions. The purpose of the HTA process in group B countries is mainly the optimization of resources for technologies such as medicines, for which the marketing authorization holder (MAH) applies for reimbursement [26,27]. Especially for Poland and Hungary, the HTA process has a history of about 10 years, and there are efforts to take into account "social, economic and ethical aspects" in decision making [28,29]. The HTA bodies play an important role in the decision-making process; nevertheless, their recommendations are not always adopted, because specific confidential agreements with the MoH or other political implications may lead to a different decision [30].

Technology Decision Level

The main findings on the technology implementation level for both group A and B countries are presented in Tables 2 and 3.

Assessment and appraisal

The type of evidence requested is similar across jurisdictions. Evidence on clinical effectiveness, relative clinical effectiveness, safety, target population, disease characteristics, availability of other treatments for the same indication, and so forth is part of the evidence base. All countries have published guidelines in which the documentation and methodological requirements for the application are described [31]. Nevertheless, differences exist in critical points, such as the criteria for selecting or prioritizing technologies, the quality of the required documentation, and the methodological approaches used. The differences in the methodological requirements of group A HTA agencies are discussed in detail elsewhere [14,32,33]. Health economic analysis has recently been included as a requirement in the HTA process of newly marketed medicines that are characterized as innovative and are expected to have a significant impact on health care expenditure and provision in France. The results of the health economic analysis, in addition to the decision on the added therapeutic benefit, form the basis of price negotiations with the MAH. In Germany, since 2011, all newly marketed medicines and new indications are assessed for their added therapeutic benefit, but health economic analysis is performed only in those cases in which an agreement on the reimbursed price is not reached.

In group A countries, the assessment report is prepared either by internal staff (in France, Germany, and Sweden) or by external academic organizations (in England) on the basis of the dossier submitted by the MAH; additional evidence may, however, be collected via a systematic literature review and/or consultation with stakeholders. The appraisal is done by committees or boards integrated within the HTA organization [9,34–36] or by the decision-making body (e.g., in Germany) [16]. In France and Germany, the main criterion for a positive recommendation is the medicine's therapeutic benefit. In England and Sweden, cost effectiveness is an important criterion explicitly considered in the appraisal phase [2,37]. HTA is also applied for the review of already marketed medicines. This approach allows the assessment of the therapeutic value of a large number of medicines, which may result in price modifications, changes in the reimbursement level, or even delisting [2].

In group B countries, the concepts of assessment and appraisal are intertwined and are mainly based on the review of the evidence provided by the applicant. In Poland and Hungary, the applicant should present data demonstrating the cost effectiveness of the technology. The Agency for Health Technology Assessment and Tariff System in Poland and the Technology Appraisal Head Department Committee in Hungary perform de novo analysis of the submitted data. The main limitation of this analysis is that there is a lack of local data such as costs, costs per unit, the general health state of the population, epidemiological data per disease, and quality-of-life data for the weighting of financial data. There are also a limited number of registries [23,38,39]. In Bulgaria, the HTA Committee critically evaluates the application and provides a recommendation advising the final decision-making body. A common key feature is the evaluation of the added therapeutic value when compared with existing alternatives. In all group B countries, the decisions of other European HTA bodies are consulted. Moreover, in Romania and Bulgaria, the final decisions of HTA bodies in the United Kingdom, France, and Germany are considered to be important for the final positive or negative decision. In these countries, a scorecard is the primary tool used for the final decision.

The results of budget impact analysis are also important for the final appraisal decision in all countries. The budgetary impact of the introduction of a new medicine in the health system is valuable in estimating the financial implications and, hence, whether the product will be included in the health benefit basket. In group B countries, although specific appraisal criteria representative of their health system are set, their final objectives often remain unclear, which could lead to a lack of transparency [31,40].

Table 1 – Elements of an HTA system: policy implementation level—group A and B countrie.

Element	Group A				Group B			
	England	France	Germany	Sweden	Poland	Romania	Hungary	Bulgaria
Establishment: Relationship with the MoH and other organizations	NICE (1999) Nondepartmental public body Established by the DoH	HAS (2004) Autonomous public scientific authority Established by the MoH (replaced the National Agency for Accreditation and Evaluation of Health —ANAES)	IQWiG (2004) Established by G-BA as an autonomous scientific institution of the Foundation for Quality and Efficiency in Health Care	TLV (2002) Government agency	AOTMiT (2005) Autonomous organization under the supervision of the MoH	HTA unit (2014) Established inside the NDA	Office HTA (2004) In 2012 it was renamed as TAHD as a department in the National Institute for Quality and Organizational Development in Healthcare	NCPHA (2015) Under the supervision of the MoH
Objective: Broader political objectives	Development of evidence-based guidelines and advice, quality standards, and provision of information services to decision makers	To provide health authorities with the information required to make decisions on the reimbursement of health technologies; to improve quality of care; to provide information on the quality of care to the public; to provide health economics assessments and opinions on the most efficient strategies for health care, prescribing, or management	Provision of independent scientific assessments of the benefit and cost of new technologies; development of clinical practice guidelines and provision of information to the public on quality and efficiency of care	Deciding on the pricing and reimbursement of medicines; re-evaluating medicines already reimbursed; improving the quality of provided pharmaceutical care; supervising certain areas of the pharmaceutical market	Optimization of resources provided for the reimbursement of health technologies, taking into account the social, economic, and ethical aspects	Optimization of the resources that are used for the reimbursement of services or medicines	Provides high-quality, safe, effective, and cost-effective medicines to the reimbursement scheme intended either for prevention or treatment	Sets price limits for prescription drugs, records the maximum retail prices, and decides on the inclusion, amendments, or exclusion of pharmaceuticals from the positive list of medicinal products
Implementation: Scope	Medicines selected via a topic selection procedure NICE aims to consider all new significant drugs and indications	All newly marketed medicines (clinical appraisal) Since October 2013: health economic assessment for all new highly innovative (ASMR I to III) medicines with a likely significant impact on health expenditure or health care organization/provision	All newly marketed medicines and new indications	Newly marketed medicines applying for reimbursement All medicines included in the benefit scheme before 2002	For medicines that will be included in the reimbursement list, the MAH must submit a full HTA application	Newly marketed innovative medicines, new indications, and re-evaluation of medicines that are already on the reimbursement list	Newly marketed innovative medicines, new indications, or new route of administration and in the case of a price increase request	For newly marketed innovative medicines, products not included in the positive drug list

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Implementation: Role in the final decision making	Final decision taken by NICE (Transparency Committee) with legal effect	Final decision on reimbursement: UNCAM and MoH	Final decision: G-BA	Final decision with legal effect	Final decision: MoH	Final decision: MoH	Final decision: MoH and Ministry of Economy	Final decision: MoH
Transparency	Most of the produced documents and the final appraisal report are publicly available	The final assessment report and the decision are published on the HAS Web site	IQWiG publishes assessments on its Web site The G-BA assessment and the final decision are publicly available	The decisions and assessment reports are publicly available	The decision is publicly available and implemented if it is accepted by the MoH	The final assessment report is published on the Web site of the MoH; the publication of the decision is done at the Official Gazette	The decision is publicly available on the MoH Web site; the assessment report is not publicly available	The decision and assessments are not publicly available

Sources: Franken et al. [6], Stafinksi 2011 et al [4], Sorenson and Chalkidou [2], Gulacsi et al [48], Nuijten et al [76], Weill and Banta [12], Greiner and von der Schulenburg [35], Busse and Blümel [10], Panteli et al. [53], Haute Autorité de Santé [78]-, Rochaix and Herri [36], Chevreul et al [41], Annel et al [79]-, and National Institute for Health and Care Excellence [15].
ANAES; *Agence nationale d'accréditation et d'évaluation en santé* (National Agency for Accreditation and Evaluation of Health).; AOTMiT, *Agencja Oceny Technologii Medycznych i Taryfikacji* (Agency for Health Technology Assessment and Tariff); ASMR, *Amélioration du Service Médical Rendu* (Clinical Added Value); DoH, Department of Health; G-BA, *Gemeinsamer Bundesausschuss* (Federal Joint Committee); HAS, *Haute Autorité de Santé* (French National Authority for Health); HTA, health technology assessment; IQWiG, *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (German Institute for Quality and Efficiency in Health Care); MAH, marketing authorization holder; MoH, Ministry of Health; NCPHA, National Center of Public Health Analyses; NDA, National Drug Agency; NICE, National Institute for Health and Care Excellence; TAHD, Technology Appraisal Head Department; TLV, *Tandvårds- och läkemedelsförmånsverket* (Dental and Pharmaceutical Benefits Agency); UNCAM, *Union nationale des caisses d'assurance maladie* (French National Union of Health Insurance Funds).

Decision

Sweden is the only country where there is a joint decision on P&R. In France and Germany, P&R decisions are interlinked, whereas in England, NICE provides guidance on the use and reimbursement of the technology. In France and Germany, the final decision is taken by another body, taking into consideration the result of the assessment phase. In France, the assessment of clinical benefit by the French National Authority for Health is used by the *Union Nationale des Caisses d'Assurance Maladie* (French National Union of Health Insurance Funds), which is responsible for reimbursement decisions [41]. In Germany, *Gemeinsamer Bundesausschuss* (Federal Joint Committee) is the body that takes the final decision on reimbursement after the finalization of the assessment report of the German Institute for Quality and Efficiency in Health Care. In Sweden and England, the decisions of the HTA organizations that conduct the appraisal are final and mandatory for regional or local authorities [42,43]. In all the countries, the decision can be positive or negative, or reimbursement can be granted with restrictions (e.g., for specific indications or for specific patient groups) [6,44]. There may also be a decision on temporary reimbursement because of the uncertainty about the evidence provided, conditional upon the collection of additional evidence [6]. In England, France, and Sweden, risk-sharing agreements (coverage with evidence development) with the manufacturers have been introduced [45]. Finally, it is worth noting that all four countries of group A have developed faster assessment processes for the early inclusion of innovative technologies in the reimbursement list, with a commitment from the MAH to submit documentation attesting the benefit of the medicine after it is marketed [45,46].

In group B countries, the HTA agency has a consultative character and the final decision is taken by the MoH. Often a negative opinion or a bad score will result in negotiations between the MAH and the MoH regarding restrictions or risk-sharing agreements. In most cases, these are price-volume agreements [47–49]. Specific timelines for the HTA procedure that are in line with the European Transparency Directive are foreseen in all group B countries. In Poland and Hungary, the HTA has a long history of implementation, and specific scientific tools that are developed by international scientific societies such as the International Society for Pharmacoeconomics and Outcomes Research are used for the critical appraisal of the applications [21,47,48,50]. In the appraisal phase, the medicines are evaluated from social, ethical, and organizational perspectives [22,48,50]. In Romania and Bulgaria, the critical appraisal is done by a specific committee that considers comparative efficacy, pharmacoeconomic and financial data, and ethical implications [24,25,48,51,52].

Result and implementation

In all the countries, the decision implementation predominantly relates to the medicine's reimbursement rate or price. In Germany, medicines with no added therapeutic benefit are included in the reference price system. For medicines with a positive benefit assessment, a reimbursement price is set after negotiations between the Federal Joint Committee and the MAH. The negotiations must be completed within 1 year of the launch of the product. In Germany, there is only a negative reimbursement list; when a medicine is granted marketing authorization, it is considered reimbursable, unless it is included in the negative reimbursement list. In France, the medicine is included in a positive reimbursement list and price negotiations are initiated. In England, when a medicine is recommended as an option by NICE, clinical commissioning groups must ensure that it is available to patients within 3 months (funding requirement). Nevertheless, since April 2017, National Health Service (NHS) England may request for a variation to this requirement. To be specific,

Table 2 – Elements of an HTA system: technology decision level—group A and B countries: assessment and appraisal.

Element	England	France	Germany	Sweden	Poland	Romania	Hungary	Bulgaria
Assessment								
Competent organization (preparation, processing, and reporting)	NICE	HAS	IQWiG (commissioned by G-BA)	TLV/and/or Swedish Agency for Health Technology Assessment and Assessment of Social Services	AOTMiT	HTA Division in the MoH	TAHD (former OHTA)	NCPHA
Competent body	Evidence Review Group	HAS Medicines Assessment Department (clinical assessment) HAS Division of Economic and Public Health (health economic assessment)	IQWiG (consults with external medical experts and patient organizations in the assessment phase). If necessary, its Scientific Advisory Board is involved	TLV working groups	Transparency Council (Appraisal Committee)	Specialist Committee/HTA Division	TAC	Expert opinion: HTA Committee
Appraisal								
Competent organization/ committee	Appraisal Committee (independent advisory body)	Transparency Committee (reimbursement) Economic and Public Health Assessment Committee CEPS (pricing)	G-BA	TLV Board on Pharmaceutical Benefits	Transparency Council	Specialist Committee/HTA Division	TAC/NHIF	Expert opinion
Evidence and evaluation criteria								
Clinical evidence/ safety	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relative effectiveness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Economic analysis	CUA/cost comparison	CEA/CUA (pricing)	CBA in specific cases	CUA, cost comparison, cost benefit depending on the treatment	CEA/CUA	CEA/CUA	CEA/CUA	CEA/CUA
Appraisal criteria	Quality and certainty of clinical evidence Benefits and adverse events from the patient perspective Cost effectiveness Budget impact	Therapeutic benefit Disease severity Availability of other treatments Purpose of use (preventive, symptomatic, or curative) Impact on public	Therapeutic benefit Patient-relevant therapeutic effect Certainty of the evidence Budget impact for social insurance Annual treatment costs of the	Human value principle Need and solidarity principle Cost-effectiveness principle Disease severity Managed entry agreement	Clinical effectiveness and safety Economic evidence Affordability (budget impact) Disease severity Burden of disease	Scorecard with specific criteria: • Budget impact analysis • Decisions of HAS/NICE[†]/ SMC/IQWiG—G-BA • Reimbursement	Clinical effectiveness and safety Economic evidence Budget impact analysis Disease severity Burden of disease	Scorecard with specific criteria: • Clinical effectiveness and safety • Economic evidence • Budget impact analysis

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	Equality issues Disease severity Degree of innovation Costs and benefits incurred in other sectors Nonhealth benefits of the technology (only when specifically requested)	health Cost effectiveness Prices in European countries	comparator Prices in European countries	between the county councils and the pharmaceutical company		in other EU countries		Opinion in France, the United Kingdom, and Germany G-BA HTA assessments of other EU countries
Threshold cost/QALY	£20,000–£30,000 (implicit) A medicine with an ICER >£30,000 should make reference to the factors taken into consideration	No	No	No	3 times the GDP/capita	No	2–3 times the GDP/capita	No
Appraisal report publicly available	Yes	Yes	Yes	Yes	Yes	Yes	No	No

Sources: Gulacsi et al [48], Nicod and Kanavos [80], Stafinksi [4], Nuijten et al [76], Kolasa [28, 29, 39], Franken et al. [6]-, Panteli et al. [53] Bridges et al [77], Haute Autorité de Santé [78], Rochaix and Herri [36], Annel et al [79], NICE 2017a,- and- National Institute for Health and Care Excellence [15].

AOTMiT, *Agencja Oceny Technologii Medycznych i Taryfikacji* (Agency for Health Technology Assessment and Tariff); CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CEPS, *Comité économique des produits de santé* (Economic Committee on Healthcare Products); CUA, cost-utility analysis; EU, European Union; G-BA, *Gemeinsamer Bundesausschuss* (Federal Joint Committee); GDP, gross domestic product; HAS, *Haute Autorité de Santé* (French National Authority for Health); HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IQWiG, *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (German Institute for Quality and Efficiency in Health Care); MoH, Ministry of Health; NCPHA, National Center of Public Health Analyses; NHIF, National Health Insurance Fund; NICE, National Institute for Health and Care Excellence; OHTA: Office of Health Technology Assessment; QALY, quality-adjusted life-year; SMC, Scottish Medicine Consortium; TAC, Technology Appraisal Committee; TAHD, Technology Appraisal Head Department; TLV, *Tandvårds- och läkemedelsförmånsverket* (Dental and Pharmaceutical Benefits Agency).

Table 3 – Elements of an HTA system: technology decision level—group A and B countries: decision, appeal, and implementation.

Element	England	France	Germany	Sweden	Poland	Romania	Hungary	Bulgaria
Decision-making body	NICE/Appraisal Committee	UNCAM MoH CEPS	G-BA GKV-SV	TLV	MoH	MoH according to the scorecard	MoH	MoH according to the recommendation of NCPHA
Decision type	Recommendation on the medicine's use in the NHS	UNCAM/reimbursement level MoH/inclusion into the positive list CEPS/pricing	G-BA/reimbursement GKV-SV/reimbursed price	TLV/joint decision on reimbursement and pricing	AOTMiT/ reimbursement	HTA Division/ reimbursement	TAC/ reimbursement	NCPHA/reimbursement and pricing
Stakeholder involvement	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Possibility of restricted reimbursement (i.e., specified indications, patient groups, and settings)/or managed entry agreements	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes Price: volume agreements	Yes/Yes Price: volume agreements	Yes/No
Appeal/dissent	Yes	Yes	Yes	Yes	No information found	Yes	Yes	Yes
Revisions/ reassessment	Yes	Yes	Yes (depends on the case)	Yes (medicines before 2002)	Every 5 y	No	No information found	No information found

Sources: Gulacsi [47,48], Stafinksi 2011 et al [4], Nuijten et al [76], Kolasa [28, 29, 39], Franken et al. [6], National Institute for Health and Care Excellence [15], Panteli et al. [53], Bridges et al [77].

AOTMiT, *Agencja Oceny Technologii Medycznych i Taryfikacji* (Agency for Health Technology Assessment and Tariff); CEPS, *Comité économique des produits de santé* (Economic Committee on Healthcare Products); G-BA, *Gemeinsamer Bundesausschuss* (Federal Joint Commission); GKV-SV, *GKV-Spitzenverband* lth technology assessment; MoH, Ministry of Health; NCPHA, National Centre of Public Health Analysis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TAC, Technical Appraisal Committee; TLV, *Tandvårds- och läkemedelsförmånsverket* (Dental and Pharmaceutical Benefits Agency); UNCAM, *Union nationale des caisses d'assurance maladie* (French National Union of Health Insurance Funds).

manufacturers are required to include a budget impact analysis in their submission. For medicines with a financial impact exceeding £20 million in any of the first 3 years of their use, NHS England will proceed to commercial discussions on behalf of clinical commissioning groups. If discussions fail, NHS England can request a variation to the funding requirement up to a maximum of 3 years [15]. In Sweden, the county councils have some discretion as to the implementation of decisions made by TLV and can reach a more restrictive reimbursement decision, mainly because of budgetary considerations [42].

Reimbursement restrictions are common in all the studied countries, with variations observed as to the type of restriction: reimbursement for specific indications, patient groups, or prescriber groups. In the case of reimbursement under specific conditions, managed entry agreements are implemented. In Poland, Romania, Hungary, and Bulgaria, the medicine is included in a positive reimbursement list [21,24,25,50,53]. In Poland, an update and a reassessment of the data are requested every 5 years [30]. In Romania, if the reimbursement is under specific conditions, a reassessment is done after 1 year and the MAH is required to submit additional data. Nevertheless, no other details are given in the relevant law [48]. For Hungary and Bulgaria, no information could be found on a reassessment procedure of all the reimbursed medicinal products.

Discussion

The results of the present review confirm that the two groups of countries are going through different phases in the evolution of HTA. Group A countries (England, France, Germany, and Sweden) have a long experience of more than two decades in the implementation of HTA [37,54] and have made a significant investment in the development of the HTA process. Results of the HTA process are used in P&R decisions and also as input in the development of clinical guidelines (e.g., in England) [2,55]. The main objective of the introduction of HTA in group A countries was improving quality of care, ensuring equal access to care, and assessment of the value for money of reimbursed medicines [2,56]. Although health care cost considerations have led to the systematic assessment of innovative medicines recently in Germany and France, the assessment results are used to negotiate "fair" prices for social insurance. The HTA process in group A countries has reached a high level of maturity, and therefore the question is how the institutionalization of HTA has influenced policy and what was its impact on health care delivery. At the same time, these countries are trying to convey their expertise and knowledge at the European and international levels. They are in what is characterized by Battista and Hodge [57] the "expansion phase."

HTA has developed over the last two decades and has been institutionalized and implemented in Poland, Romania, Hungary, and Bulgaria. Poland and Hungary have a longer history of HTA compared with Romania and Bulgaria. These group B countries have adopted the formal conditions for implementing HTA and have established relevant HTA agencies, although these differ in organizational structure and operations, size of human resources, and extent of influencing decision making [58,59]. These countries have generally followed the standards of other more mature HTA organizations, and occasionally they have established advisory relationships with them. In Romania and Bulgaria, it is officially accepted to use the appraisal decision of other European countries (the United Kingdom, France, and Germany), and this plays an important role in the final decision. The key question in this case is whether this information can be used as such, and to what extent it can reflect the conditions of the third country that uses them [48,60–62]. Group B countries, having completed the first phase of the standardization and institutionalization of HTA, are now in the stage of further developing the HTA process, using local data as input for decision making so that final conclusions are based on national priorities and values [48].

The present review provides an overview of the HTA procedure in countries with a different degree of maturity in the use of HTA. The commonalities and differences between these HTA systems can inform the development of short- and long-term plans for the introduction and subsequent development of the HTA procedure in countries that are planning to introduce a "fourth hurdle" in their P&R system. During the planning phase, the new HTA comers should first decide on the type of their HTA agency and establish specific rules governing its relationship with other organizations and decision-making bodies. The vision and the main scope of the organization should be clearly defined. Another important point to be decided upon is whether the HTA agency will have an advisory or regulatory role. While designing a new HTA organization, the total available budget, the available personnel with appropriate training and knowledge, the availability of data, and the ability of the health care system to use the results should be taken into account [63]. Second, at the technology level, clear rules and guidelines for the applicant should be available, describing also the evaluation criteria to be applied.

Independence and transparency are key issues to be considered. In most jurisdictions the data are submitted by the MAHs of the technology, and thus the independence of the assessment is of great importance [63]. In all the studied countries, the assessment of the submitted evidence is performed by an independent committee. It is also suggested that the appraisal report and the final decision be fully justified, transparent, and publicly available. A procedure of appeal could also be considered and described. Finally, a reassessment of the decision must be a part of the HTA procedure because when a new medicine is marketed the information about its long-term benefit is limited, whereas the initial economic assessment has been performed mainly with data from phase 3 clinical studies. The collection of real-world evidence can be a requirement in some cases, and its reassessment over a predetermined period (e.g., 3 or 5 years later) should be considered.

Another crucial point is the transferability of HTA results across countries, specifically whether the data on the effectiveness and costs can be transferred from one country to another. The differences that may exist in epidemiological data, such as disease incidence or mortality, prove to be a barrier in the transfer of results between countries [47,48,60]. In general, clinical data may be transferred, particularly within Europe, because there are no significant genetic or other differences between European nations [60,62]; the target population, however, should be concretely defined. On the contrary, cost-effectiveness data are not easily transferred from one country to another because of factors such as variations in prices of medicines and health services, the organization of health care, and the availability of financial resources. The question of other countries' data transferability may be partly answered by using appropriate testing tools (extensive checklist of critical and noncritical factors) to support an objective conclusion [64]. Taking into account available resources, each country should invest in capacity building to proceed to a stage of HTA development that entails using local data as input for decision making and basing the final conclusions on national priorities and values [65,66]. This would fulfill a basic goal of HTA implementation—early access, within available resources, for patients to new, safe, and effective technologies [67]. The next step is that of engaging the main stakeholders, especially the patients in the decision-making process [68–70].

While introducing the preliminary steps of the HTA evaluation, the use of calibrated criteria should be considered [71,72]. The result of the assessment by other countries should not be the sole

criterion for the decision of reimbursing a new pharmaceutical product but could be part of a wider scoring framework, as in the case of Romania and Bulgaria. Finally, opportunities for international cooperation should be exploited. The European Network for Health Technology Assessment aims at increasing the use of the HTA process in decision making among European countries, strengthening the relationship of HTA and health policymakers in the EU and its member states, and supporting countries with limited experience in HTA by providing tools for increasing transferability and decreasing duplication of work [73,74]. In the framework of the European Network for Health Technology Assessment Joint Actions, the possibility of cooperation between HTA agencies was studied by implementing joint HTA evaluations [75].

The present analysis has certain limitations. The main search was specifically done in the PubMed database and in some cases full access to some articles was not possible. An effort was made to validate and complement the information retrieved through searches in HTA agencies' Web sites and reports published by the European Observatory on Health Systems and Policies. Nevertheless, the data collected and the comparative analysis included in the review can be used as a source of information on the basic aspects that countries with different degrees of maturity have in common and thus are important for the initiation of a successful HTA process.

Conclusions

Among the selected countries, there are various implementation modes of HTA, leading to the conclusion that there is no specific model for the development and implementation of an HTA process. Nevertheless, it is estimated that HTA will remain the main tool for the evaluation of new medicines for P&R decisions. Countries that are at the dawn of the implementation of an HTA process should take advantage of the experience of other countries.

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