Implementation of health technology assessment in Central and Eastern European countries and its impact on pricing and reimbursement decisions

Doctoral (PhD) Thesis

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1. Introduction

1.1 Background for pharmaceutical policies

The special characteristics of the pharmaceutical market including patent protection, presence of third-party payers and low price elasticity of patients for reimbursed medicines have led to the introduction of several health policy regulations targeting third-party payers, manufacturers, prescribers, pharmacists and patients [1]. Every country employs a mix of regulatory mechanisms to contain pharmaceutical expenditures while ensuring quality and efficiency in patient care, however with varying configurations and rigor. This variation also influences the costs of publicly financed pharmaceuticals [2]. While regulations might differ, accessibility to new medicines has become an important health policy issue all over Europe in recent decades. Particularly, high-priced medicines have pushed the issue of patient access high on the policy agenda [3]. In general, pharmaceutical policy deals with the principles guiding decision-making in the field of pharmaceuticals. The goal of pharmaceutical policy is (similar to other social policies) to contribute to the overall health, welfare and well-being of society by improving or regulating registration, reimbursement, and distribution of pharmaceuticals [4].

Important differences in patient access to medicines exist between European countries, particularly between Western and Eastern countries. The high variability stems from differences in the economic status of countries (i.e. reflected by the GDP per capita), the health system governance, the public expenditure on healthcare, the marketing and product launching strategies by pharmaceutical manufacturers, the local pharmaceutical prices, and utilization of medicines and other health services [3]. It is important to consider that because of lower salaries in the healthcare sector, the costs of non-pharmaceutical health services are lower in Central and Eastern European (CEE) than in Western European countries, whereas prices of innovative pharmaceuticals are not significantly different mainly because of external price referencing and the potential of parallel trading across countries. Therefore, CEE countries tend to spend higher percentages of their healthcare expenditure on pharmaceuticals compared to high-income Western European countries [5]. In addition, external price referencing is also suspected to result in significant delays in the launch of new pharmaceuticals in lower income countries [6, 7].

External price referencing is one of the most frequently applied regulations in health policy to control pharmaceutical prices thus many CEE countries have also implemented it [8]. External price referencing is the practice by which a country's authority uses prices of pharmaceutical products from other countries as a benchmark for setting the price of the same product in their own country

[9]. From a broader perspective the implication of this policy is suspected to be price-convergence across countries. At a European level, external price referencing leads to a relatively narrow price corridor for pharmaceuticals across countries compared to non-pharmaceutical services or to the variability in GDP per capita [10]. The narrow price corridor of pharmaceuticals may cause limited affordability and patient access to high priced medicines in lower income CEE countries as manufacturers tend to carefully determine their strategic launch sequence, starting launches of their new medicines in countries with traditionally high prices, which dictates a higher price-level from that moment on in other European countries as well [11]. Accordingly, external price referencing gives a false promise of effectively reducing drug prices, therefore, countries were recommended to move towards more sophisticated pricing mechanisms to facilitate the value assessment of pharmaceutical therapies according to their context and environment, such as the implementation of health technology assessment (HTA) combined l with confidential managed entry agreements [10].

HTA is a health policy tool using a systematic approach to support prioritisation in healthcare funding and it aims to help policymakers obtain better value for their money. Ideally, this should consequently lead to a more rational and targeted investment of available resources via the reimbursement of cost-effective medicines and other healthcare technologies [3]. In other words, HTA aims to reduce the opportunity cost of inappropriate health policy and resource allocation decisions [12].

HTA has been defined as a form of policy research that systematically examines the short- and long-term consequences, in terms of costs and benefits related to the application of a health technology and set of related technologies or technology-related issues [13]. By its nature, HTA is a multidisciplinary activity which systematically evaluates the effects of a technology on health, on the availability and distribution of resources and on other aspects of healthcare system performance [13].

HTA is increasingly utilized to inform reimbursement decision-makers in Europe [14]. Furthermore, using the approach of HTA to support coverage decisions in healthcare has become more and more popular world-wide [15-17]. In most countries HTA is used initially for pharmaceuticals and it is implemented in the form of Single Technology Appraisal process developed by the Scottish Medicine Consortium. This process involves the submission of an evidence dossier by the manufacturer of the technology [18]. These submitted evidence dossiers will from here on be referred to as HTA reports in this dissertation. The content and the requirements for such reports differ, but usually include at least information on the efficacy from clinical trials, the expected effectiveness in the real world,

economic evaluations estimating the cost-effectiveness and budget impact analyses. The preparation of HTA reports is supported by national guidelines detailing how to prepare the required analyses. These documents contain instructions on how to conduct for instance pharmacoeconomic evaluations of medicines with appropriate methodology (i.e. how to select comparator technology, what discount rate to use, etc.). A wide list of country-specific guidelines across the world is collected by the International Society for Pharmacoeconomics and Outcomes Research [19]. More general recommendations from international organizations such as the International Network of Agencies for Health Technology Assessment have also been published [20]. In the Single Technology Appraisal process, the submitted HTA reports are usually evaluated by internal or external experts of the HTA body, whose appraisal contributes to making pricing and reimbursement decisions about health technologies. This process can also be standardized by checklists for critical appraisal, which can further improve the objectivity in the HTA process. These are mostly internal documents within an HTA organization but some of these have also been placed in the public domain [21].

HTA reflects many of the important attributes of fashionable policy thinking over the past few decades: it is evidence based (i.e. it is an output of research activities), it relies on input from experts, it is associated with public agencies or other non-governmental organizations and one of its mantras is the "quest for transparency". In addition, HTA gained considerable interest on a European and international level through the establishment of national HTA bodies and international networks or alliances (e.g. the EUnetHTA) [22]. On the other hand, the HTA process, if performed appropriately and with good quality, can be very resource intensive. Therefore, considerable time and effort may be consumed in demonstrating whether a particular technology should be granted public reimbursement or not [23]. Eventually, building sufficient human resource and financial capacities is a key success factor for HTA implementation coupled with robust HTA methodology [24]. HTA capacity building was defined recently by the Health Technology Assessment International (HTAi) as "the process by which individuals and organizations develop or strengthen abilities related to understanding, providing input to, conducting, or utilizing HTA for health policy and decision-making, as well as, developing awareness and support in the environment within which HTA is being used" [25].

Although HTA capacity is essential for implementation, when it comes to the operation phase, the effectiveness of an HTA program depends on its influence: the extent to which information provided for decision support (i.e. in the HTA reports and in the consecutive appraisal) and then later on the extent to which this information is used by decision-makers. This influence or impact is represented by the actual role of HTA in the process of pricing and reimbursement decision-making [26].

Although it is expected that HTA will lead to improved and more equitable allocation of resources in healthcare due to its evidence-based approach, the empirical evidence of the HTA's impact on either health outcomes or spending is still scarce [27]. In addition the current European HTA environment is very diverse [14]. Therefore, it is difficult to make any general conclusions concerning the impact of HTA since its investigation cannot be conducted without considering regional- or country-specific contexts.

1.2 The implementation of HTA across European countries

A massive body of evidence is available on the implementation of HTA in Europe. For instance, a full European overview is available on mapping the institutional context of HTA procedures [14]. Another recent overview on pharmaceutical regulation across CEE countries claimed that the systematic assessment of new drugs and their corresponding evidence submissions (i.e. HTA reports) are obligatory for pricing and reimbursement decisions in most of the countries in the region [28]. Furthermore, a recent special issue in the International Journal of Technology Assessment in Health Care described the national healthcare systems and the practices of pricing and reimbursement decision-making, where special attention was given to the experiences and perspectives of HTA implementation in twelve Central, Eastern, and Southern European countries [29]. These general overviews are important to capture the most basic information at a health system level. On the other hand, CEE countries are less likely to be involved in more in-depth policy research on important aspects of HTA implementation such as: comparison of reimbursement recommendations by HTA agencies on a list of original medicinal products [30, 31]; comprehensive exploration on the potential underlying reasons for different reimbursement recommendations [32]; assessing the definition of value in the HTA for medicines in different jurisdictions [33]; comparison of value assessment methodologies by European countries [34]; defining the role and the governance of HTA in coverage and pricing decisions [35]. These studies along with other examples, claim that their objective was to provide a European perspective, however, they neglected countries from the CEE region (or in a few instances including only one country from the region, typically Poland or Hungary). This shows that HTA in CEE is slightly overlooked in the current literature on HTA implementation.

The limited focus regarding the in-depth analyses on HTA in CEE countries can be explained by several factors. First, information on how HTA analyses are conducted is less likely to be available in the public domain from these countries, therefore researchers could only select from a limited pool of countries to investigate. This explanation is supported by a study that found similar requirements for HTA analyses in CEE and Western European countries but identified major differences in data

availability. Authors claimed that these differences lead to less accurate and reliable inputs for analyses on CEE countries [36]. Similarly, transparency is also more limited on HTA procedures and related policy decisions among most CEE countries. A former research looked at six elements of transparency (requirements for reimbursement; availability of submitted HTA documents; formal appraisal of HTA reports; HTA recommendations; reimbursement decision; follow-up on decisions) in 3 CEE countries. It showed that many of these elements were not publicly available from the investigated countries [37]. Besides data availability and transparency, another explanation could be that the major pharmaceutical markets in terms of market value, research & development or production can be found in the western part of Europe (e.g. Germany, France, United Kingdom, Spain) [38]. This may indicate that there is a considerably lower interest in conducting research on HTA implementation in CEE countries.

From a historical point of view, in the European region the organizational frameworks of HTA were first established in Western European countries (e.g. United Kingdom, Sweden) in the 1990s. These agencies had independence in terms of evaluating health technologies and gained some regulatory power over time. They were tasked to provide specific expertise (e.g. perform evaluation of costs and benefits based on their health economics knowledge) and advice for decision-makers or in specific cases to make decisions themselves on reimbursement matters. Then, in the second wave of this health policy trend, during the mid-2000s, other countries followed suit. Again, these were mainly Western European countries along with only a few CEE countries. As a recent policy paper noted on this difference, “in reality the former Iron Curtain division is still visible in the world of health care reimbursement decisions” [22].

Accordingly, the patterns of European HTA agencies can be outlined with three major groups:

- Forerunners: Countries which shaped the concept and created their HTA agencies in the 1990s or earlier.
- Mainstreamers: Countries which set up HTA agencies in the mid-2000s. During this era the idea of an institution of public interest charged with HTA spread more widely.
- Non-adopters: Countries which postponed or opposed creating an HTA agency and those where the organizational framework was not established formally.

A chronological taxonomy was published in 2015 and included the 28 European countries. It is illustrated on Figure 1. Besides Hungary and Poland, which were considered mainstreamers in this taxonomy, all CEE countries were categorized as non-adopters. It must be noted that some aspects of HTA are surely used in non-adopter countries as well. Principles of health economics or specific elements of the HTA concept are indeed used by either a group of academics or decision-makers.

Therefore, it can be stated that no country in the EU today disregards HTA, however the decisive step of creating an institution whose main responsibility would be to perform HTA analyses has not been taken in the non-adopting, mostly CEE countries [22].

Forerunners	Mainstreamers	Non-adopters
Sweden (SBU, 1987)	Belgium (KCE, 2004)	Bulgaria
Finland (FinOHTA, 1995)	Croatia (AAZ, 2009)	*Cyprus*
Denmark (DACEHTA, 1997)	France (HAS, 2004)	Czech Republic
United Kingdom (NICE, 1999,	Germany (IQWiG, 2004)	Estonia
SMC, 2002)	Hungary (GYEMSZI, 2004)	*Greece*
Spain (COHTA – Catalonia, 1991,	Poland (AHTAPol, 2005)	Lithuania
Osteba – Basque, 1992,	Austria (LBI, 2006)	*Luxembourg*[a]
AETS – central, 1993,	Netherlands (CVZ, 2006)[a]	*Malta*
AETSA – Andalusia, 1996)	*Ireland* (HIQA, 2007)	*Portugal*
	Italy (AGENAS, 2006)	Romania
	Latvia (VEC, 2009–11)[a]	Slovakia
		Slovenia

1. Figure: Taxonomy of countries in term of establishing HTA agencies (Reference: [22])

As a consequence of the above-mentioned reasons, the majority of the scientific literature addresses the HTA among Western European countries. Still, a few recent studies can be found that have particularly focused on CEE countries. A qualitative study focusing on Central, Eastern and South Eastern Europe found that there is a high level of heterogeneity related to the degree of development of HTA structures, methods used and processes followed [39]. Countries such as Hungary and Poland have more formal HTA systems in place, while other countries in the region remain in the early stages [39]. Another study with a similar focus concluded that in the first two decades of HTA since the early 1990s, many CEE countries learned how to put together an HTA report, how to conduct at least some of the related evaluations, and attempted to incorporate the approach of HTA into their own healthcare decision-making processes. However, much more is needed in order to make these procedures function well [40].

Even in countries with considerable experience in HTA such as Poland or Hungary, challenges remain when it comes to the role of HTA in healthcare decision-making as well as to the availability of resources and capacities to further improve the HTA system of the countries [41].

1.3 Objectives and scope of the dissertation

The objective of this dissertation is to conduct a policy research and investigate the implementation of HTA in CEE countries from different aspects of health policy. These aspects reflect on key issues regarding the implementation of HTA for which currently the evidence is limited in the investigated CEE countries. Accordingly, the following diverse research questions regarding HTA implementation were proposed for which this dissertation provides answers:

1) How to establish an HTA system in a country where HTA formerly was not used before? What key recommendations can be defined based on the perspective of different national stakeholders?

2) Who are those involved in the preparation of the HTA reports of pharmaceuticals intended to be used for decisions? How these actors operate? Are the HTA reports prepared appropriately to support the decision-making process?

3) How and to what extent is HTA utilized for actual decision-making in practice? What is the impact of a national HTA agency responsible for appraising the submitted HTA reports on pricing and reimbursement decisions?

To answer these questions, three countries were selected as case studies and the following specific objectives were outlined:

- ***Ukraine*** was selected to answer the first research question as there was no formal HTA in place in this country before 2016. Although the recognition of the need for evidence based decision-making dates back to 2013, the first attempt to introduce HTA for pharmaceuticals was never implemented nationally [42]. Then a new reform of the regulation of pharmaceutical pricing and reimbursement took place in 2016-2017 including a program that gave HTA special attention as an important objective for their healthcare reforms.

  Therefore, ***the first part of this dissertation aimed 1) to describe the environment of HTA at the initiation point of its implementation; and 2) to explore the long-term perspectives for HTA based on the input of a wide range of stakeholders*.**

- ***Poland*** was selected to answer the second research question because the country has a long history of HTA as the national agency for HTA (called AHTAPol) responsible for reviewing HTA reports of pharmaceuticals was established in 2005 [43]. Furthermore, over the years, the Polish system has become more and more transparent and has ensured the public availability of documents generated at various stages of the HTA process [44].

Therefore, ***the second part of this dissertation aimed 1) to explore who are those preparing the national HTA reports of pharmaceuticals; 2) to describe the market and the operation of HTA doers; and 3) to analyse the extent to which these HTA reports meet the official requirements published by the Ministry of Health.***

- ***Hungary*** was selected to answer the third research question in that similar to Poland, Hungary also has a long tradition in HTA, having established a national HTA Department in 2004, an organization tasked with reviewing HTA reports for making recommendations on the reimbursement of health technologies, most importantly on pharmaceuticals [45]. Although there have been detailed studies on particular elements of the HTA system, there is a lack of adequate understanding of how HTA can actually impact the decision-making on public reimbursement in Hungary.

  Therefore, *the* ***third part of this dissertation aimed 1) to identify institutional characteristics of HTA that may either facilitate or restrict the decision supporting role of the public HTA body; 2) to assess the influence of the public HTA body on other key stakeholders engaged in the reimbursement decision-making process; and 3) to determine whether the current operational form of the HTA process delivers 'good value for the money' based on the opinion of various stakeholders****.*

1.4 Starting points related to studies presented in the dissertation

There are some key determinants from the health policy literature that directly relate to the three case studies presented in this dissertation. These publications provide the starting point and the background information that were preconditions to perform the analyses presented in the next chapter of this dissertation. These studies are summarized briefly below highlighting those concepts and results that relate to the three case studies.

Starting point related to the Ukraine case study

To investigate the HTA implementation in Ukraine a survey was used that we formerly developed and published in a scientific article [46]. It was designed to assess the current status (i.e. at the time of the study) and the preferred status (i.e. 10 years later after the time of the study) of HTA implementation by focusing on eight key components:

(1) ***HTA capacity building*** - Survey domain: *Education* - 4 answer options were defined in the survey.

(2) ***HTA funding*** - Survey domains: *Financing critical appraisal of technology assessment* - 3 answer options were defined in the survey; *Financing health technology assessment research* - 4 answer options were defined in the survey.

(3) ***Legislation on HTA*** - Survey domains: *Legislation on the role of HTA in decision-making process* - 4 answer options were defined in the survey; *Legislation on organizational structure for HTA appraisal* - 7 answer options were defined in the survey.

(4) ***Scope of HTA implementation*** - Domains: *Scope of technologies where HTA is applied* - 6 answer options were defined in the survey; *Depth of HTA use* - 4 answer options were defined in the survey.

(5) ***Decision criteria*** - Domains: *Decision categories* - 7 answer options were defined in the survey; *Decision thresholds* - 4 answer options were defined in the survey.

(6) ***Quality and transparency of HTA implementation*** - Domains: *Quality elements of HTA implementation* - 5 answer options were defined in the survey; *Transparency of HTA in policy decisions* - 3 answer options were defined in the survey; *Timeliness of HTA procedures* - 3 answer options were defined in the survey.

(7) ***Use of local data*** - Domains: *Requirement of using local data in technology assessment* - 3 answer options were defined in the survey; *Access and availability of local data* - 4 answer options were defined in the survey.

(8) ***International collaboration*** - Domains: *International collaboration, joint work on HTA and national/regional adaptation* - 4 answer options were defined in the survey; *International HTA courses for continuous education on HTA* - 3 answer options were defined in the survey.

The proposed HTA implementation survey was designed to set up long-term objectives for a country- or regional-specific roadmap. Particularly, it aimed to provide a tool for researchers and other stakeholders that facilitate and support the improvement of HTA implementation in CEE and other less affluent countries. These countries were targeted because of their poor population health and highly limited healthcare resources, and due to the fact that the opportunity costs of sub-optimal health policy decisions are greater in CEE compared to Western European countries. CEE countries could pay an even higher price for inappropriate reimbursement and resource allocation decisions, especially in difficult economic periods. CEE decision-makers as HTA users, must improve the appropriateness of their decisions and should aim to obtain better value for the money.

Starting point related to the Polish case study

General recommendations to increase transparency of HTA and related decision-making processes are commonplace [20, 47], but systematic evaluations of the levels of transparency achieved by individual HTA agencies in practice have been relatively rare thus far. To address this gap in research, our former study analysed the level of transparency of HTA in Poland and compared it with the transparency of the National Institute for Health and Care Excellence (NICE) in England [44]. This research was a prerequisite for the Polish case study presented in this dissertation since it revealed that the essential information to explore concerning the stakeholders who prepared HTA reports was available and could be analysed systematically.

The study analysed verification analysis documents produced by the Polish HTA body, the AHTAPol. These are assessments of HTA reports compiled by drug manufacturers that play a key role in developing HTA recommendations and then in reimbursement decisions. These assessments can be considered as equivalent to Evidence Review Group (ERG) reports within the single technology appraisal undertaken by NICE. The study focused on two aspects in Poland: transparency of the HTA process and the transparency of HTA outputs. The study also conducted an exploratory analysis of a sample of NICE's ERG reports and compared the levels of AHTAPol's transparency with that of NICE.

The analysis suggests that, overall, the AHTAPol meets or even outperforms the transparency of NICE in several areas. However, there were also areas where AHTAPol's transparency did not perform as well as NICE's, and areas where both agencies could improve. The AHTAPol seems to

have reached the standards set out by NICE in transparency of HTA outputs. The decreasing share of verification analyses with redacted conclusions regarding the nature of the health problem, description of the medical technology, its clinical effectiveness and safety were clear signs of improvement identified by this study.

The AHTAPol seems to perform just as well as, if not better than NICE in certain aspects of the HTA process. It systematically publishes its assessment reports, verification analyses and provides key types of information on reimbursement applications, including clinical indications and the names of requested reimbursement schemes. The AHTAPol seems to outperform NICE in providing reasons for redactions in documents and applying them systematically in assessment reports. Verification analyses also acknowledged that manufacturers' HTA analyses might have been outsourced to consultants. Finally, the AHTAPol did a better job at reporting the beginning of the assessment process systematically (not included in ERG reports) and, even more importantly, providing tables summarising expert opinions.

There were, however, important areas of the HTA process in which the AHTAPol underperformed in comparison to NICE. The baseline transparency related to authors, clinical experts and other contributors was very low and decreased even further over time with the disappearance of the relevant section from verification analyses. While the removal of information on external experts was somewhat compensated by a separate section summarising expert opinions, the same cannot be said for other contributors. It remained unclear, therefore to what extent, for instance, the AHTAPol relied on the assistance of consultants in developing the appraisals for the verification analyses. Crucially, unlike NICE, the ATHAPol rarely reported on the nature, extent or type of commercial interest involved in incidences where the expert reporting had a conflict of interest. . Furthermore, no information was provided on AHTAPol's processes for managing conflicts of interest. Inevitably, this diminished the accountability of decisions regarding the exclusion – or admission – of expert opinions associated with conflicts of interest.

In conclusion the study highlighted that in HTA reports, verification analyses were regularly published by the AHTAPol and indicated that the authors of the HTA reports (i.e. consultants to whom manufacturers outsourced the preparation of required analyses) were available, which was essential for the Polish case study.

Starting point related to the Hungarian case study

Hungary played an important role in CEE in terms of developing and implementing novel health policy methods in the past few decades. For instance, Hungary was among the first countries in the

region who implemented a DRG system for financing hospitals in 1993. HTA related activities also date back to 1993, and its institutionalization also has more than a decade of history. The main objective of implementing HTA in Hungary has always been to support the national decision-making process [45]. Our former publication provided a comprehensive description of the Hungarian HTA through the previously described HTA roadmap survey elements which helped to identify major challenges that HTA experts face in the country and those areas where Hungary has good potential for further improvement [45].

Information which identified the challenges and potential improvements of HTA was key to define the scope and the approach of the Hungarian case study presented in this dissertation. Particularly, the challenges resulting from the HTA Department's limited access to information, the problem of human resource capacity and lack of transparency guided the Hungarian case study to focus on exploring what real impact the HTA Department had on the healthcare decision-making process in Hungary. The identified challenges and potential improvements that were found and included in this publication are briefly described below.

Challenge (1): Limited accessibility of pricing information for the HTA body

The Hungarian healthcare reimbursement system remains complex, and for pharmaceuticals, risk-sharing agreements (e.g., price-volume agreements) are mandatory between the national payer and the manufacturers applying for public reimbursement. This leads to the situation where the official list price of new products and the price that the payer actually pays for the drugs differs in most cases. The details of these confidential price reductions are not shared with the HTA Department in Hungary. Hence they can only use the official list price for the appraisal of economic evaluations. However, comparing the list prices or using them for cost-effectiveness estimates and budget impact analyses highly limit the meaningfulness of the appraisal on HTA reports and corresponding recommendations.

Challenge (2): Retention of personnel at the HTA body

The fluctuation of employees (i.e. health economists, medical experts) working at the Hungarian HTA body was reported to be very high, especially when compared to other governmental bodies in Hungary. In many cases, the employees leave the organization and join pharmaceutical or HTA consultant companies after they reach senior status, which leads to a continual need for basic human resource investment to maintain their capacity.

Challenge (3): Transparency

When the study was conducted, neither the HTA reports by manufacturers nor the conclusions of the critical evaluations of HTA reports were published. Nor could they be used for research

purposes. This practice highly reduced the transparency of the evaluation process of pharmaceuticals and medical devices leaving no opportunity to assess the validity of evidence and the objectivity of the appraisal prepared by the HTA Department.

Potential improvement (1): Re-evaluation

In Hungary, HTA is not used for the re-evaluation of already reimbursed products or disinvestment decisions. This could be an additional task delivered by the HTA Department and a potential way of improving the HTA system. Re-evaluation would ensure an improved evidence base for policy decisions, but it would necessitate further specified capacity building, better transparency and probably additional financial resources as well.

Potential improvement (2): Mandatory submission of models

Transparency, usefulness, and the thoroughness of critical appraisals conducted by the Hungarian HTA body could be improved significantly by making the submission of the health economic models mandatory. These models usually simulate the cost-effectiveness and the expected budget impact of the technology. A thorough review of these models would help in identifying methodological flaws, biases and even misinterpretation of the entire HTA reports.

Potential improvement (3): Budget allocation

In regards to increased public funding of the HTA Department several changes could be made in the current practice. HTA research could be extended to investigate health technologies not marketed by private manufacturers, for horizon scanning of upcoming technologies or introducing revisions of previous reimbursement decisions. These new tasks may necessitate increased personnel at the HTA body or active collaboration with academic centers.

2. Case studies

In this chapter the 3 case studies are presented, which answer this dissertation's research questions proposed in the previous chapter. The case studies also directly reflect on the key literature presented above as the starting points. It is important to note that the studies were structured in a scientific manuscript format since each of them has already been published in peer reviewed journals in English [48-50]. The same content that was uploaded to the scientific journals after official acceptance were used here, and the structure of the studies meets the journals' predefined requirements.

It should be noted that since the studies were published in different health economics and health policy journals, they are presented in a slightly different format. For instance, the summaries are presented in the requested abstract format of the journals, therefore, they differ in terms of lengths and structure. Also in the Polish case study, instead of having a conclusion section, policy recommendations were requested by the journal. Tables and figures of the studies were included in the main text and were placed similarly as in the publication. However, tables and figures were numbered continuously throughout the dissertation. The supplementary materials were included at the end of the relevant study. References were adjusted to the requirements of this thesis and were numbered continuously in the document.

2.1 Health Technology Assessment Implementation in Ukraine: Current Status and Future Perspectives

Published in: *International Journal of Technology Assessment in Health Care*

Reference: *Csanádi M, Inotai A, Oleshchuk O, Lebega O, Alexandra B, Piniazhko O, Németh B, Kaló Z. Health Technology Assessment Implementation in Ukraine: Current Status and Future Perspectives. Int J Technol Assess Health Care. 2019. 35(5):393-400*

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Summary of the Ukrainian case study

The need for improving healthcare decision making by implementing health technology assessment (HTA) has been a top priority in Ukraine since 2016. This study sought to provide a tailor-made HTA implementation roadmap, drawing on insights from national stakeholders.

We conducted a survey using a questionnaire already applied in previous HTA research. We assessed the status of HTA when reforms were initiated in 2016 and examined perspectives on possible future developments among policy makers and representatives of pharmaceutical companies and patient organizations.

Thirty-two respondents answered the survey. Forty-eight percent of respondents were not aware of HTA training in Ukraine, but 91 percent preferred having either a graduate or postgraduate training. Experts stated that funding for HTA research and for critical appraisal of HTA submissions was limited, but in the future, they would increase funding mainly from public sources. A public HTA agency with academic support was the most preferred organizational structure. Eighty-eight percent of respondents opted for full transparency, making the HTA agency's recommendations and the related appraisal reports publicly available. A great majority of participants preferred mandating the use of local data in certain categories and indicated the importance of evaluating the transferability of international evidence. Healthcare priority and cost-effectiveness were the most important criteria for decisions, applied with a soft explicit threshold.

Ukraine is in the early phase of implementing HTA and our study provides a clear vision of national stakeholders about the future directions. In addition, learning from the experiences of other countries may help the implementation process.

2.1.1 Introduction

Health technology assessment (HTA) has been one of the most popular policy tools in healthcare reimbursement, pricing and procurement over the last few decades [27]. Several developed countries within and outside Europe have developed national or regional public HTA agencies by the 90s [51]. These bodies deal with conducting and critically appraising assessments that examine the short- and long-term consequences of the application or use of technologies. More recently, several low and middle income Asian, Latin American and Central and Eastern European countries have followed suit [52, 53]. The implementation and the development of HTA structures are well documented. For example, a recent special issue in the International Journal of Technology Assessment in Health Care described the national healthcare systems and the practices of pricing and reimbursement decision-making with a special attention on experience and perspectives of HTA implementation in 12 Central, Eastern and Southern European countries based on accounts from national HTA experts and professionals [29]. Although the special issue captured a wide scope of countries from the region, one of the largest European countries with the population of over 40 million, Ukraine, was not covered. Former studies about Ukraine focused on the pharmaceutical system in general [54] or proposed reimbursement frameworks [55], but no scientific research has been performed specifically on the perspectives of HTA in Ukraine.

Ukraine is facing major challenges in implementing universal health coverage, which is illustrated by limited accessibility and affordability of medicines and the high out-of-pocket expenditure (46% of total health expenditure in 2014) [56]. The first attempt to introduce HTA was the establishment of the Ukrainian Agency of HTA in 2013, but it was never implemented nationally [42]. The need for improving the evidence base of healthcare decision-making has been recognized in recent years by the Ministry of Health. In this context, a reform of the regulation of pharmaceutical pricing and reimbursement took place in 2016-2017 including the reimbursement program called “Affordable Medicines” introduced in April 2017. The focal points of the national reforms were the development of the National Essential Medicines List (NEML) and the establishment of the NEML Expert Committee [57]. Along with the NEML development process, the first steps of HTA implementation within the reforms were a series of HTA trainings for the NEML Committee members, proposals for HTA institutionalization and methodological guidelines.

By definition, essential medicines are those that satisfy the priority healthcare needs of a population. According to WHO guidance the development of the NEML must be transparent, conducted within a specific timeframe and should be based on objective and verifiable criteria in order to justify the allocation of public resources [58]. HTA standards introduce objectiveness and

transparency into the development of the NEML process by its clear problem formulation, consideration of different domains (e.g. efficacy, safety, cost-effectiveness, budget impact) and explicit methodology [59]. Consequently, to make evidence informed decisions on the procurement and reimbursement of medicines as well as to establish NEML, HTA could be a useful policy tool in Ukraine. Notably, a recently published summary of a development project related to the Ukraine NEML establishment declared that "Recommendations on further elaboration and updating of the NEML have been implemented, which [are] the basis for HTA implementation into the public health system of Ukraine" [60].

Although there are similarities between national approaches to implement HTA, there are also major differences of HTA practices among European countries [31]. Even among Central and Eastern European countries the development status of HTA is heterogeneous, including the adopted assessment and appraisal methods and the implemented procedures [39]. Given this heterogeneity a tailor-made HTA implementation roadmap is necessary in the early phases of HTA implementation in countries such as Ukraine by taking into account the opinion of different national stakeholders. Such an approach may facilitate consensus about the establishment of organization structures, procedures and legal frameworks and on the other hand it may restrain potential resistance from key domestic actors.

Our study aimed to describe the environment of HTA at the initiation point of reforms in 2016 and to explore the long-term perspectives for HTA in Ukraine. The current and the preferred HTA status in 10-years (i.e. by 2026) were summarized by capturing the opinion of a wide spectrum of Ukrainian stakeholders.

2.1.2 Methods

We conducted a survey among different stakeholders: the NEML Committee members (with different primary affiliations including academia and healthcare providers), Ministry of Health representatives and representatives of pharmaceutical companies and patient organizations. We applied purposive sampling, aiming to include individuals with an in-depth understanding of pharmaceutical pricing and procuring in Ukraine. Respondents were identified by the NEML Committee leadership who had extensive network of Ukrainian individuals with expert knowledge. We used an HTA implementation survey designed to support the formulation of HTA roadmaps [46]. The survey has been applied earlier successfully at national and regional level in other countries [45, 61].

A glossary of the key terms and expressions related to the HTA implementation roadmap was also distributed with the questionnaire electronically to facilitate the common understanding and prevent misuse of the survey. The glossary contained explanations in few sentences and examples or where relevant references to the key terms. The survey was distributed electronically with personal invitations to participate in the study. The survey informed participants in a written form that the individual survey participation will be kept strictly confidential and only aggregated results will be disseminated. Respondents were anonymized after receiving the completed answer sheet. All invited stakeholders filled in the survey. Answers were received between June and July 2016. Opinions of the respondents about the HTA implementation in Ukraine were collected and aggregated in eight dimensions: capacity building, HTA financing, process and organizational structure, scope of HTA, decision criteria, standardization of methodology, use of local data and international collaboration.

Completed surveys were considered valid if not more than three answers were missing or invalid (e.g. providing multiple answers for a single choice question). Results of an invalid survey were excluded from the dataset. During the data processing of valid surveys, the invalid answers of the included surveys were not considered, therefore those had no influence on the results presented in this paper. Individual results were aggregated and the distribution of survey answers were calculated as percentages of the total sample.

As a final step, interpretation of aggregated results were discussed with members of the NEML Committee.

2.1.3 Results

A total of 33 Ukrainian stakeholders filled in the survey and one survey was considered invalid due to the high number of missing answers. From the total sample of 32 included surveys, 21 (66%) of the participants were employed in the public, 9 (28%) in the private sector and 2 (6%) indicated employment in both sectors as multiple affiliations were allowed to report. More specifically, among the respondents there were 10 potential HTA users (decision-maker, policymaker or payer roles), 10 individuals with academic affiliations, 1 public healthcare provider, 9 healthcare industry representatives, 1 consultant and 3 representatives of patient organizations. All survey respondents represented Ukraine. Table 1 contains further background details of the survey participants.

Total number of valid surveys	n = 32
Age groups	
Below 30	0%
30 - 50	78.1%
Over 50	21.9%
Main employment	
Public sector	65.6%
Private sector	28.1%
Both	6.3%
Educational background	
Economics	6.3%
Pharmacy	18.8%
Medicine	37.5%
Other health care (e.g. nursing, dietetics)	0%
Multidisciplinary (at least two master degrees from the above list)	25.0%
Other	12.5%

1. Table: Background details of the survey participants

Aggregated answers are reported in three tables, including Table 2 on capacity building and international collaboration, Table 3 on funding and legislation of HTA and Table 4 on various topics of HTA implementation.

HTA capacity building

Regarding HTA education, 48% of respondents were not aware of any type of HTA-related training, while 42% indicated that there were some project-based trainings in Ukraine. On the other hand, 91% preferred having either a graduate or post-graduate training program (41% and 50%, respectively) established in 10 years.

International collaboration

Although 87% of participants indicated that collaboration on international HTA courses was limited, everyone preferred changing this practice by participating or even developing such courses with other countries or international organisations. Limited capacity of HTA expertise can be partially overcome by participation at joint international work or reuse of HTA outputs from other countries. Most respondents (79%) indicated that Ukraine was not involved in joint international work on HTA or adaptation of HTA documents from other countries. However, in the future 66% of respondents preferred having active involvement in joint international work (e.g. European Network for Health Technology Assessment [EUnetHTA]). However, only half of participants (50%) indicated that joint works could be adapted to the Ukrainian context and 47% preferred adapting works performed by foreign HTA bodies.

Dimensions of HTA implementation survey with answer options	current status in 2016	preferred status in 10 years
HTA capacity building		
Education (*single choice*)		
- No training	48%	0%
- Project based training and short courses	42%	9%
- Permanent graduate program with short courses	10%	41%
- Permanent graduate and postgraduate program with short courses	0%	50%
International collaboration		
International collaboration, joint work on HTA (joint assessment reports) and national/regional adaptation (reuse) *(multiple choice)*		
- No involvement into joint work; and no reuse of joint work or national/regional HTA documents from other countries	79%	3%
- Active involvement in joint work (e.g. EUnetHTA Rapid REA, full Core HTA)	17%	66%
- National/regional adaptation (reuse) of joint HTA documents	3%	50%
- National/regional adaptation (reuse) of national/regional work performed by other HTA bodies in other countries	0%	47%
International HTA courses for continuous education on HTA *(single choice)*		
- Limited interest in (1) developing / implementing of and (2) participating at international HTA courses	87%	0%
- Interest only in regular participation at international HTA courses	7%	0%
- High interest in (1) developing / implementing of and (2) participating at international HTA courses	7%	100%

2. Table: Results on capacity building and international collaboration from HTA implementation survey

HTA funding

Experts reported limited funding for HTA as around half of the respondents indicated lack of funding for the critical appraisal process (55%) and for the research part of HTA (48%). Nevertheless, in the future the majority of participants (81%) would like to ensure sufficient funding from public resources for HTA research activities. For financing the critical appraisal process in HTA, the majority of participants preferred the public funding to private funding (e.g. submission fees by pharmaceutical companies) in the future (83% vs. 17%).

Legislation on HTA

More than half of participants (61%) indicated that HTA had no formal role in the decision-making process, while some indicated that international HTA evidence was considered. All participants preferred relying more HTA evidence based on local data in the future. However, 69% of them preferred that locally developed evidence should have an additional role without mandating it and on the other hand 31% indicated that it should be mandatory in 10 years. Regarding the organizational structure, the most preferred option among respondents (52%) was the

establishment of a public HTA institute with an academic support. Only minority of the respondents (26%) considered that several HTA bodies with central coordination would be the preferred option.

Dimensions of HTA implementation survey with answer options	current status in 2016	preferred status in 10 years
HTA funding		
Financing critical appraisal of technology assessment (*single choice*)		
- No funding for critical appraisal of technology assessment reports or submissions	55%	0%
- Dominantly private funding (e.g. submission fees) by manufacturers for the critical appraisal of technology assessment reports or submissions	42%	17%
- Dominantly public funding for critical appraisal of technology assessment reports or submissions	3%	83%
Financing health technology assessment (i.e. HTA research) (*single choice*)		
- No public funding for technology assessment; private funding is not needed or expected	48%	0%
- No or marginal public funding for research in HTA; private funding is expected	52%	3%
- Sufficient public funding for research in HTA; private funding is also expected	0%	81%
- HTA research is dominantly funded from public resources	0%	16%
Legislation on HTA		
Legislation on the role of HTA process and recommendations in decision making process (*single choice*)		
- No formal role of HTA in decision making	61%	0%
- Dominantly international HTA evidence is taken into account in decision making	32%	0%
- International and additionally local HTA evidence is taken into account in decision making	6%	69%
- Local HTA evidence is mandatory in decision making	0%	31%
Legislation on organizational structure for HTA appraisal (*single choice*)		
- There is no public committee or institute for the appraisal process	70%	0%
- Committee is appointed for the appraisal process	13%	0%
- Committee is appointed for the appraisal process with support of academic centers and independent expert groups	13%	16%
- A public HTA institute or agency is established to conduct formal appraisal of HTA reports or submissions	3%	6%
- Public HTA institute or agency is established to conduct formal appraisal of HTA reports or submissions with support of academic centers and independent expert groups	0%	52%
- Several public HTA bodies are established without central coordination of their activities	0%	0%
- Several public HTA bodies are established with central coordination of their activities	0%	26%

3. Table: Results on funding and legislation from HTA implementation survey

Scope of HTA implementation

Although most respondents reported that HTA was not applied for any type of health technologies in 2016, all of them preferred using it for pharmaceuticals in the future. The majority of respondents also preferred expanding the scope of HTA beyond pharmaceuticals for evaluating medical devices (74%) and prevention programs (81%). Some respondents (55%) indicated that HTA should be used even for evaluating surgical interventions. The majority of the participants (84%) would introduce HTA for all new health technologies applying for public reimbursement together with an additional revision process of the former assessments. Only the minority (9%) of experts considered that only those new technologies should be evaluated in the future, which indicate high budget impact.

Decision criteria

Almost all of the respondents (97%) preferred applying the cost-effectiveness and the healthcare priority criteria for decision-making of public reimbursement. Budget impact (80%) and therapeutic value (77%) were rated as the third and fourth most important criteria in future decisions, while unmet medical need received the lowest score (30%). None of participants preferred introducing implicit thresholds for these criteria in the future. The majority of experts (87%) preferred applying soft explicit thresholds, which would allow some deviation in exceptional cases (e.g. acceptance of higher incremental cost-effectiveness ratio for orphan medicines). Few experts (10%) preferred using hard explicit thresholds without exceptional cases. 72% of the respondents indicated that multi-criteria decision analysis (MCDA) would be a preferred method in the future HTA framework.

Quality and transparency of HTA implementation

In 2016, there were lack of quality assurance elements implemented to support the use of HTA for decision-making in Ukraine. In the future, 87% of respondents preferred having a publicly available critical appraisal checklist for standardizing the evaluation process of HTA submissions. 61% preferred having published methodological guidelines for the preparation of HTA documents and 58% would introduce the practice of regular follow-up research on previous HTA recommendations. Almost all respondents (88%) preferred having full transparency by making the HTA agency's recommendations and the related appraisal reports available in the public domain, while the remaining participants preferred publishing only the HTA recommendations. Nearly all participants (97%) preferred introducing transparent and continuous timelines for the appraisal of the HTA submissions and for publishing the following recommendations.

Use of local data

The great majority of respondents (93%) indicated that in 2016 using local data as the inputs for the assessment of health technologies was not mandatory in Ukraine. On the other hand, 94% preferred using local data to develop HTA evidence, or in case it was not available, they would mandate the transferability assessment of international HTA evidence whether it could be used for local decisions. Respondents reported that there were a lack of local / national registries for data collection and the accessibility of payers' database was limited. Overwhelmingly, they (90%) preferred changing this practice and investing into up to date registries and practices to make payers' databases available for preparing evidence based on local data for HTA submissions.

Dimensions of HTA implementation survey with answer options	**current status in 2016**	**preferred status in 10 years**
Scope of HTA implementation		
Scope of technologies (*multiple choice*)		
- HTA is not applied to any health technologies	77%	0%
- Pharmaceutical products	23%	100%
- Medical devices	0%	74%
- Prevention programs and technologies	0%	81%
- Surgical interventions	0%	55%
- Other	0%	0%
Depth of HTA use in pricing and/or reimbursement decision of health technologies (*single choice*)		
- HTA is not applied to any health technologies	83%	0%
- Only new technologies with significant budget impact	10%	9%
- Only new technologies	7%	6%
- New technologies + revision of previous pricing and reimbursement decisions	0%	84%
Decision criteria		
Decision categories (*multiple choice*)		
- None of the below categories are applied	37%	0%
- Unmet medical need	22%	30%
- Health care priority	33%	97%
- Assessment of therapeutic value	26%	77%
- Cost-effectiveness	19%	97%
- Budget impact	22%	80%
- Other	4%	7%
Decision thresholds (*single choice*)		
- Thresholds are not applied	84%	3%
- Implicit thresholds are preferred	16%	0%
- Explicit soft thresholds are applied in decisions	0%	87%
- Explicit hard thresholds are applied in decisions	0%	10%
Multi criteria decision analysis (*single choice*)		
- Explicit multi criteria decision framework is applied	25%	72%

Quality and transparency of HTA implementation		
Quality elements of HTA implementation (*multiple choice*)		
- None of the below quality elements are applied	87%	0%
- Published methodological guidelines for HTA/economic evaluation	6%	61%
- Regular follow-up research on HTA recommendations	0%	58%
- Checklist to conduct formal appraisal of HTA reports or submissions exists but **not available** for public	6%	6%
- Published checklist is applied to conduct formal appraisal of HTA reports or submissions	0%	87%
Transparency of HTA in policy decisions (*single choice*)		
- Technology assessment reports, critical appraisal and HTA recommendation are **not published**	93%	0%
- HTA recommendation is published without details of technology assessment reports and critical appraisal	7%	12%
- Transparent technology assessment reports, critical appraisals and HTA recommendations	0%	88%
Timeliness (*single choice*)		
- HTA submission and issuing recommendation have no transparent timelines	87%	0%
- HTA submissions are accepted/conducted following a transparent calendar, but issuing recommendation has no transparent timelines	0%	3%
- HTA submissions are accepted continuously and issuing recommendation has transparent timelines	13%	97%
Use of local data		
Requirement of using local data in technology assessment (*single choice*)		
- No mandate to use local data	93%	3%
- Mandate of using local data in certain categories **without** need for assessing the transferability of international evidence	0%	3%
- Mandate of using local data in certain categories **with** need for assessing the transferability of international evidence	7%	94%
Access and availability of local data (*single choice*)		
- Limited availability or accessibility to local real world data	97%	0%
- Up-to-date patient registries are available in certain disease areas, but payers' databases are not accessible for HTA doers	3%	10%
- Payers' databases are accessible for HTA doers, patient registries are not available or accessible in the majority of disease areas	0%	0%
- Up-to-date patient registries are available in certain disease areas and payers' databases are accessible for HTA doers	0%	90%

4. Table: Results on implementation and use of local data from HTA implementation survey

Comparing the opinion of public vs. private sector respondents

Survey answers were analysed separately for those who indicated employment in the private or in the public sector. The opinion of these two groups of stakeholders related to the capacity building, HTA funding, scope of HTA, local data and international collaboration was similar (i.e. they preferred similar options for all the questions in these dimensions). They also had same preferences regarding

transparency (i.e. publishing HTA recommendations with appraisal reports) and timeliness (i.e. transparent and continuous timelines for the appraisal and issuing recommendations).

Respondents' opinion differed more substantially in five areas. More public sector respondents preferred introducing follow-up evaluations of former HTA recommendations (65% public vs. 40% private). Their opinion also differed related to the decision criteria that should be applied. Although for both groups the cost-effectiveness and the healthcare priority were the most important criteria, budget impact ranked higher for public stakeholders (86%) compared to private stakeholders (60%). Difference was also observed in the decision threshold question. Although for both groups soft explicit thresholds were the most preferred option (95% for public vs. 64% private), some private sector stakeholders preferred having explicit hard threshold (27%) or oppositely no thresholds (9%). Their opinion also differed regarding HTA legislation. Less private sector respondents preferred mandating the use of local data for HTA evaluation (39% public vs. 18% private) and consequently more private sector respondents preferred only an additional (i.e. not primary) role for the local data used for HTA evidence (61% public vs. 82% private). Regarding the organizational structure, more private sector stakeholders preferred introducing a public HTA institute with academic experts (41% public vs. 73% private). Some public sector respondents preferred several HTA bodies with central coordination, while this option was less preferred by private sector respondents (32% public vs. 9% private).

2.1.4 Discussion

Recommendations for facilitating HTA implementation

Our manuscript describes initial results of an ongoing policy initiative, which has to be followed by additional steps to clarify further details. However, our findings could already identify several key points which could facilitate implementation of HTA in Ukraine.

First, the availability of trained human resources is crucial to implement HTA. Our survey indicates that graduate and post-graduate education should be established. Experts from such programs may contribute to different stages of the HTA process: preparing submissions in line with official requirements, delivering high quality appraisals of submissions and conducting HTA-related policy research activities (e.g. continuous improvement of HTA methodologies or timely revision of former submissions). Trained experts enable meaningful participation in international collaborations and adoption of international research in the national context. There are several options for increasing the number of HTA professionals, including graduate and post-graduate education and training programs.

Second, stakeholders conceded that sufficient public resources should be available in the development and operation of HTA in Ukraine. Therefore, political commitment to allocate public funding for continuing and expanding already initiated activities is paramount.

Third, survey results indicated that in certain categories (e.g. cost) the locally collected data in HTA submissions should receive higher priority and decisions should not depend solely on evidence generated in other countries. Further, public resource allocation decisions of new health technologies should be based on local priority ranking of disease areas and cost-effectiveness of the intervention, as these were the most important criteria by survey respondents.

Fourth, the set-up of the HTA process should be designed in collaboration with academic professionals. National stakeholders had a clear preference for a transparent HTA system. Investment and academic input are needed to develop quality assurance elements in order to increase the objectivity and transparency of HTA recommendations.

Fifth, to maximise the potential for HTA in Ukraine, a multi-stakeholder approach in designing and periodically revising the HTA system is necessary. Our findings and recommendations were formulated according to the opinions of national healthcare policymakers, members of the NEML Committee, pharmaceutical industry representatives and even patient organization representatives. While for most dimensions of HTA implementation there were no differences in the preferred long-term objectives, in some questions (e.g. legislation of HTA, decision criteria and introducing revision process of former decisions) further research and discussion is needed between public and private sector stakeholders to find the common ground.

Recent developments in Ukraine

Recently, some improvements have been implemented regarding the quality and transparency of HTA process in Ukraine, which are in line with the proposed recommendations and the envisioned 10-year perspectives in the current HTA roadmap. After the Ukraine NEML was established [62], HTA was included to the Fundamentals of Ukrainian Health Law, which was approved by the Ukraine Parliament in 2017 [63]. Following these legal steps of HTA institutionalisation, the NEML Committee developed a draft guideline for outlining the requirements of HTA submissions, which was made publicly available to receive feedback [64]. The NEML also moved towards transparency by making the HTA applications by pharmaceutical companies and the corresponding recommendations by the Committee available on its website [65]. Furthermore, EML Committee members have initiated research on quantifying the cost-effectiveness threshold for Ukraine and considering its applicability for healthcare decisions [66]. International collaborations have been

also established by experts in the NEML Committee who are active participants of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) organization. The Committee also joined to the EUnetHTA as associate partner.

Opportunities for learning from other countries

Ukraine can certainly learn a lot from countries with similar healthcare system, economic status or cultural and social values (e.g. Central and Eastern European countries) and take advantage of some good practices. To increase the number of experts in the country the example of Hungary could be followed where the spectrum of available HTA education ranges from 1-week short courses to accredited post-graduate programs [59]. Regarding the participation in international networks to increase awareness of HTA, positive experiences of Croatia or Slovakia could be mentioned [67, 68]. The transparency of the Polish HTA system shows that with appropriate legislation and corresponding online platform, the full HTA submissions, corresponding critical evaluations and recommendations can be published. Notably, in certain aspects the Polish system was shown to be more transparent than the NICE in England, such as providing summaries of expert opinions on the HTA submissions [44].

On the other hand, the potential challenges and suboptimal policies can also be identified based on the examples of other countries so Ukraine can learn from the shortfalls in the practices followed. The examples of Bulgaria and Poland show that there is an important need to harmonize the organizational responsibilities related to HTA and the corresponding legislation of the pricing and reimbursement of health technologies. In Bulgaria there was a controversy concerning which public institute should deal with HTA methodology and implement HTA procedures and how HTA recommendations should be taken into account in pricing and reimbursement decisions [69]. Reportedly, in Poland it is still required to achieve better consistency between HTA recommendations and national reimbursement decisions [70]. In Romania only international cost-effectiveness evidence is taken into account in reimbursement decisions without considering transferability, which makes results of national cost-effectiveness studies irrelevant [71]. Finally, in Hungary, the lack of transparency and the low level of stakeholder engagement limit the potential of HTA to support evidence-based decision-making and marginalise the influence of the national HTA agency on pricing and reimbursement decisions [50].

Limitations

The most important limitation of our study is the relatively low sample size of survey respondents. Unfortunately, room for recruitment of more participants was fairly limited due to the low number

of experts with good understanding of HTA principles in Ukraine. This limitation has an even more important implication on the findings of the subgroup analysis by different employment status (public vs. private), where sample sizes were even lower.

2.1.5 Conclusion

To reflect specific national and regional characteristics, it would be important for Ukraine that HTA methodology development and implementation are based on a clear roadmap. Frequent changes in strategic directions of healthcare governance makes the consistent implementation of longer-term investments, such as HTA capacity building or institutional setup challenging. This study attempted to define these long-term objectives based on the opinion of Ukrainian professionals with in-depth knowledge of HTA practices and thorough understanding of the national health policy objectives, clinical practices, unmet medical needs and economic constraints. This process might be supported by the guidance and experience of international experts and by understanding the good practices and pitfalls from other countries. There were important improvements recently but further steps outlined by our roadmap are required to complete. Learning from the mistakes or the good practices form other countries, however, may make the long and bumpy road of HTA implementation for Ukraine smoother and more impactful.

2.2 Shedding light on the HTA consultancy market: Insights from Poland

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Summary of the Polish case study

Research on health technology assessment (HTA) from a policy perspective typically examines public HTA bodies, with little attention devoted to how manufacturers develop their evidence submissions.

Taking Poland as a crucial case, we explored the market of HTA consultancy firms which assist drug manufacturers in developing these submissions, called HTA reports. We reviewed 318 HTA reports from 2012 to 2015, data from the Polish National Company Registry, the content of HTA consulting firms' websites, and appraisal reports developed by the Polish HTA body.

We identified HTA consultancy firms which developed 96–98% HTA reports. We found that the transparency of information about the authors of HTA reports provided by the HTA body had improved between 2012 and 2015. Six companies with market shares from 10 to 30% dominated the market. The market size was estimated to be 5–6 million EUR annually. HTA consultancies had a broad service portfolio related to preparation of HTA reports. Over 90% of HTA reports did not meet the official minimum quality requirements, and only half of the resubmissions took into account remarks made by the HTA body.

Our study provides insights into the structure, evolution and role of the for-profit HTA consultancy market as a crucial part of the public HTA system. This raises important policy points about transparency and regulation at the intersection of public and private sectors in HTA.

2.2.1 Introduction

Policy studies of health technology assessment (HTA) have examined in detail public HTA bodies that evaluate evidence submissions supporting technologies applying for reimbursement [14, 30, 31, 34, 53]. However, little attention has been given to how manufacturers prepare these submissions. Recent research suggests that this often involves assistance provided by private sector consultancy firms specialising in data collection, evidence synthesis and report preparation [50, 72, 73]. Limited knowledge about the operation and characteristics of these firms is a major gap in research, given their role in the development of evidence underpinning subsequent HTA recommendations, often with major budgetary and public health implications. This paper contributes to addressing this gap by focusing on HTA consultancies in Poland, a country with a well-established HTA system.

Consulting in HTA is part of a broader phenomenon of drug companies outsourcing services to specialist consultancies. A key example of this is subcontracting the conduct of clinical trials to Clinical Research Organizations (CROs) [74], typically explained by the increase in the magnitude of clinical research and the drive towards a more efficient and flexible organization of research and development [75, 76]. Similar reasons, namely limited "head-count" within pharmaceutical companies, coupled with the rise in regulatory requirements necessary for obtaining public funding, are likely to drive outsourcing to HTA consultancies.

HTA consultancy firms are private companies that generate or synthesize evidence and input for funding decisions. They employ experts in health economics, medicine, statistics and pharmacology, who can be described as "HTA professionals". Like other experts involved in regulatory science [77], they have their professional conventions, experience and a shared body of knowledge and methods, developed in national and international networks, such as the International Society for Pharmacoeconomics and Outcomes Research and its local chapters, and specialized training programs, including MSc programs in health economics [24, 78, 79]. Given their highly specialized, knowledge based, service oriented and data driven approach, a strong HTA consulting market may function as an incubator of expertise, particularly important given the many recommendations to build capacity in order to strengthen HTA systems [80, 81]. On the other hand, especially in countries with low public sector resources, the revolving door between consultancies and public HTA bodies has led to conflicts of interest, and often dramatic loss of expertise in the public sector [50, 82-84].

To contribute towards assessing the risks and benefits associated with HTA consultancy markets, we provide a first exploratory overview of the HTA consultancy market in Poland. We focus on the following objectives. First, to identify HTA consulting firms that collectively make up the HTA

consultancy market in Poland. Second, to describe the HTA market structure and estimate its size. Third, to examine the evolution of the HTA consultancy market and the key activities of its players. Finally, to analyse the quality of HTA reports given to HTA consultancy firms by the Polish Agency for Health Technology Assessment (AHTAPol).

We select Poland as a crucial case because, first, HTA consultancy firms have developed in parallel to the institutionalization of public HTA in Poland. Notably, the first commercial HTA consultancy firms were established around 2002 in Kraków by former employees of the first public organization working on HTA [43]. Since then, experts representing those firms have contributed to the development of the official HTA guidelines issued by the AHTAPol [85-87]. Second, since its establishment in 2005 [70], the AHTAPol has consistently pursued an HTA model similar to the Single Technology Appraisal (STA) process developed by the Scottish Medicine Consortium and adopted by the English National Institute for Health and Care Excellence in 2005 [88, 89]. Within the STA process, the core pharmacoeconomic evidence is generated by manufacturers. These evidence submissions, which we simply call "HTA reports", are then evaluated by internal or external experts, whose appraisal (called "verification analysis" in Poland) forms the basis of subsequent discussions held by the members of an appraisal committee. Consistent reliance on this model of HTA in Poland has created conditions for the emergence of consultancy firms assisting manufacturers in preparing country-specific HTA reports based on the AHTAPol's guidelines. Third, as HTA and the reimbursement processes are interconnected and some staff in HTA consultancy firms have worked for public institutions involved in drug reimbursement, HTA consultancies are uniquely positioned to advise manufacturers on the broader regulatory environment [82, 83], which has evolved significantly since the early 2000s [90, 91]. Fourth, as Poland is an important European pharmaceutical market there are a steady number of drugs applying for HTA appraisals annually ranging from approximately 80 to 100 [90, 91]. This, too, is a good proxy for a strong demand for services provided by HTA consultancy firms. Finally, unlike in some other countries, the analysis of the HTA consultancy market in Poland has been enabled by the public availability of documents generated at various stages of the HTA process [92-96].

2.2.2 Materials and methods

We adopted a mixed methods study design, summarized in Table 5.

Topics and objectives	Data sources	Methods
Transparency of information provided by the AHTAPol To identify HTA consultancy firms	HTA reports submitted to the AHTAPol in 2012-2015 *i.e.: each comprising different types of analysis: clinical assessments, economic analyses, budget impact analyses, rationalization analyses*	Extracting the authors of analyses*
Market structure To calculate market share per consultancy firm	HTA reports submitted to the AHTAPol in 2012-2015	Calculating the number of analyses prepared by each HTA consultancy firm
Market size To estimate the total size of the HTA consultancy market	Polish National Company Registry	Calculating annual net revenues from sales for each HTA consultancy firm**
Qualitative exploration of the consultancy market To describe evolution and the key activities of HTA consultancy firms *i.e.: year of establishment, location, mission statement, number of employees, services provided and partner or collaborator organizations*	Websites of HTA consultancy firms	Quantitative content analyses of data extracted from the websites
Quality of HTA reports To evaluate feedback on quality of HTA reports given to HTA consultancy firms by the AHTAPol *i.e.: the extent to which HTA reports meet the minimum quality requirements set by the Ministry of Health*	Appraisal reports ("verification analysis") of submitted HTA reports published by the AHTAPol	Data extraction to a structured spreadsheet

5. Table: Summary of study topics, objectives and corresponding data sources and methods

*Detailed description in Supplementary material 1
**Detailed description in Supplementary material 2

The extent to which we were able to identify HTA consultancy firms was affected by the transparency of information regarding the authors of the HTA reports, as provided by the AHTAPol. To identify the HTA consultancy firms we extracted data from HTA reports submitted by drug manufacturers and published on the AHTAPol website [97]. We considered HTA reports submitted to the AHTAPol between 2012 and 2015. We selected 2012 as the start date because in this year the AHTAPol started publishing HTA reports under the provisions of the Reimbursement Act in 2011. The AHTAPol has a duty, introduced by the Reimbursement Act, to make HTA reports and corresponding verification analysis publicly available online [44]. We end our analysis in 2015, as this was the last year for which a full set of HTA reports and verification analyses was available at

the time of data collection. From January to March 2018, we downloaded and reviewed all analyses available as part of each HTA report, namely decision problem analysis, clinical assessment, economic analysis, budget impact analysis, and rationalization analysis (these are proposals for addressing additional expenditure resulting from the reimbursement of the health technology; they outline where savings could be achieved in the pharmaceutical spending to ensure sufficient resources for the new drug). Given frequent redactions in the available analyses (e.g. author names or organizational details removed), we had to rely, where necessary, on logos, document design or website links to identify authors of analyses. Supplementary material 1 describes the complete process of identifying HTA consultancy firms.

To analyze the HTA market structure we calculated the market share of each identified company based on the HTA reports. We calculated the number of HTA reports prepared by HTA consultancy firms on a yearly basis. As one type of analysis in the HTA reports, decision problem analysis, was sometimes a subsection of the clinical assessment analysis or, at other times, a standalone document, we excluded decision problem analyses from the analysis.

We estimated the size of the Polish HTA market using the number of HTA reports prepared by each HTA consultancy firm and their annual net revenues from sales obtained from the Polish National Company Registry [98]. As the data included in the Registry was limited and insufficiently detailed, our calculations are based on certain assumptions, which are detailed in Supplementary material 2, including our approach to market size estimation.

To describe evolution and the key activities of HTA consultancy firms we analyzed data downloaded in June and July 2018 from the websites of HTA consultancy firms we had identified. We extracted the year of establishment, location, mission statement, number of employees, services provided and partner or collaborator organizations from the English language version of the websites [99-104]. Due to the heterogeneity of information available on services and mission statements, information was coded inductively, and then at a later stage codes were merged and code families and networks were established, to best reflect the main themes emerging from the data.

Finally, we investigated the quality of the HTA reports, understood as compliance with the submission requirements specified by the Ministry of Health (MoH) [105]. Specifically, we examined verification analyses (VAs), which are documents in which the AHTAPol appraises HTA reports [44]. We considered VAs issued in 2012-2015 in which all four types of analyses included in this study (that is, clinical assessment, economic analysis, budget impact analysis, and rationalization analysis) were prepared by the same consultancy firm. We downloaded and analyzed the VAs in June 2018 and extracted data from sections in which the AHTAPol judged whether HTA reports had met the

regulation on minimum requirements set out by the MoH [105]. For each company we calculated the percentage of HTA reports that met the MoH requirements among the total HTA reports. We also collected data from VAs on whether 1) at least one specific reason for not meeting the minimum requirements was provided by the AHTAPol; 2) the MoH requested the applicant to supplement the reimbursement application, including the HTA reports; 3) revised HTA reports were provided by the applicant; and 4) the revised HTA reports took into account the remarks for not meeting the minimum requirements.

We analyzed all data descriptively in Excel.

2.2.3 Results

In total, we analyzed 336 manufacturer submissions, with 63, 80, 106 and 87 coming from 2012, 2013, 2014 and 2015, respectively. We excluded 12 submissions as they were either not available online or were duplicated in the database. Duplication occurred when a manufacturer submitted exactly the same HTA report for different forms of administration of the same drug. We excluded six further applications because the analyses comprising the HTA reports were prepared jointly by more than one consultancy. Following on from this, 318 manufacturer submissions were analyzed (inclusion rate: 94.6%).

Transparency: Identification of HTA consultancy firms

The analyzed HTA reports contained 315 clinical assessments (CA), 314 economic analyses (EA), 313 budget impact analyses (BIA), and 242 rationalization analyses (RA). The company name was visible in 76%, 76%, 75% and 79% of the cases for CA, EA, BIA and RA, respectively. We were able to identify the HTA consultancy firms based on logos, document design or website links in additional 21%, 22%, 21% and 20% of the cases for CA, EA, BIA and RA, respectively. As a result, authors' names were identified in 97%, 98%, 96% and 99% of the cases for CA, EA, BIA and RA, respectively. Transparency of the AHTAPol's reporting in relation to consultancy firms increased steadily between 2012 and 2015, as the company name was visible in only around 40% of the cases in 2012, and around 95% of the cases in 2015 (Table 6). There were 227 HTA reports where the same HTA consultancy firm was identified for all four types of analyses.

Different types of analyses part of the HTA report	Number of analyses	Author identified	Company name visible
2012			
Clinical assessment	57	52 (91%)	25 (44%)
Economic analysis	57	53 (93%)	26 (46%)
Budget impact analysis	56	50 (89%)	24 (43%)
Rationalization analysis	40	35 (88%)	16 (40%)
2013			
Clinical assessment	75	75 (100%)	51 (68%)
Economic analysis	75	75 (100%)	51 (68%)
Budget impact analysis	74	73 (99%)	49 (66%)
Rationalization analysis	58	56 (97%)	41 (71%)
2014			
Clinical assessment	98	96 (98%)	83 (85%)
Economic analysis	97	95 (98%)	81 (84%)
Budget impact analysis	98	95 (97%)	81 (83%)
Rationalization analysis	74	74 (100%)	66 (89%)
2015			
Clinical assessment	85	84 (99%)	81 (95%)
Economic analysis	85	84 (99%)	81 (95%)
Budget impact analysis	85	84 (99%)	81 (95%)
Rationalization analysis	70	69 (99%)	67 (96%)

6. Table: Number analyses reviewed for each year, percentage of the cases when the author name was recorded and percentage of the cases when company name was visible

Market structure: Calculation of market shares

For those CA, EA and BIA analyses with identifiable authors, all analyses had been prepared by an HTA consultancy firm, while in case of RA there were 2 cases where we identified a drug manufacturer and no HTA consultancy firm.

More than 90% of HTA report analyses were prepared by 6 HTA consultancy firms: HealthQuest, MAHTA, Instytut Arcana, HTA Consulting, Aestimo and Centrum HTA. (Table 7). During this period, HealthQuest had the largest market share with more than 25% for all four types of analyses. Two additional consultancy firms were identified, too, namely Pracownia HTA, NUEVO HTA. However, these companies prepared the analyses included in only 10 HTA reports over the four-year period.

Total study period (2012-2015)								
	Health Quest	MAHTA	Instytut Arcana	HTA Consulting	Aestimo	Centrum HTA	Other firms	Not identified
Clinical assessment	27.9%	16.2%	14.9%	14.6%	10.5%	9.5%	3.8%	2.5%
Economic analysis	28.3%	16.2%	14.6%	14.3%	10.8%	9.6%	3.8%	2.2%
Budget impact analysis	27.5%	16.3%	14.4%	14.4%	10.5%	9.6%	3.8%	3.5%
Rationalization analysis	28.9%	18.2%	12.4%	15.3%	9.9%	8.3%	3.7%	3.3%

7. Table: Market share of HTA consultancy firms according to the four types of analyses in the HTA reports

The market shares of the six major companies were relatively stable over the years. The largest changes were observed in 2014, when the market share of HealthQuest increased over 30% and the market share of Centrum HTA decreased below 5% (Supplementary material 3). While HealthQuest maintained its market leader position in each year, the company with the lowest market share varied. Nevertheless, each major HTA consultancy firm developed at least four HTA reports annually.

Market size: Estimation of the HTA consultancy market

Based on the Polish National Company Registry data, we estimated the average annual market size at approximately €5.5 million (details of the assumptions behind the analysis are included in Supplementary material 2). Based on the annual revenues and the annual number of HTA reports we considered that the average revenue per HTA report was €70 000. Since our market estimation reflects the number of HTA reports per year, the largest market size was observed in 2014 with more than €6.5 million, and the lowest was observed in 2012 with €4 million. In a scenario analysis assuming lower revenues per HTA report (€60 000), we estimated approximately €4.5 million average annual market size, with the highest in 2014 around €5 million and lowest in 2012 around €3.5 million. In a scenario analysis assuming higher revenues per HTA report (€85 000) we estimated approximately €6.5 million average annual market size, with the highest in 2014 around €8 million and lowest in 2012 around €5 million.

Evolution and the key activities of HTA consultancy firms

There were two waves of establishing HTA consultancy firms in Poland, with the first two companies established in 2002 (HTA Consulting and Instytut Arcana), while the remaining four major companies were established between 2008 and 2011. The two companies with minor market shares, Pracownia HTA and NUEVO HTA, were also established around the second wave, in 2010 and in 2012, respectively. There were two companies established in Warsaw (HealthQuest, MAHTA), which were also the market leaders during the study period. All remaining companies, including the two smaller

ones, were based in Kraków. This also indicates that the market shares by the two largest cities were almost even (a little higher in Kraków). Numbers of employees were available only for four companies from their websites. The two oldest companies, HTA Consulting and Instytut Arcana had the largest number of employees with more than 50 and more than 40, respectively, according to their websites. HTA consultancy firms established in the second wave had lower number of employees with reportedly more than 20 for MAHTA and 12 for Aestimo. We found no information on the number of employees in the remaining companies, including the market leader (HealthQuest).

Companies' mission statements were centered around supporting decision-making on medical technologies. Only one company (HealthQuest) did not state clearly in the mission statement that developing HTA reports was their core activity; instead, it implied as much by saying: "to support decision making in healthcare [based] on credible data and proper methods". Evidence-based medicine is another key concept used by HTA consultancy firms, which appeared in the mission statement of several companies. Yet another key concept is credibility, since 4 out of the 6 major companies mentioned it in their mission statement. Many mission statements emphasized the length of experience, especially in case of the more established consultancies, and the large number of HTA reports they had created.

The service portfolio of HTA consultancy firms was very wide. The core service offered by all companies was preparing HTA reports including all types of analyses required by the MoH and the AHTAPol. Three or more companies provided the following additional specialized services: strategic consulting, preparing qualitative studies (surveys, interviews), qualitative database analysis, consulting on negotiation strategies with payer representatives, real world data analyses and training courses. One or two HTA consultancy firms provided the following services: participating in advisory boards, performing systematic literature reviews, conducting network meta-analyses, performing feasibility studies or rapid reviews and conducting epidemiological or pharmacovigilance studies.

Two companies (Instytut Arcana, HTA Consulting) emphasized providing services outside Poland – in the Central and Eastern European region. Further, three companies mentioned partner organizations. Specifically, HTA Consulting established an alliance in collaboration with a Hungarian consultancy firm; Instytut Arcana was found to be part of a global organization in population health intelligence; and HealthQuest started a strategic cooperation with a company focusing on medical data management, statistics and programming. Collaborations with universities were not mentioned, although it was apparent that some companies key personnel had university affiliations

as well (e.g. Warsaw School of Economics, Medical University of Warsaw and Jagiellonian University in Kraków).

Quality of HTA reports evaluated by the AHTAPol

According to the reviewed VAs issued by AHTAPol, out of the 227 HTA reports in which all four reviewed analyses were prepared by the same company, only 15 (6.6%) satisfied the minimum quality requirements set out by the MoH. According to the AHTAPol, 207 (91.2%) HTA reports did not meet the requirements, and the remaining five cases (2.2%) were unclear. The AHTAPol explained why the requirements were not met only in 70 (33.8%) cases, did not provide any reasons in 136 cases (65.7%), and in one case a reason was redacted. Within reports that did not meet the requirements, the MoH requested the applicant to revise the HTA report in 162 (78.3%) cases, and in the remaining 45 (21.7%) cases this was not clear from the VAs. Within the 207 reports that did not meet the requirements the applicant provided revised analyses in 157 (75.8%) cases. In 47 (22.7%) cases this was unclear, and in 3 (1.5%) cases revised analyses were not provided. Finally, we analyzed those sections of the VAs which reported whether the revised analyses took into account all AHTAPol's remarks. From those 157 revised analyses when the applicant provided revised analyses, 71 (45.2%) took into account the remarks, 62 (39.5%) did not and in 24 (15.3%) cases it was not clear.

There were small differences between the consultancy firms in the share of HTA reports not meeting the MoH requirements as reported by the VAs (Table 8). The highest percentage was observed for Centrum HTA (95%) and the lowest for HTA Consulting (88.9%) However, a relatively larger difference was observed in terms of the reasons for not meeting the requirements. In this regard, reports by MAHTA and Instytut Arcana received reasons by the AHTAPol for not meeting the minimum requirements in 39.5% and 39.3% of the cases, respectively. However, for instance reports by HTA Consulting received reasons for not meeting the requirements only in 21.9% of the cases. The percentage of HTA reports in which the MoH requested supplementing the reimbursement application ranged from 82.3% (HealthQuest) to 72.7% (Aestimo). The share of HTA reports for which revised analysis was submitted ranged from 79% (HealthQuest) to 68.2% (Aestimo). We observed a relatively large difference in the percentage of the reports in which the revised analyses took into account the AHTAPol's recommendations for revising the analyses. Here, the rate of reports building on AHTAPol's advice was the highest for Aestimo and HTA Consulting (60% and 56.5%, respectively); this rate was the lowest for MAHTA and Centrum HTA (33.3% and 30.8%, respectively).

	Health Quest	MAHTA	HTA Consulting	Instytut Arcana	Aestimo	Centrum HTA	Other
Number of HTA reports where all four types of analyses were submitted by the same consultancy firm	68	42	36	30	24	20	7
% of HTA reports not meeting the MoH requirements	91.2%	90.5%	88.9%	93.3%	91.7%	95.0%	85.7%
% of HTA reports where reason was provided for not meeting MoH requirements	33.9%	39.5%	21.9%	39.3%	27.3%	36.8%	50.0%
% of HTA reports where the MoH requested to supplement the application	82.3%	76.3%	78.1%	82.1%	72.7%	73.7%	66.7%
% of HTA reports where revised analyses were provided by the applicant	79.0%	78.9%	71.9%	78.6%	68.2%	68.4%	83.3%
% of resubmitted HTA reports where the revised analyses took into account AHTAPol's remarks	46.9%	33.3%	56.5%	45.5%	60.0%	30.8%	40.0%

8. Table: Analysis of verification analyses per HTA consultancy firm

2.2.4 Discussion

In this paper, we identified key players of the Polish HTA consultancy market for pharmaceuticals, described its size, structure and evolution, and analysed the AHTAPol's comments on the quality of HTA reports prepared by HTA consultancy firms. Our research contributes to the literature on stakeholder involvement in HTA [106-108] by demonstrating that the scope of stakeholders in HTA to consider is broader and may include private-sector companies. Further, in contrast to studies focusing on later stages of the HTA process, especially the discussions held by appraisal committees, here we point to the less visible stage of technology assessment [44, 90-92], which has so far largely escaped research attention.

Researching HTA consultants reflects broader transparency challenges facing HTA systems. Unlike many public HTA bodies, expert consulting has no specific regulations pertaining to, for example, putting information on its activities in the public domain. The availability of information on consultants, then, largely depends on the openness of the public bodies with which they interact. In the field of HTA, any systematic examination of the market for HTA services requires, at the very least, publicly available HTA reports, which include the names of their authors. In this regard, countries like Poland, which adopted HTA later, can, perhaps surprisingly, could be more transparent than early adopters [44]. In this regard, consistent with recent research on the

transparency of the AHTAPol's work [92], we found that the transparency of information about the authors of HTA reports provided by the AHTAPol had improved steadily between 2012 and 2015. The evaluation of the quality of analyses developed by consultants requires even more detailed information about the outcomes of appraisal processes undertaken by HTA bodies. For instance, a recent study into HTA in Hungary was unable to use documentary analysis, unlike the present paper, because relevant data was not publicly available [50].

We found that the HTA market for pharmaceuticals in Poland was dominated by six companies, with new market entrants unable to gain larger shares. This suggests that the dominant HTA consultancy firms have accumulated significant expertise and created strong working relationships with their clients. These findings are consistent with earlier research showing the sustained influence on the Polish HTA system of the first cohort of experts who received formal training in HTA [43, 84]. A similar market structure including 3-4 major HTA consultancy firms was also found in Hungary, a country with a comparable HTA model and history [50]. Future empirical research could test whether this model holds in Western European countries.

The size of the Polish HTA consultancy market for pharmaceuticals, estimated at €5-6 million annually, reflects Poland's role as an important market in the region. Correspondingly, the market was almost two times larger than the same market in Hungary estimated at around €3-3.5 million annually using a similar method of calculation [50]. Notably, the size of Poland's HTA market for pharmaceuticals considerably exceeds the AHTAPol's annual budget of €2.5 million [109]. Similarly, with at the least 120 employees, HTA consultancy firms together dispose of significant manpower compared to the AHTAPol, which has 65 full-time equivalent employees [109]. The contrast between resources available to the public and commercial HTA sector is a function of the Single Technology Appraisal model of the HTA process, which confines the role of public HTA bodies to evaluating evidence submitted by manufacturers. In the Polish context, this model of HTA was introduced and solidified, via subsequent versions of AHTAPol's HTA guidelines, largely based on contributions from experts from the major HTA consultancies [85-87]. In fact, the emergence of some of the first consultancies preceded the establishment of the AHTAPol as such, which can be interpreted as the public HTA body complementing the nascent HTA market, and not the other way round. This may be problematic, especially given the well-documented permeability of the commercial and the public HTA sectors, including high-level transfers from the AHTAPol to HTA consultancies, which potentially leads to conflicts of interest [82, 83].

Our results also suggest that HTA consultancy firms considerably expanded their services. They started their activities by preparing HTA reports for manufactures in the early 2000s [43], and

although this remains their core activity, new types of services, such as strategic consulting, organizing training courses or preparing qualitative studies emerged throughout the years.

Finally, our findings based on AHTAPol's assessments of commercial HTA reports, called verification analyses, are perhaps the most puzzling. Here we established that the majority of HTA reports did not meet official MoH criteria, and only about half took into account the AHTAPol's formal feedback in their resubmissions. Although, as noted below, our findings are themselves determined by the quality and consistency of reporting of relevant information by the AHTAPol, this finding raises concerns about a HTA process relying heavily on the quality of manufacturer submissions. Of course, the commercial evidence is scrutinized by AHTAPol's staff developing verification analyses, and the number of shortcomings identified underscores the critical importance of the appraisal stage of the HTA process. However, the apparent scale of the problem is considerable, and is likely to translate into increased workload for the publicly funded HTA body, which, as mentioned above, is significantly under-resourced compared to the consultancy sector.

The apparent low quality of HTA reports might have several reasons. One, it could suggest that the MoH minimum requirements are not fit for purpose and their guidance does not correspond to the practical possibilities of what data HTA consultancies, or perhaps their industry clients, can deliver. However, this interpretation does not sound plausible because there seem to have been no formal policy discussions on calls for the revision or refinement of the minimum requirements. Two, the AHTAPol might not use the requirements faithfully (e.g. by interpreting them overly strictly or expansively). To explore whether this is the case it would be important to check whether the scope of AHTAPol's requests for revisions was consistent for all consultancies and pharmaceutical companies, to exclude possible preferential application of rules for some. Finally, some consultancies might have not understood the requirements and are unable, or unwilling, to learn from their past mistakes, as suggested by the variable and relatively low rates of companies taking the AHTAPol's comments into account when submitting revised analyses. Given that the HTA consultancy market comprises just a handful of key players, this would be worrying and put a question mark over whether the HTA market operates in the public interest.

Our study has several important limitations. First, our codebook for identifying the HTA consultancy firms was developed via an iterative process, possibly not identifying all authors. Second, the market size estimation is only a rough estimate, since data from the Polish National Company Registry was limited. Future research could possibly verify our indicative findings regarding the estimated market size via primary data collection from HTA consultancy firms. Third, the thematic analysis of the websites of the HTA consultancy firms relied on companies' self-presentations. While this is useful

to gain a sense of the companies' public presence, it does not necessarily provide reliable information on the full spectrum of their business activities and priorities. Fourth, one specific part of the HTA reports, decision problem analysis, was not included in our study, given the lack of consistency in HTA reports. Finally, our analysis of the quality of HTA reports was limited to the understanding of "quality" as per the minimum quality requirements by the Ministry of Health, which could be better framed as formal completeness or comprehensiveness of HTA reports, rather than an assessment of more substantive quality issues such as the choice of comparators or validity of economic models. Furthermore, the information included in verification analyses was often unclear, which is why we were unable, at times, to collect the explicit reasons of why HTA reports did not meet the official requirements.

2.2.5 Policy recommendations

Based on our Polish case study, we can extrapolate several takeaways regarding HTA consultancy markets for other countries, particularly those that rely on the STA model. First, there is a clear need for detailed reflection on conflicts of interest that may emerge at the intersection of public HTA bodies and HTA consultancies. The permeability of the two sectors is likely not a Polish exception and appropriate, context-specific regulation of the "revolving door" in HTA should be considered. Second, when HTA reports are not meeting the official requirements, further investigations are required to explore the underlying reasons. Third, HTA bodies should periodically subject their relationships with individual HTA consultancies to conduct critical analysis to eliminate potential bias. Fundamentally, to allow for external analysis, public availability of documentation of HTA submissions, including information on authors of HTA reports, is paramount to ensure the transparency of the HTA process. Reasons for confidentiality of this information should be re-interrogated in countries that practice extensive redactions or do not make HTA documentation public.

2.2.6 Supplementary material

Supplementary material 1: Identification of HTA consultancy firms in the Polish case study

Since the documents of HTA reports were frequently redacted we scanned them carefully to identify any feature of HTA consultancy firms that could be helpful (i.e. company logos, document design and style or website links within the text). From these features a code book was developed. This was an iterative process, therefore our codebook was evolving during the data extraction. When our codebook was considered to be complete after reviewing the documents of the first two years (2012, 2013), we re-evaluated those, where the HTA consultancy firm was not identified and double checked those that were already identified. We had separate coding for those documents where the company name was not blacked out, and for those when the name was blacked out and our codebook was used to identify the company.

Supplementary material 2: Estimation of the market size in the Polish case study

Annual net revenues from sales provided by the Polish National Company Registry was used in order to estimate market size. Since the received net revenue data was available only for two of the major HTA consultancy firms, these were used as bases for estimating the total market with the following calculations. First the annual net revenues were divided by the annual number of submitted HTA reports in case of the two companies for each years. Then the mean of these ratios was multiplied with the annual number of submissions for those companies where data was missing on the net revenue. The sum of these multiplications were used for estimating the total market size. In scenario analyses the lowest and the highest ratios of the annual net revenue / annual number of submitted HTA reports were used. These calculations assume that the major HTA consultancy firms in Poland generate similar revenue at company level by preparing an HTA report. Although this assumption cannot be validated, this method seemed to be the only reasonable option for the market size estimation within the scope of this study. Since we aimed to calculate a rough estimate, data was not corrected for inflation and current exchange rate from 2018 July was used to express values in EUR. Further data from the Registry's website was scrapped to complement information collected from the companies' websites on year of establishment and location.

Supplementary material 3: Market share of consultancy firms according to the four types of analyses in the HTA reports reported for each years of the study interval

Clinical assessment	No. analyses	Health Quest	Mahta	Instytut Arcana	HTA consulting	Aestimo	Centrum HTA	Other firms	Not identified
2012	57	22.8%	10.5%	14.0%	21.1%	8.8%	10.5%	3.5%	8.8%
2013	75	30.7%	21.3%	14.7%	12.0%	9.3%	10.7%	1.3%	0.0%
2014	98	33.7%	13.3%	14.3%	13.3%	14.3%	4.1%	5.1%	2.0%
2015	85	22.4%	18.8%	16.5%	14.1%	8.2%	14.1%	4.7%	1.2%
Economic analysis	No. analyses	Health Quest	Mahta	Instytut Arcana	HTA consulting	Aestimo	Centrum HTA	Other firms	Not identified
2012	57	24.6%	10.5%	12.3%	21.1%	10.5%	10.5%	3.5%	7.0%
2013	75	30.7%	21.3%	14.7%	12.0%	9.3%	10.7%	1.3%	0.0%
2014	97	34.0%	13.4%	14.4%	12.4%	14.4%	4.1%	5.2%	2.1%
2015	85	22.4%	18.8%	16.5%	14.1%	8.2%	14.1%	4.7%	1.2%
Budget impact analysis	No. analyses	Health Quest	Mahta	Instytut Arcana	HTA consulting	Aestimo	Centrum HTA	Other firms	Not identified
2012	56	23.2%	10.7%	10.7%	21.4%	8.9%	10.7%	3.6%	10.7%
2013	74	28.4%	21.6%	14.9%	12.2%	9.5%	10.8%	1.4%	1.4%
2014	98	33.7%	13.3%	14.3%	12.2%	14.3%	4.1%	5.1%	3.1%
2015	85	22.4%	18.8%	16.5%	14.1%	8.2%	14.1%	4.7%	1.2%
Rationalization analysis	No. analyses	Health Quest	Mahta	Instytut Arcana	HTA consulting	Aestimo	Centrum HTA	Other firms	Not identified
2012	40	27.5%	12.5%	5.0%	20.0%	7.5%	7.5%	7.5%	12.5%
2013	58	29.3%	25.9%	8.6%	13.8%	6.9%	10.3%	1.7%	3.4%
2014	74	35.1%	13.5%	17.6%	13.5%	13.5%	4.1%	2.7%	0.0%
2015	70	22.9%	20.0%	14.3%	15.7%	10.0%	11.4%	4.3%	1.4%

2.3 When health technology assessment is confidential and experts have no power: the case of Hungary

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Summary of the Hungarian case study

Health technology assessment (HTA) is not simply a mechanistic technical exercise as it takes place within a specific institutional context. Yet, we know little about how this context influences the operation of HTA and its ability to influence policy and practice.

We seek to demonstrate the importance of considering institutional context, using a case study of Hungary, a country that has pioneered HTA in Central and Eastern Europe. We conducted 26 in-depth, semi-structured interviews with public- and private-sector stakeholders.

We found that while the HTA Department, the Hungarian HTA organisation, fulfilled its formal role envisaged in the legislation, its potential for supporting evidence-based decision-making was not fully realised given the low levels of transparency and stakeholder engagement. Further, the Department's practical influence throughout the reimbursement process was perceived as being constrained by the payer and policy-makers, as well as its own limited organisational capacity. There was also scepticism as to whether the current operational form of the HTA process delivered 'good value for money'. Nevertheless, it still had a positive impact on the development of a broader institutional HTA infrastructure in Hungary.

2.3.1 Introduction

Health technology assessment (HTA) supports decision-makers in allocating scarce resources for expensive medical technologies, primarily pharmaceuticals [13, 51, 110]. It offers particular opportunities in settings such as Central and Eastern European (CEE) countries [111] that face significant budgetary constraints and where sub-optimal investment decisions bring substantial opportunity costs [112]. The potential benefits of HTA include more rational use of resources, improved patient outcomes resulting from greater use of evidence-based technologies [113, 114], and more generally, by contributing to a climate that values evidence in healthcare policy and practice [115]. Yet, these benefits may not always be achieved in practice. The few studies that have examined the institutional characteristics and context of HTA have reached conflicting conclusions [116, 117] so any effects of different institutional contexts on HTA processes are far from clear [118] and recommendations on best practices in HTA implementation are difficult to generalise [46].

Hungary was among the pioneers of HTA in Central and Eastern Europe [22]. In this paper, we examine the institutional arrangements within which HTA in Hungary takes place, its influence on decision-making, and how its benefits and costs are viewed by key stakeholders. While the precise arrangements that exist in Hungary are unique to the country, we offer this paper as an example of the importance of understanding the HTA function within a broader context, and in doing so, hope that it will provide lessons for other countries seeking to implement or strengthen their own HTA systems.

The development of HTA in Hungary and its institutional basis have been described in detail elsewhere [24, 119-121]. Moreover, there have been detailed studies of particular elements of the process, including the continuing development of methodological guidelines for economic evaluations [41, 122], the application of multi-criteria decision-making in assessing technologies [123], and developing a critical appraisal checklist [21]. However, we still lack an adequate understanding of many aspects of how HTA and its process of making decisions on reimbursement actually operate, in part because of a lack of basic documentation in the public domain. Notably, while previous studies suggest the existence of informal rules and practices that may complement or circumvent the formal reimbursement process, these have not been subjected to in-depth scrutiny. Consequently, we know very little about the role and influence of key stakeholders, including the public HTA body, in final reimbursement decisions. Nor has the existing literature sought to identify the benefits and costs associated with the existing model of HTA in Hungary.

The aim of this paper is therefore threefold. First, to identify institutional characteristics of HTA that may either facilitate or constrain the decision-supporting role of the HTA Department. Second, to

assess the influence of the HTA Department in relation to other key players engaged in the reimbursement process. Third, to determine whether various stakeholders consider the current HTA system to represent good "value for money" and how they perceive its costs and benefits.

In the next section, we provide a brief overview of the Hungarian reimbursement system. We then explain our methods. In the remainder of the paper we answer each of the three research questions in turn. We conclude that Hungarian HTA has faced challenges in adapting to changing circumstances and suggest reasons why this may be so.

2.3.2 Overview of the current Hungarian reimbursement and HTA procedures

Hungary established its own HTA Department, an organisation tasked with reviewing proposals for reimbursement of health technologies, in 2004. It had just acceded to the European Union (EU) and this was means of complying with the EU's Transparency Directive [124, 125]. Since its inception the HTA Department has moved among various organisational structures and currently lies within the National Institute of Pharmacy and Nutrition (NIPN), a licensing authority for pharmaceutical and public administrational matters.

The HTA department is part of a broader process of reimbursing new medical technologies. In line with Ministerial Decree No. 32/2004. (IV. 26.), any manufacturer seeking reimbursement of a new pharmaceutical or a price increase or new indication for one already on the market must submit a full HTA dossier. The most common "normal" reimbursement procedure starts with the submission of a reimbursement application to the National Health Insurance Fund (NHIF). The application is then passed to the HTA Department and the relevant College of Medical Professionals. These bodies are responsible for, respectively, conducting a critical appraisal of the submission, and providing an expert opinion on the technology. The reimbursement procedures are coordinated by the Department of Reimbursement (DR) at the NHIF, which also prepares a preliminary opinion on the submission.

The critical appraisal document, the medical expert opinion, and the preliminary opinion of the DR are discussed by the Health Technology Assessment Committee (HTAC), based at NHIF. Approximately 10 people attend HTAC meetings but the precise mix may vary according to the technology being considered. There are usually 5-6 NHIF representatives, 2-3 medical professionals who are permanent members, representatives of the HTA Department and relevant advisors from the College of Medical Professionals. However, only NHIF representatives and the permanent medical professionals have voting rights. The HTAC makes a recommendation on reimbursement, either positive or negative, and decides the appropriate reimbursement scheme. The HTAC

recommendation is reached by a simple majority vote among those with voting rights. Subsequently, the DR prepares a final recommendation for the Director-General of the NHIF. In some cases, the Director-General has the authority to make the final decision based on the recommendation of the DR. However, in many cases a positive reimbursement decision requires changes in the legislation for reimbursing health technologies (Annexes of the Ministerial Decree No. 32/2004) for instance where a new indication is added. In such cases, the Ministry of Human Capacities, a super-ministry that includes the State Secretary of Health and the Ministry of National Economy are involved in the decision-making process.

2.3.3 Methods

We applied a single case study approach [126] using qualitative data from 26 in-depth, semi-structured expert interviews with major stakeholders involved in HTA in Hungary. The interviews were conducted between August 2016 and January 2017 in Budapest. We applied purposive sampling, aiming to include key categories of stakeholders involved in the HTA procedures in Hungary, namely the HTA Department, the NIPN, the NHIF, the Ministry responsible for health (i.e. Ministry of Human Capacities), academia, manufacturers, consultant companies, and patient organisations (Table 9). The interviews were carried out by Researcher A (in Hungarian, 13 interviews in total), Researcher B (in English, 7 interviews) and Researcher D (in Hungarian, 6 interviews in total). All the interviewers had been involved in the study from the outset and are experienced in HTA in Hungary. The vast majority of interviews were conducted in person; only 4 interviews took place via Skype. A typical interview lasted around one hour.

Organisation	Number of completed interviews	Refusals and non-responses	Total approached
Public sector			
HTA Department and National Institute of Pharmacy and Nutrition	4	1	5
Ministry responsible for health	3	0	3
National Health Insurance Fund	3	2	5
Academia	3	0	3
Private sector			
Manufacturers	5	1	6
Consulting companies	5	1	6
Non-governmental organisations			
Patient organisations	3	0	3
Colleges of Medical Professionals	0	2	2
Total	**26**	**7**	**33**

9. Table: Categories of interviewees

Potential interviewees were selected based on their current or previous institutional affiliations, their expert status evidenced by, for example, authoring scientific articles or participation in relevant conferences, or recommendations by other interviewees. The expert knowledge of our interviewees was also evidenced by their multiple prior affiliations. The interview guide was agreed on at the beginning of the fieldwork and comprised mainly broad open-ended questions. These questions asked the interviewees' opinions on the following topics:

- the most important benefits of HTA in Hungary
- potential benefits which cannot be achieved with the current HTA system
- key challenges facing the HTA process in Hungary
- is the system being fit for its purpose?
- transparency of procedures
- costs associated with HTA in Hungary

Additionally, more detailed questions were also asked in subsequent interviews, drawing on emerging results. These concerned issues such as:

- movement of professionals between the private and public sector
- the market for HTA consultancies
- the quality of HTA dossiers
- the data availability for appraisals by the HTA Department

We encouraged interviewees to elaborate on their points in depth to maximise the value of their unique expert knowledge. With seven non-responses or refusals, we achieved a 79 percent response rate. Non-responses were distributed evenly across the key stakeholder categories, with the exception of medical professionals whom we were unable to reach. This was presumably because of their time pressured working conditions or a lack of awareness of HTA operation in the healthcare system.

Our research was approved by the Ethics Committee at the Department of Sociology at the University of Cambridge. All interviewees were briefed about the objectives of the study, the interview procedure, and our intention to analyse data and publish our findings. We reassured interviewees about our commitment to protecting their anonymity by creating broad interviewee categories. As an additional reassurance, we offered them the option of accepting or refusing tape recording. Six interviewees refused such a recording. In these cases, extensive notes were taken during and immediately after the interview.

For each interview, detailed interview protocols in English, omitting redundant material clearly irrelevant to our research, were prepared by Researcher A and Researcher D based on recordings (where available) and extensive notes. The interview data were analysed by Researcher A and then discussed with Researcher B, C and D. Researcher E, F and G contributed to their interpretation. A thematic analysis [127], facilitated by NVivo 10, allowed an initial coding of the interviews based on concepts derived from the research questions. At a later stage, some codes were collapsed and code families and networks were established, to best reflect the main themes emerging from the data. We present quotations expressing views that were shared by the interviewees representing various stakeholder perspectives. The interviewer's ID number is given in brackets. Since many of the interviews were recorded in Hungarian, they are paraphrased here in English. Where statements offered by the interviewees differ, we chose quotations that appeared the most appropriate in light of the entire dataset.

2.3.4 Findings

<u>The role of the HTA Department</u>

Our interviewees pointed to a number of areas in which the HTA Department successfully fulfilled its formal role of providing evidence for reimbursement decisions, as set out in the legislation. Appraisals undertaken by the HTA department were widely viewed as independent, and conducted according to predefined criteria. A high-ranking NHIF official stressed, "*The HTA Department (…) is more like an independent group of experts to support the NHIF*."(12) According to a former HTA Department senior official, "*These [appraisal documents] have fifty-sixty pages which is too much but it is a comprehensive description on efficiency and safety, health gain, and review [on] the health economic analysis, which includes the price of the product and the comparator. And at the end there is an opinion.*"(20) A further strength of the HTA Department was its timeliness in conducting appraisals. Interviewees typically reported that the Department normally achieves the preparation of an evaluation within the 45 day time-window. A consultancy company manager highlighted, "*There is no such thing as having the submission on hold [at the HTA Department]*."(10)

Nevertheless, some interviewees still saw the HTA Department's role in supporting evidence-based decision-making as suboptimal. Most notably, the assessments provided one-off snapshots in time – the HTA Department only contributed to the earliest phases of the reimbursement process, with unrealised potential for subsequent contributions. According to a former HTA Department employee, "*[HTA Department] has only 45 days to assess the technology. So if something changes, for example new evidence comes out or the price is changed, the HTA Department is not involved*

anymore."(15) A drug company representative also noted the absence of a process to revise previous decisions: "*the follow-up process is missing. This is an important limitation of the [reimbursement] system.*"(4)

The interviewees conceded that there was insufficient commitment of decision-makers to publicly disclose information on technology assessment documents that would justify decisions on public reimbursement. An academic explained, "*if there is no need for justification, implicit judgment becomes the most important part [in decision-making]. And those consultants who got the insights on how the implicit judgments are made become successful.*"(14) Although HTA experts, and even, occasionally, policymakers, publicly acknowledged the importance of transparency, concrete remedies were not put into practice. A senior HTA consultant explained: "*actually in public no one is against it. The answer that people usually say is that they want do it [put HTA documents in the public domain] in the near future (…) but it just never happens.*"(15) An interviewed academic was emphatic on this point, "*Unfortunately we were not brave enough to move into a direction where we can operate HTA in a transparent way.*"(14)

This institutional shortcoming could be addressed in the future, as is being suggested in on-going consultations about possible publication of executive summaries from appraisals including major questions on elements from the submission (e.g. comparator, cost-effectiveness ratio etc.). A member of the HTA Department emphasised, "*I don't want to be a part of a black box*."(17) Yet the proposed improvements to transparency may face opposition from some stakeholders, including the manufacturers. A pharmaceutical company representative explained that more transparency could even be risky for manufacturers: "*If an evaluation is negative by the HTA Department and then the NHIF still makes a positive recommendation, it would be immediately attacked by competitor companies. They would use these information against each other*."(9)

A related area of unrealised potential arose from the limited extent of consultations with key stakeholders, especially clinicians, manufacturers, and patient organisations. According to a current HTA Department employee, "*There is a need [for consultation with clinicians] and the HTA Department would like to have more support from external experts especially in the clinical part (…) There were no attempts [to formalise consultations] and also it is hard to motivate the busy physicians. This is not in the everyday practice.*"(24) This is the situation even though representatives from the Colleges of Medical Professionals also give their opinion at the HTAC. Moreover, former HTA Department employees explained that, "*This [consultation with clinicians] is sub-optimal. There should be a well-regulated process of doing this*"(15) and "*Key opinion leaders are not really interested in HTA. They have a perception of HTA that it is a bureaucratic thing, shifting papers back*

and forth."(3) Similarly, manufacturers complained about the limited feedback on their submissions "*A basic problem is that this process is not a consultation type process. There are no consultation opportunities to conduct a proper and objective evaluation of the submission.*"(9) This issue was recognised by those conducting assessments; negotiations are underway to create a platform for sharing health economic models to facilitate two-way discussion between the HTA Department and manufacturers. Unlike the situation in some other countries, patient organisations have no formal contact with the HTA Department. A representative of a patient organisation explained: "*In general a Hungarian patient or a Hungarian patient organisation never hears about HTA. They are not aware of the process in which the HTA Department is involved. (…) On the other hand, (…) it is not facilitated to invite [patient organisations] to collaborate. This is not even on the agenda*."(21)

Influence of the HTA Department

The influence of the HTA Department on reimbursement processes was widely viewed as limited. A former key governmental official emphasised, "*The influence of HTA is smaller than it would be required. This is changing and there are steps forward but still it is smaller than required*."(25) This point was summarised, perhaps most vividly, by a high-ranking government official, "*The HTA Department works as an ante-room, where people wipe off their shoes.*"(19)

Many of our interviewees stressed that the HTA Department had limited influence on the NHIF. A senior consultant stressed, "*there is an ambivalent relationship between the NHIF and the HTA Department. (…) for the NHIF the technology assessment is too academic and requires that everything should be perfect.*"(10) A key issue was the narrow scope of appraisals, including only evaluations on the validity of data included in manufacturer submissions. According to a high-level governmental official, "*they only review that an analysis is appropriate or not, in the context of the given methodology. This is too narrow a perspective*."(19) Contrastingly, some interviewees felt that the HTA Department should be providing more direct advice to decision-makers. An academic explained, "*The result of this kind of restriction, [is] that the opinion is usually quite neutral and you can interpret it in different ways. (…) But they never made a strong statement like 'the quality of the submission is extremely poor, extremely biased and there is no evidence on some point'*."(14) Some of our interviewees also mentioned opaque phrasing of recommendations provided by the Department that were ill- suited to real-life decision-making purposes. An NHIF employee noted, "*It is not helpful for instance when they say that the cost-effectiveness is uncertain*."(12)

Even more important was the lack of inclusion of a NHIF institutional perspective in appraisals undertaken by the HTA Department. A former NHIF employee added, "*The main weakness is that [HTA] does not serve the interest of the payer. Because it does not lead to better decisions.*"(3)

Specifically, the HTA Department does not prepare recommendations on whether a new technology should be reimbursed or not. This disjuncture of organisational perspectives could, in certain circumstances, lead to the by-passing of the HTA Department by the NHIF. This was particularly the case when the NHIF had enough knowledge about the technology, and the agreement with the manufacturer on price was seen as acceptable. In this case the NHIF saw the contribution from HTA as redundant. "*Instead of a normal procedure it could be acceptable to have a simplified procedure*"(12) was an assertion made by a high-ranking NHIF employee. Consequently, it appeared that in some cases emerging recommendations from the HTA Department were disregarded a priori. A former HTA Department employee stressed, "*In some cases the final decision is made before the opinion [of the HTA Department] is discussed. (…) NHIF already has information whether the drug has a place in the therapeutic practice in Hungary or not*."(20)

Yet another factor limiting the HTA Department's influence on the NHIF was its reliance on list prices as opposed to the actual, often discounted, prices negotiated with drug manufacturers. While the Hungarian system relies heavily on price-volume agreements between the manufacturer and the NHIF, the HTA Department is not provided access to the details of any negotiations taking place in parallel to its appraisal process. An NHIF employee explained, "*There is an information asymmetry between the HTA Department and the national payer [NHIF]. This is the result of the confidential prices which are set through national tendering or negotiation process in case of innovative products*."(12) The HTA Department has no information regarding the state of negotiations on actual prices. According to a representative of a drug company, "*From this point on the whole HTA system worth nothing. Manufacturers submit analyses which have completely wrong input data as price*."(6) Similarly, a former HTA Department employee reacted to this situation by saying, "*Basically sometimes you are just comparing two numbers that have nothing to do with reality. Of course nobody cares what the result of the comparison is, because it is nonsense*."(15)

The HTA Department had even less influence on decision-makers in ministries. A former NHIF employee saw the HTA Department's impact as negligible. "*Generally, the government decisions are so centralised and so hierarchical that the information [from the HTA Department] is not valuable in terms of [evidence-based] decision-making*."(3) Other interviewees pointed out that the influence of the HTA Department was constrained by political considerations that top-level decision-makers were sometimes inclined to prioritise over HTA. A former NHIF official elaborated, "*the final decision is made by politically influenced stakeholders who absolutely do not understand this way of analysing drugs. There is a gap and this gap is quite huge. (...) There is a need for a stronger relationship between HTA and decisions*."(16) Reimbursement procedures and the related timeline

of decisions are only transparent until a certain point. Once ministerial bodies (e.g. state secretary of health or Ministry of Finance) got involved very frequently their opinions drove decisions and delayed announcements on reimbursement status. "*Timelines are not transparent in the governmental sector. The fact that the Ministry of Finance has such a significant influence on the reimbursement of health technologies blocks constantly the planned timelines and the deadlines that should be maintained throughout the entire reimbursement decision-making process*."(8)

In addition to factors constraining the HTA's influence in relation to the NHIF and the Ministry of Health, the influence of the HTA department was undermined by problems pertaining to its organisational capacity. A NHIF official stressed, "*The HTA Department currently does not have the capacity to become a prominent body in the technology assessment.*"(13) There are approximately 80-100 submissions on pharmaceuticals and a similar number on medical devices per year. There are 13-15 permanent employees who work on evaluating the submissions and representing the HTA body in committees. The impact of these organisational constraints was exacerbated by the tight timelines imposed by the reimbursement legislation. A former HTA Department employee stated: "*The 43 days for evaluation (…) does not make sense*."(23) A former senior officer at HTA Department explained that the time-window also includes holidays, and therefore it "*actually becomes 30 days of evaluation that is done by one health economist and one medical expert, who have more submissions in parallel*."(20)

Human resource considerations were even more critical because of revolving door between the HTA Department and manufacturers and consultancies. A former HTA Department employee explained, "*the biggest barrier of the development [of the Department] is the high fluctuation. (…) The entire staff (…) changed in the last 3.5 years. There is no continuity at the institution*."(23) A key factor in this brain drain from the HTA Department was the low level of remuneration given the high level of skills and expertise of its employees. A consultancy employee pointed out the usual career path of young health economists: "*people start their career at the public sector, work there for four-five years and then go to manufacturers or consultancies.*"(15) A NHIF employee described this process as "*unfortunately the HTA Department works as a spring board for young people*."(13)

Yet low salaries were only one reason for the outflow of highly qualified personnel. Many interviewees stressed that the limited influence on the reimbursement system can also contribute to decisions to move to the private sector. As a former NHIF employee pointed out, "*they [HTA Department employees] also understand that it is not only about money, but what they do is essentially without impact on the final decision. It results a huge frustration.*"(3) A former HTA

Department employee criticised the system as "*You are in a job where you compare two numbers and nobody cares about it*."(15)

Finally, there was also evidence of a vicious cycle whereby the HTA Department's limited impact on the reimbursement process encouraged actions by other stakeholders that further diminished its influence. This was perhaps best illustrated by the persistent low quality of manufacturers' HTA submissions. A HTA department employee explained that "*people who worked in the HTA Department now work for pharma. They saw no impact, so they don't want to create a normal dossier.*"(17) Similarly, a former NHIF employee noted that "*If someone would take the real decisions based on HTA submissions [by manufacturers], then the HTA submissions would have been revised and rethought years before. At the level of real decisions, [the decision-makers] are not interested in the HTA submission. That is why the HTA submissions are not for decision-making but for themselves*."(16) However, there were other reasons behind the low quality of submissions, including limited data availability. As a representative of academia emphasised, "*Source of valid information is an important challenge for the HTA submission. Manufacturers, consultants and the governmental sector including the HTA Department do not necessarily use the same source for data*."(8)

<u>Perceived costs and benefits of the HTA system</u>

Although the HTA Department has limited perceived influence on the reimbursement process, it still provided many important benefits. Given the lack of available data from HTA dossiers, appraisal documents by the HTA Department, or price negotiation contracts between the NHIF and manufacturers, it is not currently possible to express these benefits in monetary terms. Nevertheless, it was clear that the HTA Department was seen as creating many important intangible benefits for the Hungarian health policy in the long-run. These spillover benefits were most commonly associated with developing experience in applying HTA principles in policymaking, including awareness of their practical advantages and disadvantages. A senior manufacturer employee maintained, "*There was "hurrah-optimism" at the beginning [HTA implementation in Hungary], but this is over. We realised how and what can be used from an HTA system. And we also know what the HTA system is not useable for.*"(6) Consequently, even senior NHIF officials ignored some of the recommendations coming from the HTA Department but they still relied on the principles of HTA in developing health policy. Ministerial policymakers tended to be even more strategic in this regard, showcasing HTA as a key achievement in building an evidence-based policymaking infrastructure. A former high-ranking NHIF employee emphasised, "*We can tell the world that we have a good HTA system*."(16)

A key specific benefit achieved by the HTA Department was the institutionalisation of explicit criteria for evaluating health technologies. A HTA consultant explained, "*It is good that there is a platform to consider cost-effectiveness*."(10) A former key HTA Department official stressed, "*at least someone sits down at some point, thinks about, reads and evaluates the report about the technology. And this is forwarded to the decision-makers*."(20) This was associated with curtailing informal influence wielded by economically powerful players such as drug companies. A former high-level governmental official recalled, "*Before the establishment of HTA system there was a "free-robbery" by companies. Before [the introduction of HTA in] 2004, pharma companies did whatever they wanted.*"(1) This has changed dramatically thanks to the operation of the HTA Department and the requirement to submit HTA dossiers. An academic reported, "*It is very rare that someone wants to receive reimbursement based only on lobbying*."(8)

Last but not least, the HTA Department underpinned a broader HTA system, including a range of educational activities unparalleled in the CEE region. As an academic expounded, "*We have a HTA agency and many trained HTA experts in Hungary, which is unique in the region. There is an opportunity to study [HTA] in a post-graduate program without leaving the country*."(14) In particular, the HTA Department was a key element of the infrastructure allowing for participation in international collaborations. A former HTA Department official stressed, "*the Department was successful in joining to international programs and teams. This results in more experience*."(20)

Notwithstanding the benefits of the HTA system in its current form, our interviewees also pointed out its costs. Overall, public resources spent on the Hungarian HTA system are considered to be negligible and the direct costs of the HTA system are mainly borne by manufacturers. From the manufacturer's perspective, a key cost associated with the current form of the appraisal process led by the HTA Department is the administrative fee for each reimbursement submission, amounting to 1,500,000 HUF (approximately €5,000) per reimbursement application for pharmaceuticals, and 700,000 HUF (approximately €2,300) for simple medical devices.

Estimating the public costs associated with running the HTA Department proves more difficult. First, administrative fees levied on drug companies are shared between the NHIF and the HTA Department, based on an agreement whose details are not publicly disclosed. According to a senior NHIF employee, *"[the share from the fee] is based on a contract between the organisations. So there is no need for case-by-case negotiation."*(12) It is estimated that the HTA Department receives 80 percent of the fee for pharmaceuticals and 30 percent of the fee for simple medical devices. The HTA Department also has some external funding, for instance grants from the European network for Health Technology Assessment (EUnetHTA). The HTA Department's annual budget then

according to these estimates should be between €400,000 and €450,000. However, since the operational costs of the Department are not separated from the cost of the NIPN, to which the HTA Department belongs, it is not clear whether the revenue generated from administrative fees plus income from externally funded projects is sufficient to cover its running costs.

An additional cost, from the manufacturers' perspective, is incurred by having to develop HTA submissions, a task commonly outsourced to external consultancy companies. While the prices of developing submissions are not publicly available, the average price mentioned by most interviewees was around €10,000, with the lowest limit of about €4,000. According to a manufacturing company's representative, referring to a general submission, "*For this cost they [consultants] collect the input data for the [health economic] model. (…) Then they evaluate the results, make the sensitivity analysis and prepare all the required appendix or attachments*."(9) New health economic models for economic evaluation are rarely developed for Hungarian submissions; in most cases global models are adopted to the Hungarian context. Prices of consultancies may increase if a new model needs to be developed, local data collection from primary sources is required, or if consultations with experts or additional studies such as systematic reviews are needed. In such cases, a very complex submission is typically priced at around €35,000 – €45,000.

Estimating the total annual cost of developing HTA submissions by the pharmaceutical industry is challenging. A reasonably reliable method considers official yearly revenues of 3-4 major consultancies that focus on developing HTA submissions. There are also a handful of smaller companies with negligible annual revenue compared to the size of the consultancy market. Calculated this way, the consultancy market can be estimated to be around €3,000,000 – €3,500,000. While this figure is likely to overestimate the market size (the consultancy firms may still provide other services not related to HTA), it was recognised as a reasonable estimate by a number of interviewees familiar with the sector.

As the perceived benefits of the HTA system were intangible and its costs were difficult to estimate, some interviewees maintained that public and private money spent on the system did not represent good value. This was evident given the low adherence of decision-makers to HTA recommendations. A high level government official explained, "*Currently the importance and the role of the technology assessment disappears quickly from the system. So we could say that funds spent on this process are wasted money*."(19) A former NHIF employee criticised the system by saying that early developments should not be the only perceived values anymore: "*HTA moved the system from pre-historic stage to (...) an Anno Domini stage. But that it is. And how long can you be grateful to this?*"(3)

Some interviewees noted that, even if manufacturers have to bear administrative costs and the costs of consultancies, the most important beneficiary is still the private rather than the public sector. Other interviewees pointed out that this system has only one clear winner, the consultancy sector. A representative of a consultant company pointed out that "*benefits are there for all the consultants who are doing the [HTA] dossier[s]*."(16)

Yet the perceived balance of costs and benefits could be altered by very recent policy changes, including a formal review of the methodological guideline for economic evaluation to better reflect the needs of the decision-maker, improve the skills of HTA Department workers in the validation of health economic models, build an international network and initiate direct communication to manufacturers. A former HTA Department employee explained, "*It is not the worst system in the world. But it would be so easy to improve it. (…) We just need to write a few additional legal texts here and there, and we would have a much more efficient and transparent system*."(15)

2.3.5 Discussion and conclusion

Our findings show that even if an HTA body fulfills its intended formal role of supporting evidence-based policymaking, it may face major institutional constraints. Based on the Hungarian case, its contributions to the pricing and reimbursement process can, for example be limited to its earliest phases, without considering subsequent contributions (e.g. involvement in pricing negotiations or revision procedures). We also found that the perceived influence of an HTA body on the reimbursement process may be limited, indicated by its inferior position in relationships with payers and health policymakers. Despite calls for increased openness of HTA as one of the founding principles of the field, in practice HTA can be associated with limited transparency and insufficient consultation with experts, manufacturers and patient organisations. Similar results were found in a recent overview on the HTA implementation in Hungary [45]. This raises obvious normative concerns and may, as in Hungary, contribute to a further diminishing of the HTA body's role in pricing and reimbursement decision-making.

Our findings from the Hungarian case also suggest that an HTA body may have a positive impact on the development of a broader HTA system in a country, by laying the foundational infrastructure of evidence-based policymaking in healthcare and promoting an understanding of internationally accepted HTA principles [128]. While costs and benefits of the Hungarian HTA system were difficult to quantify, there was strong scepticism as to whether it represented "good value for money". It is quite unusual that none of our interviewees mentioned financial or health benefits of the HTA system, as the benefits of HTA are typically thought of in monetary terms or savings and a more

rational use of resources. A reason for this can be the methodological challenge of estimating the benefits of HTA for populations or health systems [27]. Some attempts have been made previously [113, 114, 129]. However, these studies relied mainly on published HTA reports and other related documents that were not available in our case. Yet more plausibly, we can attribute this non-finding to the lack of influence the Hungarian HTA Department has on eventual reimbursement decisions.

More fundamentally, despite the shared diagnosis of the major drawbacks of the HTA process, including the lack of access to actual prices, lack of transparency or capacity limitations at the HTA Department, none of the major stakeholders seemed to have a sufficient interest in initiating substantive reforms. To begin with, consulting companies have a stable and predictable market where competition is low due to the small number of established companies. Manufacturers' submissions for HTA evaluation create the basis for their business operations and their service portfolio can be diversified with HTA-related activities. Their human resource capacity is ensured by the education system and by the underpaid but experienced governmental officers from the HTA Department or from the NHIF. Manufacturers, on the other hand, seemed to have considered HTA as a tick-the-box exercise and therefore were willing to bear the associated costs, which seems to be minor from their perspective. These costs are predictable and rely heavily on consulting companies. Manufacturers understand that relevant questions of reimbursement are not discussed at the level of the HTA Department, but rather at the NHIF through price negotiations, or at a higher, health policy level, which is neither transparent nor predictable. Moving on to the national payer although it considered the opinion of HTA Department, it did not fully utilise the HTA submissions and the related appraisals in its decision-making. The NHIF has a monopolistic position during price negotiation with manufacturers. This gives it great bargaining power and it is not willing to share any information with other parties. Although the concept of HTA is accepted by the NHIF, there is no intention to utilise HTA to take account of changing circumstances, such as new evidence on effectiveness or costs. Further, HTA as a policy practice was poorly understood, which could be a key reason for a lack of concrete proposals to increase transparency or strengthen the evidence base for decisions. Finally, the voice of the academic sector was constrained by its limited involvement in compiling HTA dossiers, and patient organisations played no role in the HTA process.

On balance, our findings suggest that the HTA Department was the only stakeholder with an interest in realising the potential of the Hungarian HTA system. This echoes similar findings from other CEE countries [72]. Recent initiatives by the Department, such as renewing its methodological guidelines or increasing international collaboration through EUnetHTA were noted by other stakeholders. However, limited staffing, a substantial brain drain on the industry, time-pressure on submissions

and huge workloads are significant barriers to achieving a stronger role in the reimbursement process. The current organisational structure, with the Department embedded in the NIPN, responsible for regulatory affairs, provides many opportunities for the HTA Department to achieve greater prominence. This could mirror a similar partnership between the European Medicines Agency and EUnetHTA at the EU level [130].

From a regional perspective, HTA in Hungary can be compared with that of Poland. The organisational and legal framework of the Polish Agency for Health Technology Assessment (AHTAPol) were also established after joining the EU, in 2004. The political significance of AHTAPol recommendations in the reimbursement process was reported to be important and their support is vital for legitimising reimbursement decisions [82, 84]. HTA recommendations are publicly available from AHTAPol's website, and therefore HTA activities can be monitored and compared to reimbursement decisions to gain more understanding on potential influence of AHTAPol [92, 93]. Further, the availability of HTA assessment reports, albeit frequently heavily redacted, makes it possible to investigate the role of various considerations (e.g. recommendations of other HTA bodies) in the recommendation by AHTAPol [94]. Similar studies would be highly welcomed in Hungary but the lack of relevant publicly available data makes them impossible. In addition, the public availability of HTA recommendations would make it possible to quantify their impact on subsequent reimbursement decisions, as has been done in Poland recently [90]. Notably, these new findings point to a lower policy impact than suggested by assessments made by stakeholders [82, 83]. Another similarity between the two countries was the extensive movement of staff from HTA bodies to private sector firms [131].

While many of our findings are specific to the Hungarian context, there are others from which lessons can be extrapolated across jurisdictions especially for those that are currently implementing or reforming their own HTA systems. A recent stakeholder analysis from Chile, for instance, revealed that Chilean stakeholders are aware of many potential shortcomings of an HTA body although there is a consensus on the need for such a body [132]. In particular, they are concerned about the danger of creating an HTA body without meaningful impact on policy. As the Hungarian example shows, this can happen because of bureaucratic turf wars between institutions, understaffing, or brain drain to the private sector. Our findings are also relevant to those countries where capacity building is seen as a crucial step in improving their HTA systems such as Croatia, Greece, Slovenia [67, 133, 134]. Without downplaying the efforts to increase human capacities, the Hungarian case suggests that creating large numbers of HTA experts may not be sufficient to build effective HTA institutions if these experts are drawn into the private sector after gaining experience. This means that countries

with less competitive public sector salaries should pay attention to retention of staff in addition to recruitment and training. The Hungarian example also highlights the risk, also affecting some high-income countries, of creating a powerless institution which will, ten years later, face a reform stalemate and act as a tick-the-box bureaucratic exercise while stakeholders accept its costs without utilising its outputs. Finally, our observed benefits of training substantial numbers of HTA experts and promoting the culture of evidence-based policymaking are also likely to be replicated in other countries, and should be considered by countries considering HTA.

Two key weaknesses of our study must be mentioned. First, as suggested above, given the non-existence of publicly available documents on HTA and our lack of access to internal documents, we were unable to corroborate our qualitative data with primary sources (such as manufacturers' submissions or appraisal reports by the HTA Department, as well as their impact on final reimbursement decisions). Ideally, if documents related to HTA become publicly available, we would be able to triangulate some of our findings. This would most importantly involve comparing the HTA Department's opinions with reimbursement decisions at NHIF or at the ministerial level. In the absence of documentary data, we triangulated information by verifying it with multiple stakeholder groups. Second, since we were unable to reach representatives of clinicians, their perspective on the Hungarian HTA system was inferred by those interviewees who had experience collaborating with them. A key policy implication arising from these findings is that the Hungarian HTA system must review whether the reimbursement process requires strengthening the formal role of the HTA Department. We believe that studies on manufacturers' submissions and appraisal reports by the HTA Department are vital to answering this question. A first step towards a comprehensive review of the Hungarian HTA system depends on policymakers, as it involves increasing the transparency of the process.

3. Discussion

The dissertation investigated the implementation of HTA from a health policy point of view in the CEE through a series of country-specific case studies. An important methodological strength of this dissertation was the combination of different methodologies that were used to answer the proposed research questions. A qualitative survey was used among Ukrainian stakeholder. Both a document and content analysis of publicly available materials were conducted in Poland and in-depth semi-structured interviews with experts were performed in Hungary. Another key strength was that the research questions were specifically targeted to the context of the investigated countries which reflected on research gaps identified by a set of former research studies completed before this dissertation. The research questions were also aligned with the history and tradition of HTA implementation in the investigated countries.

While the investigated country-specific case studies with specifically targeted health policy research questions can be considered as a strength of this dissertation, it can also be considered as a weakness due to the slightly limited generalizability of the findings. Furthermore, the case studies (particularly the Hungarian and the Polish ones) were limited in terms of health technologies since their focus was mainly on pharmaceuticals. While these limitations are acknowledged, they are further discussed in more details later in this chapter.

The discussion is organized in the following way: first, the novel findings are presented in respect to the objectives defined at the beginning of the introduction. Then the dissertation findings are placed into a broader health policy context. In the remaining parts, reflections are given for the key limitations. Accordingly, to overcome the national scope of the case studies, the global perspective of HTA will be discussed. Then the use of HTA for non-pharmaceutical technologies will be shortly introduced. The final two topics of the discussion will go even further in widening the scope of the dissertation by first, discussing the spread of HTA beyond health policy research and involving a broader social science perspective of HTA; and finally, the last part of the discussion will introduce alternatives to HTA that can be used for specific cases (particularly for pharmaceuticals) in the health policy decision-making.

3.1 Outline of novel findings

The novel findings of the dissertation are presented below and they cover 8 topics from the 3 case studies. Results for each topic are described briefly in 2-4 bullet points highlighting the key points. The first 2 topics relate to the implementation of the HTA (current and preferred future status). The next 3 topics cover how HTA reports are prepared and evaluated. The final 3 topics outline the influence of HTA on pricing and reimbursement decisions.

The covered topics in general have an impact on each other and in an ideal setting the associations can be interpreted as; when the HTA system is well-designed and considers the need of each relevant stakeholder, when the HTA reports are prepared with high standards and when the recommendations that are based on the evaluation of the reports can effectively support policymakers to make better decisions for the society. This ideal setting highlights the importance of planning the implementation of the HTA.

In this dissertation the Ukrainian case study re-emphasizes the findings of other studies about how to establish an HTA system in a country from scratch. These findings are confirmatory to the current literature and its novelty is related specifically to Ukraine, where research for this kind of planning has never been addressed before.

The Hungarian and the Polish case studies go beyond their national relevance and provide novelty even at an international level because research with a similar approach and findings cannot be found in the scientific literature. The case studies revealed that the lack of properly implemented HTA fundamentals may create situations where 1) the HTA reports are prepared with questionable or insufficient quality not meeting the requirements and 2) the recommendations by the HTA agency do not help the decision-making process on pharmaceuticals in practice. These unwanted situations have not been addressed in the literature before.

The list of novel findings of the dissertation can be found in bullet points below.

1) The environment of HTA at the initiation point of its implementation.

Key findings from the Ukraine case study:

- When the need for improving the evidence base of healthcare decision-making is recognized at national level the implementation of HTA becomes important.
- Without comprehensive HTA-related trainings the human resource capacities that are necessary for the systematic and comprehensive approach of HTA cannot be ensured.
- Until it has no formal role in the reimbursement decisions and standardized procedures along with quality assurance tools are missing, the HTA cannot contribute to better allocation of resources at health policy level.

2) Long-term perspectives for HTA based on the input of a wide range of stakeholders.

Key findings from the Ukraine case study:

- The establishment of graduate and postgraduate educational programmes is preferred for training experts who can contribute to the preparation of HTA reports, perform high-quality appraisals and conduct HTA-related policy research.
- Ensuring sufficient public resources by policymakers committed to evidence-based decisions is considered a key success factor of the implementation.
- The locally collected evidence for the analyses in the HTA reports should receive high priority, in order to make informed, evidence-based decisions, and cost-effectiveness analyses should be considered as a key input.
- The objectivity of HTA recommendations can be facilitated by the establishment of a transparent system with academic collaborations.

3) Exploratory research on who prepares the national HTA reports of pharmaceuticals.

Key findings from the Polish case study:

- The market for preparing HTA reports of pharmaceuticals is dominated by a limited number of companies providing consultancy services, while new market entrants providing similar services face strong market entry barriers.
- The consultancy firms can accumulate significant expertise and strong working relationships with their clients (i.e. manufacturers).

4) Description of the market and the operation of HTA consultancy firms.

Key findings from the Polish case study:

- The HTA consultancy market for pharmaceuticals in Poland is estimated to be approximately 5–6 million annually.
- The consultancy firms together possess a significant amount of manpower in the field of HTA research, even when compared to the national public HTA body.
- While the preparation of HTA reports for manufactures remains the core activity of consultancy firms, they are able to expand their services considerably and provide new types of services.

5) Analysis on the extent to which HTA reports meet the official requirements.

Key findings from the Polish case study:

- Publicly available documents from the HTA body can be used to systematically explore whether the submitted HTA reports can meet the official criteria published by the local authorities.
- Published documents can also be used to further investigate whether the formal feedback by the HTA body is taken into account during the resubmission of HTA reports not meeting the criteria.
- Major concerns can be raised about the Polish HTA process which relies heavily on manufacturer submissions. These concerns are related to either the quality of the HTA reports or the expectations by the local authority.

6) Institutional characteristics of HTA that may either facilitate or restrict the decision-supporting role of a public HTA body.

Key findings from the Hungarian case study:

- Even when an HTA body fulfils its intended formal role of supporting evidence-based policy-making, it could face major institutional barriers limiting its actual impact in public reimbursement decisions.
- Low levels of transparency in HTA procedures coupled with limited organizational capacity, particularly in human resources can be the key barriers.

7) The influence of the public HTA body on other key stakeholders engaged in the reimbursement decision-making process.

Key findings from the Hungarian case study:

- The HTA body's impact is limited, when its contribution to the pricing and reimbursement process is restricted to the earliest phases without considering the potential subsequent contributions.
- The limited influence of the HTA body on the reimbursement process can be also indicated by its inferior position in relationships with other stakeholders, particularly payers and health policymakers.
- The HTA body can have however, a positive impact on the development of a broader HTA ecosystem by laying down the foundational infrastructure of evidence-based policy-making.

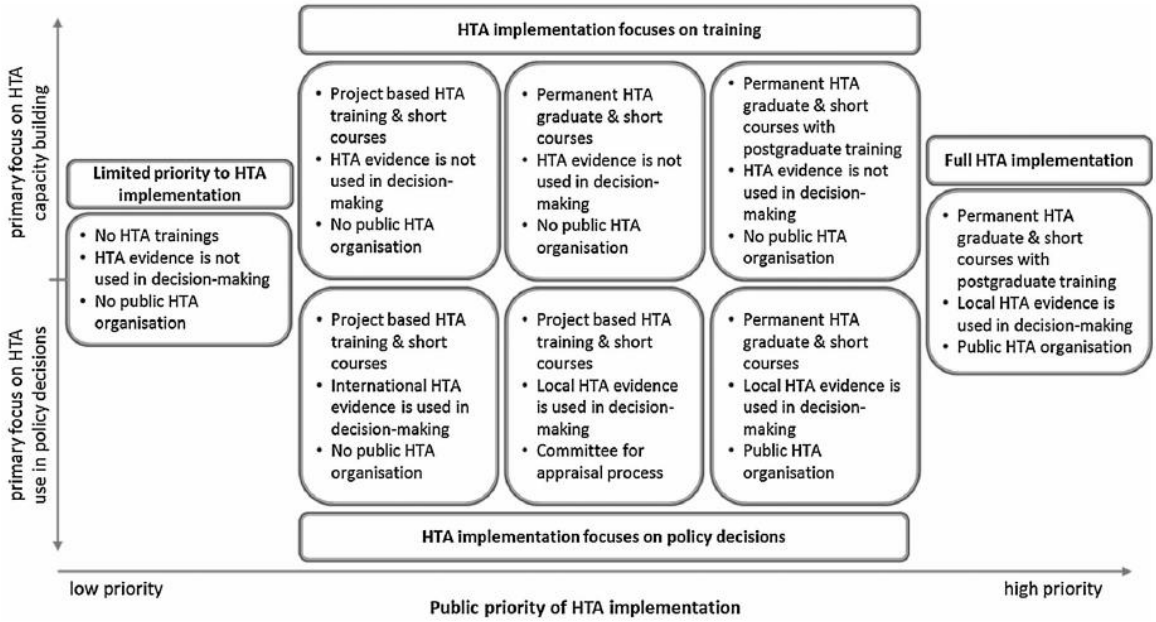
8) Judgement on whether the HTA system delivers 'good value for the money' based on the opinion of various stakeholders.

Key findings from the Hungarian case study:

- Strong skepticism may arise regarding whether the HTA body represents 'good value for the money' when its benefits are negligible for the health system.
- Despite the minimal benefits, situations might occur when none of the major stakeholders of the HTA system have sufficient interest in initiating substantive reforms.

3.2 Dissertation findings from a broader health policy context

To put the research findings into a broader health policy context and to shed light on the long-term implications of the findings, two important aspects should be considered. The first aspect is the public priority that HTA receives by the healthcare policymakers and other influential players in a given country. The second aspect is the question of whether HTA is fulfilling its purpose, as a systematic and comprehensive approach for real-world decision-making regarding healthcare resource allocations. Based on these two aspects, the general patterns and the major types of HTA implementation practices in the CEE countries can be illustrated. These are shown on Figure 2.



2. Figure: Major types of HTA implementation practices (Reference: [135])

The case studies presented in this dissertation can be placed at the two opposite ends of the figure's spectrum.

In Ukraine, there was only some project-based training for HTA capacity building and the priority of HTA implementation started to increase in 2016. Therefore they seem to have just started the process with the aim of having a full HTA implementation in the upcoming years. To this end, the Ukrainian case study provided clear perspectives and objectives for healthcare policymakers. Even though some recommendations seem to be simple or too general from an international perspective, they have never been addressed from a Ukrainian context where much-needed persuasion is necessary for healthcare policymakers to establish the HTA system with a carefully designed plan based on the needs of different stakeholders. For instance, these stakeholders clearly preferred establishing a local university program for capacity building and providing public funding for HTA purposes. However, unfortunately, several CEE countries still cannot allocate the necessary

resources to substantiate their coverage decisions with timely and scientifically solid HTA recommendations [136]. Therefore, providing sufficient human and financial resources should be on the agenda of healthcare governance, otherwise the HTA implementation might not be as successful as it could be or should be.

Through gradually improving the HTA training programs and adopting appropriate methodologies to assess technologies, the full potential of this policy tool can hopefully be achieved. The study also presented the most recent improvements that were achieved after the research was completed. These indicated that the macro-level support from healthcare policymakers was not diminishing and the aim for more effective resource allocation still had high priority on the policy agenda. Such governmental support should encourage educational trainings and wider involvement of professional institutions as it was highlighted in a recent publication [137]. Replicating our study in a few years (3-5 years) in Ukraine could validate whether the proposed perspectives and objectives were valid and efforts to take the next steps were made or not. Furthermore, replicating this study in 10 years could also check whether the HTA was fully implemented in Ukraine and whether the strategic objectives were achieved or not. It might also assess whether a period of 10 years was sufficient, underestimated or overestimated to achieve certain proposals (i.e. having a post-graduate program focusing on HTA research or using local evidence for HTA recommendations).

Hungary and Poland, however, represent the other end of the figure's spectrum, by having a fully implemented HTA system. Accordingly, when a recent study created a chronological taxonomy of HTA agencies in Europe, both countries were considered *mainstreamers*. As described before, this second wave of HTA agencies following the *forerunners* relates to the mid-2000s when the idea of an institution of public interest galvanized by HTA as a tool to aid coverage decision-making made its way into mainstream health-policy in Europe [22]. The investigation of these countries required different perspectives compared to those where the public priority on HTA was just emerging (i.e. in Ukraine). In these cases the focal point of the research was on whether HTA is fulfilling its purpose, namely to be a tool for real-world decision-making that leads to better resource allocation decisions.

This question was particularly answered by the Hungarian case study that showed how the work of the Hungarian HTA Department was neglected in actual policy decisions. This limited influence of HTA was explained by the lack of transparency of HTA procedures, the limited availability of useful data, the inappropriate institutional design, the human resource constrains (i.e. brain drain to the private sector) and the lack of interest by high-ranking healthcare policymakers and politicians. An interesting finding of this study was that these problems were visible for all relevant stakeholder groups. Most importantly, this gave strong validity to the findings. Furthermore, we also found that

unfortunately none of the influential stakeholders seemed to have sufficient interest in changing the current system. The study explained in details how private sector players (i.e. manufacturers and consulting companies) as well as public sector players (i.e. national payer, ministry of health, academic sector, and patient organizations) have either disinterest or limited opportunity to reform the HTA system. Nonetheless, with our study, these issues were put into the public domain and will hopefully raise attention to strengthen the formal role of the HTA Department in pricing and reimbursement decisions. Future studies should investigate whether Hungary is opting to move in this direction or rather maintain the status quo by exploring the positions of key stakeholders towards the benefits of having an HTA system in the upcoming years. Ideally this could be investigated after a relatively short period of time (i.e. in 3-5 years). Furthermore, future studies should also explore whether the impact of different identified factors that led to the current situation were mitigated. These would be clear signs of striving for a more impactful HTA system in Hungary.

Our investigation of the other mature HTA system in Poland focused on the preparation of HTA reports in the HTA process. This research can be considered highly unique with its innovative approach, since our study provided the first exploratory overview on how manufacturers prepare their submitted documents (i.e. HTA reports). First of all, we showed that in almost all cases this work was outsourced to specific consultant companies in Poland who collectively constituted the HTA consultancy market. This was explored through the market structure, market size, evolution of key market players and their activities and services. We showed that six consultancy companies with significant market shares dominated the market and they all had a broad service portfolio related to the preparation of HTA reports. Secondly, we linked over 200 HTA reports with appraisal documents published by the Polish HTA agency, and pointed out that the majority of the HTA reports had not met the official requirements published by the Ministry of Health. When the HTA reports and their appropriateness were analysed according to the identified consultancy companies, we found that all of them performed poorly in this respect. Besides revealing this system level anomaly, in the paper we also pointed out potential explanations that should be validated in the future including poorly defined requirements by the Ministry of Health, the misuse of requirements by the HTA body or the misunderstanding of requirements by consultant companies. Although future research should specifically define these underlying reasons for the problem, the magnitude of the issue points toward a more general concern, which might challenge the common practice of heavily relying on manufacturers' submissions in the HTA process. This directly influences the actual benefit that an HTA system might deliver. The problem might also lead to a more extensive use of other

alternative solutions to support patient access. These will also be further discussed in a chapter below (Alternative reimbursement schemes of pharmaceuticals).

When considering the generalizability of this dissertation, the topics discussed and the issues raised in the three case studies almost fully overlap with the top 10 HTA challenges identified by the International Network of Agencies for Health Technology Assessment [138]:

- No. 1: Scarcity of human resources to conduct HTA;
- No. 2: Need to design better approaches to involve stakeholders in HTA;
- No. 3: Pressure to develop existing HTA methods and processes further;
- No. 4: Inadequate data management and the declining quality and validity of evidence;
- No. 5: Fragmented health systems and shifting political contexts;
- No. 6: Enlarged scope of HTA and increased range of demands placed on HTA agencies;
- No. 7: Increasing the impact and influence of HTA;
- No. 8: Increasing demand for HTA and pressure for rapid assessments;
- No. 9: Translating HTA into policy and practice;
- No. 10: Insufficient financial resourcing of HTA.

This list provides a strong justification for the importance of the topics that were investigated, not only for the 3 selected countries, but generally for any HTA system.

3.3 Beyond fragmented HTA: Global perspectives and initiatives

The independent and fragmented nature of HTA implementation mainly at the national level has a valid basis. This means that HTA institutions and procedures often function independently, with little to no coordination of services and with limited cooperation across organizations [139]. This dissertation reflects on this observation seeing that different research questions were considered important for different countries. Furthermore, the opportunities to explore the HTA implementation and its impact are different for instance due to the limited publicly available information. However, many initiatives point towards mitigating such fragmentation which also prove there is a broader picture of networking among HTA organizations [139]. This is important to discuss within the scope of this dissertation. These networks are centered around international professional organizations bringing together the different stakeholders of HTA from all over the world such as the International Society for Pharmacoeconomics and Outcomes Research, International Network of Agencies for Health Technology Assessment or the Health Technology

Assessment International. These are all working on sharing best practices and harmonizing efforts in the field of HTA.

Another important cross-country imitative is the EU funded European Network for Health Technology Assessment (EUnetHTA), which particularly focuses on strengthening the collaboration among HTA agencies across Europe by providing tools and recommendations to assess health technologies [140]. The network collaborates with over 30 countries and attempts to improve the comparability, transferability and overall usefulness of economic evaluations performed in Europe. Nevertheless, there are important methodological issues that need country-specific investigation [141]. Therefore, the practical benefits that EUnetHTA can provide and their actual impact to the collaborating countries still need to be defined.

Besides EUnetHTA, another closely related EU level initiative represents the emerging concept of the global HTA perspective. In January 2018 the European Commission published a Proposal for a Regulation on HTA: "Proposal for a Regulation on health technology assessment and amending Directive 2011/24/EU" [142]. It was a welcomed initiative as it was considered to improve collaboration, reduce duplication and improve efficiency. There were however, a number of concerns including its legal basis, the establishment of a single managing authority, the preservation of national jurisdiction over HTA decision-making and the voluntary/mandatory uptake of joint assessments by Member States [143]. It is important to note that the initiative would only focus on one element of HTA and not with the entire scope of HTA. It promotes a joint relative effectiveness assessment (REA) of pharmaceuticals and certain types of medical devices. Accordingly, the scope of this European collaboration focuses on the centralized clinical assessment part of HTA, while the economic value judgement and the contextualization part (including the critical appraisal and the applied decision rule) would still remain a national competence [144]. Even for this specific narrow scope, further methodological questions can be raised which focus on what constitutes a clinical value; how to ensure the quality of the generated evidence; what the use of real-world evidence is in joint assessments; how medical devices should be assessed considering their specific features that diverge from pharmaceuticals; and how to ensure consistency in REA interpretation [144].

The EU level cooperation is a complex issue and it impacts several stakeholder groups with different views and interests. A recent publication categorized them based on their former actions [145]. The most supportive stakeholders to facilitate the collaborations were the European Commission and HTA experts. A more cautious support can be observed from the perspective of the European Parliament, the pharmaceutical industry, EU-level patient associations and clinicians. The key opponents are some of the member states and the national healthcare payers, and also the medical

device industry [145]. It is important that the arguments of opponents be acknowledged, even by strong supporters, in order to carefully move all concerned players toward integration.

In conclusion, it is clear that in the past decades many initiatives attempted to at least partially overcome the fragmented operation of HTA systems. These were successful in scientific collaborations bringing together HTA experts and other relevant stakeholders. It can be assumed that these have translated into methodological improvements, effective communication within stakeholders and across countries and eventually contribute to making better decisions in healthcare. However, as the discussion and the issues around the specific EU-level legislation shows, much of the HTA work still belongs to national organizations aiming to support national level decision-making. This conclusion provides justification on why this dissertation worked with country-specific case studies.

3.4 Beyond the HTA of pharmaceuticals: Evaluation of non-pharmaceutical technologies

In many countries the use of HTA is limited to the comprehensive evaluation of pharmaceuticals, therefore, it can only contribute to the pricing and reimbursement decisions of medicines. Likewise, the case studies presented in the dissertation mainly focused on pharmaceuticals while less attention was devoted to other healthcare technologies. Although in Hungary the HTA Department appraises simple medical devices such as hearing aids or mobility aids, the more complex medical procedures or devices do not require any standardized evaluations by the HTA body. In Poland the HTA body started consultation on developing HTA guidelines for medical devices, however this process was only initiated in July, 2019 [146].

The pricing and reimbursement of non-pharmaceutical technologies poses an important trade-off question. The availability of the technology early on may appear attractive as it can lead to rapid clinical uptake and substantial benefit; however, decisions about the use of non-pharmaceutical technologies when the evidence base is less mature can carry substantial risks. Uncertainty about their efficacy and the learning curve to achieve the desired benefits can result in adverse consequences on patient outcomes and can lead to an ineffective use of healthcare resources [147]. Rapid approval of new technologies can also result in disincentive for manufacturers to invest in further research and data collection which could reduce the uncertainties [148]. This dilemma is very similar to the issues around reimbursing innovative pharmaceuticals (e.g. gene therapies).

Out of the different types of non-pharmaceutical healthcare technologies, medical devices have received some attention lately from the perspective of HTA in the scientific literature. These are

defined as “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination (…) to be used for human beings for the purpose of diagnosis, prevention, treatment, monitoring or alleviation of disease” [149]. It is commonly argued that medical devices require a more flexible HTA approach compared to pharmaceuticals due to the greater variety of technologies and their very different nature of complexities [150]. While for some devices a very simplified assessment can be sufficient, others need to be assessed through a full evaluation of safety, efficacy, effectiveness and economic impact [151]. Still in most countries, except for pharmaceuticals, there is no specific guidelines on how to conduct the clinical and economic analyses required for the decision-making process. A recently published systematic literature review identified 22 published official HTA guidance documents from 41 European countries and among these there were only 4 cases (England, France, the Netherlands, and Sweden) where there was a dedicated chapter or a separate document referring to medical devices [152]. Similarly, lack of standardized procedures for medical devices were found in a study investigating the HTA bodies of non-EU member states [153]. Although this latter study did find some organizational developments by HTA agencies that were related to the allocation of specific staff to the assessment of medical devices or the setup of a completely separate program within the agency for the evaluation.

The lack of emphasis on a comprehensive evaluation of medical devices by HTA has to be linked back to their specific regulatory requirements coupled with the lack of evidence for decision-making compared to pharmaceuticals. Traditionally, there have been lower requirements for the licensing of devices which mainly focus on safety and performance and less on clinical effectiveness. The lower requirements also result in more frequent problems of methodological issues such as selection bias and confounding results in the clinical evidence stemming from the lack of opportunity to conduct randomized controlled trials due to different constrains [154]. Furthermore, unlike most of the pharmaceuticals, devices often undergo incremental evolution over time for instance by “fast-followers” that can rapidly change the original technology. The pricing procedure of medical devices varies greatly and is often more dynamic due to the market entry of new device products or the ways in which procurement takes place [154]. The standardization of any procedure is even further complicated by the fact that currently there is no single harmonized international classification for devices, which makes it very difficult to conduct research studies across countries [155].

Solutions for these issues were proposed mainly from a clinical evidence point of view by focusing on changing the requirements for clinical studies in the pre-marketing phase, clarifying and explicitly defining the criteria for the substantial equivalence in decision-making and strengthening the

controls for post-market research [156]. Although these recommendations are straightforward, the implementation of any specific change in the HTA procedures takes time to be adopted and requires public resources dedicated to these issues. As one study highlighted, many countries in Europe and also the US introduced policies to provide temporary coverage and reimbursement for promising medical devices while additional evidence of value is generated. However, further actions are still greatly needed for the development of new methods to evaluate value of devices and link the evidence of value to reimbursement policy [157]. Most countries are still struggling to find the right balance between pre-market and post-market controls, which on one hand would give sufficient data for a comprehensive evaluation before the decision and, on the other hand, would ensure effective re-evaluation after approval [158]. Importantly, it must be noted that the engagement of the public sector is not enough, the manufacturers' support and their collaborative behavior is also essential [159]. Until this integration is achieved, it is difficult to expect that HTA bodies and other healthcare policymakers can provide recommendations with confidence on the pricing and reimbursement of non-pharmaceutical health technologies such as medical devices [160]. Furthermore, unlike pharmaceuticals, it is very challenging to design and conduct in-depth HTA research.

3.5 Beyond HTA in health policy: Emerging social science literature

The research on HTA is mainly concerned with health policy and health economics disciplines. Experts from these fields have an obvious disciplinary claim to HTA seeing that they are the ones proposing the regulatory framework (i.e. for legislation and organizational structure) and are developing the necessary methodologies for quantifying and comparing the value of health technologies. They also have a direct interest in understanding how their science is applied in practice (i.e. in appraisals of the analyses and in funding decisions). Therefore, the aim of health policy analyses is primarily descriptive: to document and compare what methods are considered for HTA in particular jurisdictions, how they are used in the practice of decision-making and in some cases how these findings can be compared internationally [161].

Social scientists from other fields, however, have been showing increasing interest in HTA as well. Researchers of social science have become interested in attempting to unpack the social meaning of HTA [162]. One of our recent studies presented a review on studies from specific social science disciplines such as sociology, political science, and their interdisciplinary subfields such as science and technology studies. That study reviewed common research questions, methods, and findings

from this field [161] and found that the emerging social scientific literature on HTA can be arranged into three of the most common research themes: 1) the drivers of the establishment and design of HTA bodies; 2) the effects of institutionalized HTA on pricing and reimbursement decisions, medical practice, and the broader society; and 3) the social and political influences on HTA decisions [161].

The introduction of such unique views broadens the perspective of HTA implementation. Social science disciplines such as sociology or political science can underscore how healthcare governance is highly affected by ideologies, cultures, norms and politics. These should not be ignored in HTA research [163]. For instance a recent study showed that social values and institutional context may play a role in shaping how economic evaluations, as a specific component of HTA, are used in healthcare decision-making [164]. Another example indicated that poor healthcare governance at the highest level of decision-making is suspected to be the main reason for the lack of interest in considering economic evaluations for decisions [165]. Support from social science is also essential to better understand how to deal with the ethical issues surrounding technology assessments. Although healthcare is a moral endeavor and most technologies pose complex moral challenges, HTA reports rarely include ethical analyses, and there is little agreement on methods for integrating ethics as part of the assessment [166]. Fundamental methodological questions such as the acceptance of quality-adjusted life-year (QALY) as a measure of health gain can also be better understood by taking a broader perspective across different social disciplines [167].

Among many other examples in the literature, the Hungarian case study in this dissertation also took a broader societal perspective on HTA by investigating the effect of the institutional design and addressing key players' interests in reforming HTA. The broad perspective was needed to look beyond the formal role of HTA and investigate its perceived influence on the pricing and reimbursement decisions. From this perspective a key result was the identification of the risk of creating a powerless institution that faces a reform stalemate and acts as a tick-the-box bureaucratic exercise. In such a case the public institution only has marginal benefits for the society.

Some findings of the Polish case study were also interpreted from a broad social science perspective. The observation that HTA consultant companies were established by those influential experts who used to work as public decision-makers or at least contributed to the methodological work of the AHTAPol (e.g. guideline development) may be problematic, especially in light of the widely documented revolving door effect between the commercial and the public sectors. When the chance for conflicts of interest arise, the situations should be investigated from a social science approach.

The incorporation of social science disciplines and their approach can also contribute to the argument that HTA is not a magic button that immediately solves all resource allocation problems in healthcare [168]. To pose realistic expectations on HTA implementation, it is recommended that in the future any traditional HTA expertise be coupled with the unique perspective of social science. These collaborations could address some of the so far unanswered questions around HTA, such as what HTA is actually good for; what its real-word benefits are for instance in terms of resource allocation or population health; or what the broader social implications could be [26, 27]?

From a methodological point of view, social science studies of HTA tend to emphasize the in-depth investigation of issues and tend to study crucial single cases or adopt a small-number study design. Although these small-number study designs may, in aggregate, help identify broad patterns, their ability to provide generalizable answers remains limited by the dynamically changing nature of HTA systems [161]. On the other hand, in-depth analyses with such study designs can open up the door for very specific improvements and provide strategic recommendations that target key problems. As discussed earlier, the approach followed in this current dissertation had very similar advantages and disadvantages.

3.6 Beyond HTA: Alternative reimbursement schemes

HTA is characterized by a relatively standardized process of transparent evaluation, which can support the pricing and reimbursement decisions of health technologies for specific target populations. Therefore, in principle the HTA assessment is unavoidable before the relevant patient populations get access to their therapies. However, there are situations that pose specific challenges related to the price, effectiveness or target population of the treatment. One well-known example is the case of orphan drugs, where exceedingly high treatment costs combined with small patient populations typically generate prices that exceed standard cost-effectiveness thresholds [169]. Another difficult situation for policymakers concerns medicines which are expensive but highly clinically effective where there is a very high number of patients who should have access to the treatment. In this case the budgetary impact decision becomes very challenging [170]. Among many other examples, it is expected that often standard HTA procedures may have difficulties accommodating all potential issues related to the costs and the benefits of new technologies, particularly regarding innovative medicines.

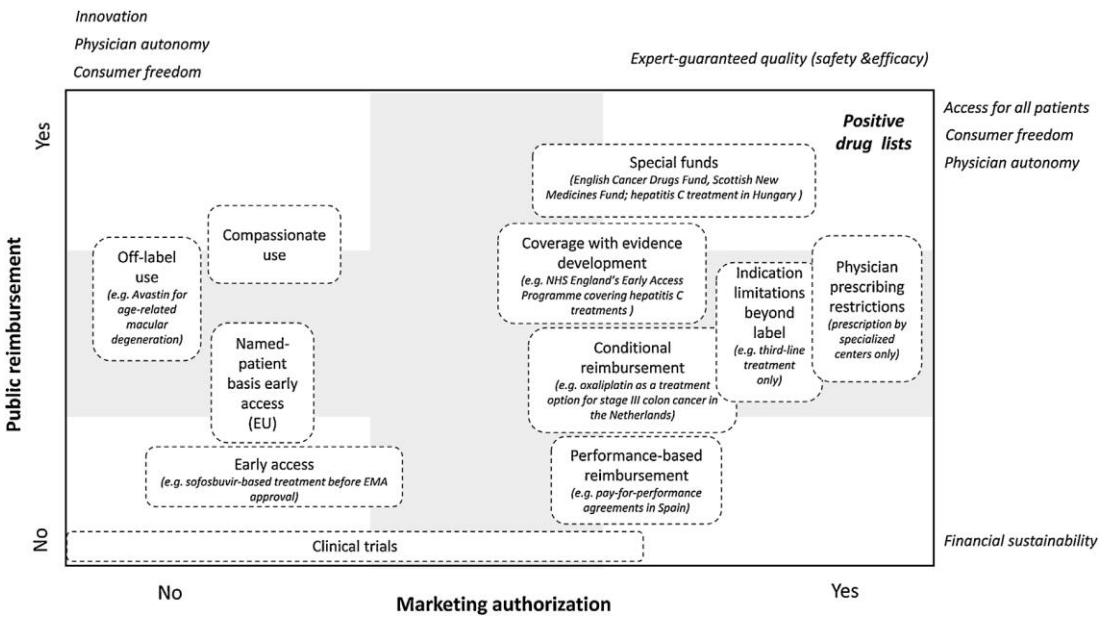
In such specific situations healthcare policymakers need to look beyond the concept of HTA and should apply a variety of formal arrangements to ensure patient access. Via these non-standard

routes new drugs can be made accessible to the patients, often through individual arrangements, even if the evaluation of a complex HTA report is delayed or when the HTA agency does not recommend the reimbursement. In a recent article these routes were called "alternative access schemes". In principle these are any formal programs that seek to provide patients with access to treatment that are not available to them via the main route of publicly funded medicines [171].

In our recent paper, we conducted a purposive review of existing literature and policy practices, and we identified the following types of alternative drug access schemes within our focus mainly on EU countries:

- *Early access programs* in the process of, or shortly after obtaining marketing authorization.
- *Compassionate use* of investigational medicines in development.
- *Named-patient basis early access* designated to decisions made for individual patients.
- *Off-label use*; drugs intentionally used for a medical purpose not in accordance with the authorized product information.
- *Conditional coverage* accompanied by evidence development, with conditional reimbursement and performance-based reimbursement.
- *Special funds* devoted to specific diseases.
- *Restrictions* on physician or provider specializations to prescribe treatment as well as limiting treatments' indication.

Our paper also introduced a tentative typology of the universe of alternative access schemes illustrated in Figure 3 below based on two perspectives; marketing authorization (regulation) and reimbursement (redistribution). The various alternative access schemes listed above can be positioned on the two-dimensional matrix in the figure, creating the typology of schemes. The starting point is the countries' positive drug list in the upper right corner, which includes treatments available to everyone who needs or demands them, and are fully authorized by the regulator. Diagonally opposite them are drugs in clinical trials, which are not funding schemes in principle, but they do provide some access to treatment to a limited number of patients, in some cases even after the drug has received marketing authorization [172]. Surely these schemes are dealing with complex, multidimensional policy trade-offs between the principles of patient freedom of choice, clinician autonomy, encouragement of innovation, evidence-informed decisions on safety and quality, access to treatment, and financial sustainability including marketing authorization and reimbursement decisions. Furthermore, they are also jurisdiction-dependent, therefore in the next paragraphs two specific examples (Slovakia and UK) representing two different regions of Europe will be discussed in more detail.



3. Figure: The universe of alternative access schemes in Europe (Reference [171])

The above-mentioned typology was specifically tested in a real case. Correspondingly, one of our recent papers investigated the Slovakian "extraordinary reimbursement regime" (ERR), which enables granting access to individual patients for drugs that were not recommended by the traditional HTA system for reimbursement and were actually denied any reimbursement status by the decision-makers [173]. We conducted interviews with local stakeholders and data analyses on a dataset that was requested by the Slovak Ministry of Health. Slovakia was a good example for such a study given that its reimbursement system has gone through several major reforms in recent years which have dramatically affected the sustainability of their pharmaceutical budget [174].

Our most interesting finding from this study was that, rather than providing a coherent funding scheme for a defined group of patients or drugs, the emerging budget of ERR encompassed different cases left behind by ordinary reimbursement rules, resulting in a complex situation with various alternative access schemes all placed into one regime. We identified the following alternative schemes: first, the ERR was used as a "backdoor market access" chiefly for new expensive drugs, circumventing Slovakia's strict rules on pricing and reimbursement. Second, it served as a compassionate use scheme for unlicensed investigational drugs, as well as a "legacy drugs fund" for old drugs no longer authorized on the Slovak market. Third, and in financial terms most importantly, it acted as a disease-specific fund for cancer and orphan drugs, analogous to the English Cancer Drugs Fund. Finally, the ERR overlapped with the positive drug list, indicative of off-label and "off-indication" use [173].

The study concluded that although the regime was used to improve equity between patient groups by granting patient access, the mixture of different schemes and the lack of criteria for making individual decisions created concerns over equity.

Unlike the Slovakian example, the Cancer Drugs Fund in the UK had a clearly defined scope. It was established in 2010 by the UK government to provide patients with access to cancer drugs not available, because the drugs had not been appraised, were in the process of being appraised, or had been appraised but not recommended by the HTA body (NICE) [175]. The budget started with £50 million per year, however, the costs of maintaining the fund rapidly increased reaching £340 million in 2015/2016. Despite having a clear scope for the fund, studies have raised concerns whether the fund can deliver meaningful value to patients or to the society. These concerns were mainly centered on the lack of empirical evidence and the limited health technology appraisal processes [175]. Furthermore, it has been debated whether such a large investment in pharmaceuticals with great uncertainty around the cost-benefit ratio is the most effective method to improve cancer care and survival in the UK and whether focusing on other aspects of diagnosis and care may improve patient survival more significantly [176].

It should be acknowledged that quantifying the actual impact of any regulatory instrument ensuring alternative or early market access for pharmaceuticals is complex, as it depends on several factors [177]. This challenge is similar to the quantification of the HTA's impact.

4. Conclusion

The use of HTA has been increasing worldwide and its potential for improving healthcare decision-making is widely acknowledged. The standardized methodology and transparent procedures of HTA ideally should lead to a more rational and targeted investment of available resources via reimbursing cost-effective and affordable medicines and other healthcare technologies. However, the implementation of an impactful HTA system is very resource intensive, therefore ensuring sufficient human and financial resources is a key success factor along with a supportive institutional environment.

In the current scientific literature the HTA implementation in CEE countries is slightly overlooked and there is a lack of in-depth analysis particularly, compared to higher income Western European countries. The few studies that were conducted in CEE show that there is a high level of heterogeneity related to the development of HTA structures, methods used and processes followed. Therefore, this doctoral thesis aimed to investigate the implementation of HTA in CEE countries from different aspects of health policy. In this dissertation 3 sets of research questions were defined for 3 CEE countries reflecting on key issues of HTA implementation for which currently the evidence is limited.

The first study focused on Ukraine and answered questions regarding how to establish an HTA system in a country where HTA formerly was not used before. It summarized the opinion of local stakeholders and identified the strategic directions that should be followed in the country. Specific recommendations were given for capacity building, facilitation of generating and using local data for evaluations, and for taking a multi-stakeholder approach in the HTA process such as the involvement of academic partners to support HTA-related research. The study also addressed the very recent improvements in the country and identified opportunities for learning from other countries.

The second study focused on Poland and answered questions concerning those who are involved in the preparation of the HTA reports of pharmaceuticals intended to be used for reimbursement decisions. This unique study addressed HTA consultancy firms who are private companies that generate or synthesize evidence and input for funding decisions. We found a highly concentrated market with companies who developed a broad service portfolio related to the preparation of HTA reports. The study showed that a great majority of HTA reports prepared by consultancies did not meet the official minimum quality requirements, which raises important policy issues about the current regulations of HTA.

The third study focused on Hungary and answered questions regarding how and to what extent HTA is utilized for actual decision-making in practice. The study showed that the Hungarian HTA body fulfilled its formal role defined in the legislation, however, its potential for supporting evidence-based decision-making in practice was very limited. The HTA body's influence was reported to be constrained by other stakeholders such as the national payer organization and policy-makers, as well as its own limited organisational capacity. Furthermore, the work of the HTA body was characterized by a low level of transparency and lack of stakeholder engagement. There was significant scepticism as to whether the HTA process can make a real impact under its current operational form.

While the Ukrainian case study re-emphasizes the results of studies conducted in other countries about how to establish an HTA system in a country, the other two case studies go beyond their national relevance and provide novelty even at an international level because studies with similar approaches and findings cannot be found in the scientific literature.

Since the case studies were specifically targeted to the investigated countries their scope was limited from many aspects. Therefore, the dissertation also provided detailed descriptions for each of its key limitations. The global perspectives of HTA chapter discussed the initiatives to overcome the national scope of HTA but also explained the challenges that lead to the fragmented operation of HTA systems. The chapter on the evaluation of non-pharmaceutical technologies explained the emerging scientific research related to the evaluation of medical devices. It also highlighted the specific issues that limit the applicability of HTA in this area (i.e. finding the right balance between pre-market and post-market regulations). The chapter on HTA research from other social science fields showed how other disciplines could complement the health policy research by responding to the so far unanswered questions on HTA, such as what the broader social implications of HTA are. Finally, our chapter on alternative reimbursement schemes explained that relying solely on HTA cannot deliver a prompt solution to all allocation problems. Therefore, healthcare policymakers are trying to find a balance between employing more standardized evidence-based decision-making supported by HTA and alternative access schemes without HTA input in granting patient access to high-cost pharmaceuticals while ensuring affordability.

List of scientific publications related to the dissertation

First-authored scientific papers published in peer-reviewed journals used as the basis for this dissertation:

- **Csanádi M**, Inotai A, Oleshchuk O, Lebega O, Alexandra B, Piniazhko O, Németh B, Kaló Z. *Current status and future perspectives of health technology assessment implementation in Ukraine.* International Journal of Technology Assessment in Health Care. 2019. **35**(5): 393-400
- **Csanádi M**, Ozierański P, Löblová O, King L, Kaló Z, Botz L. *Shedding light on the HTA consultancy market: Insights from Poland*. Health Policy. 2019. **123**: 1237–1243
- **Csanádi M**, Löblová O, Ozierański P, Harsányi A, Kaló Z, McKee M, King L. *When health technology assessment is confidential and experts have no power: the case of Hungary*. Health Econ Policy Law. 2019. **14**(2):162-181.

First-authored or co-authored scientific papers published in peer-reviewed journals used for the introduction and the discussion parts of this dissertation.

- **Csanádi M**, Kaló Z, Prins CPJ, Grélinger E, Menczelné Kiss A, Fricke FU, Fuksa L, Tesar T, Manova M, Lorenzovici L, Vokó L, Garrison LP. *The implications of external price referencing on pharmaceutical list prices in Europe.* Health Policy and Technology. 2018. **7**(3): 243-250.
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