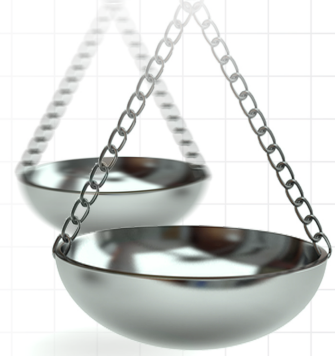
Research Article



Journal of Comparative Effectiveness Research

Adoption of trastuzumab for breast cancer in four emerging countries in the use of health technology assessment: a case study

Aim: To describe processes for the adoption of trastuzumab in four countries in the use of health technology assessment (HTA): Poland, Albania, Brazil and Colombia. **Materials & methods:** Mixed methods were used for collection and triangulation of data. Data were examined following a conceptual framework connecting HTA process steps and key principles. **Results:** Trastuzumab was generally assessed following well-structured HTA processes. Nonetheless, areas of improvement were detected in terms of transparency and inclusiveness, as well as in methods used. The extent to which different criteria influenced decisions was unclear. **Conclusion:** This study covers an area in which information may not always be available, and sets the example for emerging countries interested in HTA. Further studies to gain a better understanding on decision-making across settings are warranted.

First draft submitted: 28 December 2015; Accepted for publication: 29 March 2016; Published online: 21 June 2016

Keywords: central, eastern and south eastern Europe • comparative effectiveness research • emerging countries • health technology assessment • Latin America and the Caribbean • oncology • trastuzumab

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Cancer is a leading cause of morbidity and mortality worldwide, with increasing incidences in all countries regardless of their economic status [1]. It is estimated that in 2012 there were 14 million new cases of cancer [1], and 8.2 million related deaths [2]. In the case of breast cancer, one of the most frequently diagnosed in women, incidence rates vary greatly worldwide, ranged between 19.3 and 89.7 per 100 000 women, and in most of the developing regions the incidence rates are below 40 per 100,000 [3], representing 6.35% of all cancer-related deaths [2].

Trastuzumab is a humanized monoclonal antibody used to block the action of the *HER2* oncogene in those cancers classified as *HER2* positive [4]. In these cases, the disease typically has a worse prognosis [5]. Trastuzumab was first approved in 1998, and the NICE approved its use in a guideline published in 2006, "given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage *HER2*-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)" [6].

In 2012, Moja *et al.* [7] performed a meta-analysis with 11,991 patients, reporting that the use of this drug represents a statistically significant improvement in overall survival and disease-free survival. As adverse events, an increased risk in congestive heart failure and a decline in left ventricular ejection fraction were detected.

Trastuzumab has been recently included in the WHO list of essential medicines [8] and is covered and reimbursed in public health benefit plans in many countries [9–11]. Assessment and decision-making systems in each country have context-specific characteristics. Reimbursement decision-making is based on clini-

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cal, economic and ethical issues around which health technology assessment (HTA) processes for medicines are built. The processes typically take account of aspects relating to the effectiveness and safety of medicines, as well as value for money and/or budget impact. In particular, anticancer drugs have received special attention from HTA agencies, where other criteria other than effectiveness and cost–effectiveness typically come into play in the final reimbursement decision [10]. Moreover, the value of innovation and the constraints imposed by uncertainties are becoming important factors to consider [12,13].

Despite the extensive literature defining an ideal HTA system [12,13], there is wide variability among countries and HTA agencies regarding processes and decision-making. Thus, for the purpose of illustrating the particular case of trastuzumab, the research team embarked on the development of a multicountry case study, including a selection of countries considered emerging settings in terms of HTA experience and implementation.

Accordingly, this case study aims to describe the HTA processes and methods used in the adoption of an essential cancer drug such as trastuzumab in a selection of emerging countries in the use of HTA from the central, eastern and south eastern Europe (CESEE) and Latin America and the Caribbean (LAC) regions. The ultimate goal of this paper is to draw useful lessons for settings with evolving or newly-established HTA systems.

Materials & methods

The case study approach is a research design that allows explaining the process of and reasons behind health policy development, such as those relating to HTA [14,15]. Since the goal of this paper was to capture a variety of HTA systems among the regions of interest, a multicountry collective case study was designed.

In order to collect data in the countries selected, a survey of key informants involved in the HTA for trastuzumab in their respective countries was designed. A review of relevant HTA literature was conducted to identify good HTA practices, concepts to be used, previous HTA surveys and key informants. The questionnaire was developed in an iterative process, and pilot tested with HTA experts from different countries and organizations (e.g., for format, structure, formulation of questions and answer options). The questionnaire was based on key principles for HTA [16–18], with 39 questions divided into four themes, as follows: (1) structure of HTA programs; (2) methods of HTA; (3) processes for conduct of HTA; and (4) use of HTAs in decision-making, implementation and monitoring. The instrument (full questionnaire available upon request) included both dichotomous and multiple choice questions, as well as a number of open questions to allow for clarification and explanation of responses (see summary table of questionnaire in Supplementary Table 1).

Key informants involved in the assessment of trastuzumab from the selected countries were invited to complete the survey via email in July 2014, and followed up by email and telephone until survey completion (January 2015). We contacted 32 organizations or people related with HTA in different countries, with only four countries responding and accepting to participate. The data gathered from survey responses were examined following a content analysis approach. A conceptual framework aiming to connect the typical steps of an HTA process (topic selection, scoping, assessment, appraisal, decision-making, dissemination, implementation and monitoring of impact) with the key principles for HTA (e.g., transparency, inclusiveness, relevance) [16,17] was employed. Once the survey responses were compiled and analyzed, results were contrasted with available assessment/appraisal reports on the different websites [19–22], a previous output of the ADVANCE HTA project [23], as well as clarifications provided by the country experts involved in the respective HTA processes.

Results

The findings of the trastuzumab case study are described according to the typical steps of an HTA process. It is important to highlight that the HTA of trastuzumab was conducted at the national level in Poland (Agency for Health Technology Assessment and Tariff System [AOTMiT]), Colombia (Institute for Health Technology Assessment [IETS]) and Brazil (National Committee for Technology Incorporation [CONITEC]), whereas the process occurred at the hospital level in Albania (Tirana University Hospital Centre [QSUT] Nene Tereza). Although the steps followed in the latter case were less well defined, parallelisms have been drawn for analysis purposes. Table 1 shows the main bodies that constitute the HTA systems described.

Topic selection

The Colombian system involved the widest range of stakeholders in topic selection (e.g., patient groups, clinical experts, manufacturers), while in the Albanian hospital and in Poland clinicians and manufacturers were involved, respectively. In Brazil, the law establishes that all requests made by stakeholders (in this case, Ministry of Health and manufacturer) should be considered if they meet the criteria of efficacy, safety, cost–effectiveness and budget impact. Table 2 shows the variety of criteria for prioritization employed across settings. In addition, the drug was not considered an emerging technology in any of the settings.

Table 1. Main bodies conforming the health technology assessment system by setting and final decision on trastuzumab.

Setting	Assessment body	Appraisal body	Decision-making body	Final decision
Albania	Team of oncologists and pharmacists	DTC/MC	Hospital board	Favorable for the adjuvant treatment of patients with early-stage *HER2*-positive breast cancer, with no restrictions
Colombia	INC + IETS	IETS	MoH	Favorable for early- (and late-) stage breast cancer with recommendations and restrictions relating to dosage schedule, administration, duration of treatment, women's health status in relation to left ventricular ejection fraction, periodic cardiac functional assessment and forced expiratory volume
Brazil	CONITEC	CONITEC	MoH (SCTIE)	Favorable with restrictions or comments: price reduction; requirement for molecular examination (FISH or CISH test) for HER2 status confirmation in tumors with immunohistochemical expression yielding two to three crosses; availability of different pharmaceutical presentations; monitoring of clinical results of the use of the product, to be used only in oncology-specialty hospitals, and compliance with MoH's diagnostic and therapeutic guidelines
Poland	AOTMiT†	TC	MoH	Favorable for early (late-stage and metastatic) breast cancer with recommendations according to routes of administration. Drugs financed under 'drug programs' are free for patients, but inclusion/exclusion criteria are described in detail and a committee of clinicians makes decisions on the inclusion of individual patients

†Reviews and validates manufacturer's dossier.
AOMiT Agency for Health Technology Assessment and Pricing is an institution operating under the law on healthcare services financed from public funds and the Act of 12 May 2011 on reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices. In terms of implementation of tasks related to the assessment of healthcare services, it operates on behalf of the MoH. Also, the agency issues opinions on draft ministerial and government health programs, as well as provides information and training in the field of health technology assessment in Poland and in the world. CONITEC National Committee for Technology Incorporation in the Unified Health System was created in 2008 and is coordinated by the Department of Management and Incorporation of Health Technologies of the MoH. It makes recommendations to the SCTIE on whether to incorporate a health technology in the health system or not. IETS Institute for Health Technology Assessment, created in 2011 as a not-for-profit, public-private organization that includes other public agencies and academic institutions, scientific societies and the Colombian Academy of Medicine. The MoH and Social Protection is a member of the IETS.
AOMiT: Agencji Oceny Technologii Medycznych i Taryfikacji; CONITEC: Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde: SUS; CISH: Chromogenic *in situ* hybridization; DTC/MC: Drugs and Therapeutics Committee or Medical Commission; IETS: Instituto de Evaluación Tecnológica en Salud; INC: Instituto Nacional de Cancerología; MoH: Ministry of Health; SCTIE: Secretariat of Science, Technology and Strategic Supplies; TC: Transparency council.

Scoping

All settings performed a scoping exercise to frame the aspects that the assessment of trastuzumab would include. Although scoping appeared to be less detailed in the case of the Albanian hospital, relevant information was included throughout the assessment report (Table 2). Indications evaluated differed across settings, ranging from early-stage through locally advanced to metastatic breast cancer, reflecting different stages of the technology life cycle (2008–2014). Patients' views as well as those of experts were taken into account in the Brazilian case.

Assessment

The evaluation of trastuzumab was conducted internally by hospital clinicians in Albania and by CONITEC in Brazil, whereas external studies formed the basis of the assessments in the rest of the selected countries. Manufacturers and clinicians were also involved in the validation of the HTA study in Brazil. In Poland, AOTMiT reviewed and validated a manufacturer's HTA dossier, whereas in Colombia the assessment was initiated by the National Institute of Cancer and completed by IETS, with inputs from the manufacturer.

Most assessments relied on Phase III randomized controlled trials and systematic reviews to obtain clinical evidence. Table 2 depicts the types of clinical evidence and end points included in each assessment.

In terms of research methods (Table 3), a range of economic analyses of different levels of complexity was reported across settings. In all cases, budget impact analyses to support decision-making were conducted, except for the case of Colombia. It is also worth noting that uncertainties were only explored in the Colombian study.

Table 2. Criteria considered in topic selection/scoping, sources of clinical evidence and types of end points included in each assessment.

Topic selection criteria	Countries			
	Albania	Poland	Colombia	Brazil
Perceived impact on patient outcomes (burden of disease): mortality, morbidity, quality of life	√		√	√
Potential cost of the technology/cost of illness			√	√
Prevalence/frequency of the clinical condition	√		√	√
Medical practice variations			√	
Feasibility of assessment (e.g., available data, funding, staff)				
Technology identified by external stakeholders: manufacturer		√		√
Technology identified by external stakeholders: others				
Political concern				
Public and media concern	√			
Ethical, legal or social implications (equity included)				√
Information included in scoping:				
– Number of cases of breast cancer reported in the country	√	√	√	√
– Clinical needs and practice	√	√	√	√
– Relevant patient populations		√	√	√
– Current treatment (relevant alternatives)		√	√	√
– Evidence base		√	√	√
– Cost of treatment/cost of illness	√	√	√	√
– Expected outcomes with the new treatment		√	√	√
– Other	Burden of disease			
Sources of clinical evidence:				
– Phase I–II trials				
– Phase III trials	√	√	√	√
– Indirect comparison				
– Post-marketing registry				
– Observational studies				
– Systematic reviews				√
Types of clinical end points:				
– Overall survival	√	√	√	√
– Progression-free survival	√	√	√	√
– Relapse-free survival				
– Disease-free survival				
– Quality of life		√	√	
– Safety	√	√	√	√

Appraisal

Findings from HTAs were contextualized by appraisal committees or similar bodies (e.g., drug and therapeutics committee) in all cases (Table 1). Just in the case of Brazil, the committees' recommendations were binding to decision-making. Presumably, the committees relied on value for money and/or budget impact to recommend trastuzumab, and other criteria – if any – were not reported. However, a transparent approach for weighing different elements was reported in the case of Brazil. The Transparency Council in Poland was composed of clinicians, ethicists, payers, regula-

tors and patient attorneys. Meanwhile, there were also pharmacists, economists, public health specialists, patient and civic groups, and industry representatives at CONITEC's committee (Brazil). In Colombia, patient groups, health professionals and industry participated in the process. At the hospital in Albania, only health professionals were involved. Across settings, no obligation to publish competing interests or meeting deliberations existed. In Poland and Colombia, cost–effectiveness thresholds in line with WHO guidelines were used to determine whether to recommend trastuzumab or not (AOTMiT ~I$23.650, IETS ~I$13.360, Purchasing Power Parity 2014; CONITEC and QSUT, not explicit).

Decision-making

Appraisal recommendations and decision-making were closely linked in all countries. However, there was always a higher administrative body with the prerogative to either officially endorse (MoH Secretariat of Science, Technology and Strategic Supplies in Brazil) or reconsider the recommendations of the appraisal committees (e.g., ministerial department, hospital board in the rest of countries, as shown in Table 1). Moreover, these bodies appear to support their final decisions with additional sources of evidence, including manufacturer's dossiers and reports from HTA agencies from other settings. According to reported data, the final pricing and reimbursement decision in Poland and Brazil depended on the results of negotiation between the MoH and the manufacturer. Table 1 shows the final decisions made in each setting, all of them favorable but with some applying different restrictions.

Dissemination

IETS (Colombia), AOTMiT (Poland) and CONITEC (Brazil) reported that its HTA reports were available online. Moreover, Brazil used HTA results to inform the development of clinical practice guidelines (CPGs) for professionals, while Colombia also issued guidelines for patients and caregivers. In the case of Albania information on dissemination was unreported.

Implementation & monitoring

As for the extent to which decisions based on HTA are implemented and monitored, information was limited. Brazil only reported having a system to monitor impact (cancer referral centers), while Colombia issued indicators and recommendations for monitoring.

Discussion

Overall, this case study of the adoption of trastuzumab in four emerging countries shows that the selected technology was evaluated following well-structured HTA processes, comprising steps previously defined and somewhat consistent across settings. Moreover, these processes were generally supported by legislation. With these HTAs, researchers and policymakers attempted to respond to population health needs, taking account of economic and social impact [24]. This case study sets the example for how emerging countries can successfully implement HTA and inform complex decisions on interventions such as those relating to cancer treatments. Although final decisions were favorable in all study countries, restrictions/recommendations on treatment access and process steps followed are the elements providing an avenue for discussion in this study.

Clear recommendations on good HTA practices exist [13,16,25], although little is known about its actual implementation [25]. Some authors [25,26] have already revealed the general adherence to good practice in the Brazilian and Polish systems, but there is no information with regards to Albania and Colombia. Discrepancies were found in the case studied in Albania, although this can be explained because HTA was conducted at hospital level. Hospital-level or mini-HTA has been advocated as a better solution to translate evidence into practice due to its integration into the local context. Although mini-HTAs (by definition) are less systematic and thorough than standard HTAs, they are usually more context-specific, relevant and timely than their counterparts conducted at regional or national levels [12].

Diverse levels of stakeholders' participation in the HTAs of trastuzumab were observed, both in terms of who is involved, and when and to which extent. For instance, in some cases topic selection was determined as a result of a manufacturers' request to have their technologies included in benefit packages or from clinicians' interest. In this regard, the literature on good practices recommends the participation of different actors throughout the HTA process, and its explicit recognition as an element to promote the legitimacy of decisions [16]. In their analysis of 30 countries, however, Stephens *et al.* [25] showed that stakeholders were involved in the assessment and appraisal stages in just 50 and 65% of surveyed countries, respectively.

One of the key principles of the HTA process is to have its transparency guaranteed, understood as the environment in which information relative to policies is provided to the public in a clear, accessible and timely fashion [27]. Such a principle should be present throughout the HTA process of all technologies evaluated. It is therefore necessary to disclose the criteria taken into account in the identification and initial

Table 3. Economic methods and considerations to assess trastuzumab.

Types of economic model	Country			
	Albania	Poland	Colombia	Brazil
Cost analysis				
Cost–effectiveness analysis			√	
Cost-utility analysis		√		
Cost-consequence analysis		√		
Cost-minimization analysis		√		
Budget impact analysis	√	√		√
Types of costs:				
– Some direct costs (e.g., drugs, diagnostic/therapeutic tests)		√		
– Healthcare costs (health service perspective)		√	√	
– Healthcare costs (payer perspective)			√	
– Indirect costs (e.g., productivity gains and losses, cost for informal care)				
– No economic evaluation	√			√
Model uncertainties:				
– Clinical parameters		√	√	
– Cost–effectiveness evidence			√	
– Clinical benefit following more time in treatment			√	
– Safety		√	√	
– Sample size				
– Study design				
– Comparator		√		
– Population and generalizability		√		
– Nature of the quality of life estimate			√	
– Disease characteristics				
– Treatment characteristics		√		

selection of technologies, as well as the potential conflicts of interest of the researchers and stakeholders who participate in it [16]. Along with this information, the origin and use of the data assessed should be specified. Recommendations and guidelines have been published to support improvements in this area [28–30]. The results of this case study indicate some weaknesses in terms of transparency that the various agencies involved should address, particularly in some points regarding the information provided in their reports and across the HTA process (especially at the appraisal and decision-making levels). In general, aspects related to transparency constitute one of the main weaknesses around HTA processes, and a series of recommendations have been issued by authoritative agencies in this field [30,31].

Regarding the evidence considered in the assessment, it is noteworthy that only Brazil reported using systematic reviews, while the other countries employed data from randomized controlled trials. Systematic reviews (with or without meta-analysis) are regarded as the highest level of evidence for efficacy/effectiveness of an intervention [32], constituting an essential component of HTAs. On the other hand, selected clinical end points were clinically similar across study cases and meaningful (overall survival, progression-free survival). However, only two countries (Poland and Colombia) took account of quality of life, an outcome usually less commonly employed in oncology. Although the selection of end points depends on the type of malignancy and its stage, it is central that HTA agencies make efforts to consider the outcomes that are the most relevant to patients [33]. Engaging in early dialogue with manufacturers about the choice of meaningful end points for randomized controlled trials is a practice that could also be explored by emerging settings [34].

On the other hand, limitations in the economic evaluation methods used were found. HTA requires

robust and explicit methods that are capable of synthetizing evidence of both benefits and costs in a summary measure for decision makers to compare with competing interventions. As a result, cost-utility analysis has become the most favored type of study [35]. However, cost–effectiveness analysis (with cost per life year gained as outcome) is widely employed in the HTA of cancer drugs, since increasing survival remains as the chief objective of treatment [36]. An interesting fact is that budget impact analysis alone was employed in the cases of Albania and Brazil. As countries progress in the implementation of HTA, a shift toward including also value for money in decision-making rather than simply separate indicators of effectiveness and cost will bring notable benefits. In particular, budget impact is not generally considered as a rational criterion for decision-making on its own, which may affect the legitimacy of decisions in cases where the technology in question is rejected [37]. Moreover, the use of economic evaluation as a tool for price negotiation may help resource limited settings to increase access to high-cost technologies, such as cancer drugs [12,36]. Findings from this study show that price negotiation has become a common practice in Brazil and Poland.

Nonetheless, the most marked observation to emerge from the analysis is the fact that trastuzumab was recommended across all countries, when there is some evidence pointing to its cost–ineffectiveness and unaffordability in low- and middle-income countries [12]. The reason for this apparently contradictory result is not completely clear, but it may be due to lower trastuzumab prices being offered by industry to governments, or to a higher weight placed on other values by stakeholders. Furthermore, it is also interesting to note that fewer restrictions on the use of trastuzumab were made in Albania. This phenomenon has been observed by other authors, and can be explained in part by the type of HTA performed (with or without economic evaluation) and the relative price of the drug assessed [38].

Except for Albania, reports were disseminated and publicized to some extent or another and made available on the agencies' websites, thereby complying with good practice recommendations on this matter [16]. Colombia and Brazil are two cases in point, where the HTA report was disseminated with and/or used to inform CPGs for the early detection, integrated treatment, follow-up and rehabilitation for breast cancer. This use of CPGs contributes to diffusion of evidence among professionals [39].

The main limitation of this study lies on the fact that not all agencies publish and disseminate their reports and, therefore, some information could not be compared. Researchers have also failed to ensure that the questionnaire sent to agencies was always completed by the most knowledgeable person in the matter. Despite this, the authors were particularly careful in the process of review and triangulation of data, using different sources such as country experts and – when available – the pertinent HTA reports.

Conclusion

This paper shows the whole process of HTA of a high-cost cancer drug in settings not previously deeply studied. Although similar case studies have been conducted in countries with long-established HTA systems [40–42], this paper offers an exhaustive account of policy development rather than an analysis of external influences on decision-making. This work covers an area in which information may not always be available in the public domain or published, especially as it pertains to emerging countries. In this regard, future studies on different technologies and countries are therefore suggested in order to provide a better understanding of how difficult coverage decisions are made across settings.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2015-0006

Acknowledgements

The authors gratefully acknowledge all key informants and survey respondents who have voluntarily collaborated in the development of this study. They also thank the organizations that participated in this study and Work Package 6 partners.

Financial & competing interests' disclosure

This work is part of ADVANCE-HTA, a broader, multipartner and multidisciplinary research project (www.advance-hta.eu), funded by the European Commission's Research Framework Programme (FP7). It comprises several complementary streams of research that aim to advance and strengthen the methodological tools and practices relating to the application and implementation of HTA. This paper comes from the Work Package 6, Strengthening and Implementing HTA in Emerging Settings. The design, interpretation and presentation of results are independent from the funding organization. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- This case study shows how a high-cost cancer drug such as trastuzumab goes through the health technology assessment (HTA) process in a set of emerging countries in the use of HTA, drawing lessons for similar settings.
- Trastuzumab was generally evaluated following well-structured HTA processes, comprising steps previously defined and somewhat consistent across settings.
- Overall, the clinical outcomes that were the most relevant to patients were selected.
- Of note, budget impact was employed in two cases as single economic criterion for decision-making, in detriment of value for money.
- Trastuzumab was recommended for adoption across all countries, despite their differences in economic status.
- The setting that less restriction on the use of trastuzumab imposed was Albania, which can be explained in part by the type of HTA performed.
- With the exception of Albania, HTA reports were disseminated and publicized to some extent or another.
- Little information on implementation and monitoring of HTA impact was available. Brazil only reported having a system, while Colombia issued indicators and recommendations for monitoring.

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