Health technology assessment in low- and middle-income countries: a case study of trastuzumab for early and locally advanced HER-2 positive breast cancer in Tunisia

Pascale Dequen-O'Byrne (pascale.dequen@visibleanalytics.co.uk)
Visible Analytics Ltd https://orcid.org/0000-0002-5120-8675
Mark Sculpher
University of York Centre for Health Economics
Neil Hawkins
Visible Analytics Ltd.
Juliette C Thompson
Visible Analytics Ltd.
Keith R Abrams
Visible Analytics Ltd.

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Health technology assessment in low- and middle-income countries: a case study of trastuzumab for early and locally advanced HER-2 positive breast cancer in Tunisia

Pascale Dequen-O'Byrne MSc, PhD[1], Mark Sculpher MSc, PhD[2], Neil Hawkins MSc PhD[1,3], Juliette C. Thompson BSc[1], Keith R. Abrams MSc PhD[1,4]

1 Visible Analytics Ltd., Oxford, UK.

2 Centre for Health Economics, University of York, York, United Kingdom.

3 Health Economics and Health Technology Assessment, University of Glasgow, Glasgow, UK

4 Department of Health Sciences, University of Leicester, Leicester, UK

Corresponding author:

Pascale Dequen-O'Byrne

Visible Analytics Ltd.

3 Kings Meadow

Oxford, Oxfordshire

OX2 0DP

UK

pascale.dequen@visibleanalytics.co.uk

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1. Background

In 2014, the World Health Organization (WHO) reiterated the critical role of health intervention and technology assessment to inform priority setting and resource allocation, reduce inefficiencies, and ultimately achieve universal health coverage [1,2]. In the past decade, global stakeholders from all sectors of healthcare have embraced evidence-based health policy development and decision-making, resulting in a growing number of initiatives to promote health technology assessment (HTA) particularly in low- and middle-income countries (LMICs). Initiatives such as the Guide to Health Economic Analysis and Research (GEAR), Decide—Health Decision Hub, the International Decision Support Initiative (iDSI), Thailand's Health Intervention and Technology Assessment Program (HITAP) international unit or the National Institute for Health and Care Excellence (NICE) international services provide a collection of online resources and tools to share, establish and strengthen HTA capacity worldwide [2–5].

A key principle of HTA, widely acknowledged by international agencies—both established and emerging, is the use of scientifically rigorous and evidence driven methodology to ensure quality and consistency of assessments, over time and across health interventions, and to present these in a transparent manner [6]. In May 2020, the International Network of Agencies for Health Technology Assessment (INAHTA) released a new definition of HTA which notes the process of HTA should be: "formal, systematic and transparent, and uses state-of-the-art methods to consider the best available evidence" [7]. However, to date no universally comprehensive framework or 'how-to' methods guide for HTA currently exist, or indeed is ever likely to exist, and the practice of HTA remains intrinsically shaped by a range of country-specific factors, policy agendas and institutional contexts, as well as, social and cultural values [8]. In addition, inherent challenges of implementing HTA methods in LMICs, namely limited resources, capacity and capabilities in the key disciplines of HTA, and potential lack of local data to inform decision-making, can curtail efforts by new agencies to adhere to HTA best practice [9,10].

2. Case study: trastuzumab in Tunisia

In Tunisia, breast cancer is the primary cancer in women and represents the most common cause of cancer mortality [11,12]. The standardised incidence of breast cancer in Tunisian woman has nearly tripled since 1994, reaching 50.17/100,000 persons years in 2017 [13,14]; it is projected to grow even further in coming years to eventually match the incidence of HICs. HER-2 positive breast cancer patients represent between 15 to 25% of all cases [15]. Trastuzumab—a targeted cancer therapy—was granted market authorisation by Tunisian regulatory authorities for early or locally advanced breast cancer in 2008. Although it is considered the 'gold' standard in the adjuvant setting and already used in clinical practice in Tunisia, its funding in its licensed indication represents the

largest drug cost burden for the national health service, raising concerns regarding its cost-effectiveness and 'economic acceptability' [13,15].

The health care system in Tunisia includes both public and private sectors; however, the publicly run Caisse Nationale d'Assurance Maladie (CNAM)—the compulsory national social health insurance scheme—provides care for the majority of the population [16]. In 2013, the WHO reported more than 90% of the Tunisian population were covered through the CNAM or the free medical assistance programme for the most vulnerable [16,17]. Public sector coverage under the CNAM includes health centres providing primary care, district and regional hospitals, and university hospitals.

In May 2017, INEAS was commissioned to conduct an HTA of trastuzumab for early and locally advanced HER2 positive breast cancer; in July 2018, it published its first guidance online [15]. The scope of the INEAS assessment was to conduct a pharmacoeconomic analysis and evaluate the net clinical benefit of trastuzumab for early and locally advanced HER2 positive breast cancer. Their evaluation included: (1) a review of the literature to summarise the net clinical benefit of trastuzumab compared with standard chemotherapy; (2) a comparison of international clinical practice guidelines recommendations; (3) an international drug price comparison; (4) a survey of international HTA agencies on the assessment of trastuzumab; and (5) a CEA.

3. Objectives and methods

We use the case study of the first published HTA by INEAS—trastuzumab (Herceptin®) in early and locally advanced HER2 positive breast cancer [15]—to critically compare the approach and methods used by an emerging HTA body to widely cited good practice guidelines in HTA [18–22], given likely resource and capacity constraints. The degree to which this is possible is limited by a country's willingness to share detailed descriptions of the methods used and results of their technology assessments. The Tunisian National Authority for Assessment and Accreditation in Healthcare (INEAS) was created in 2012 with an overarching goal to regulate the national health system by promoting quality and efficiency [www.ineas.tn/fr]. Within its newly acquired mandate, HTA is at the core of its mission. In this case, we refer to the WHO's definition of HTA as: "the systematic evaluation of properties, effects and/or impacts of health technologies and interventions" [1]. This multidisciplinary process of clinical and economic *assessment* is taken as distinct from the appraisal or decision-making, informed by this assessment, but which inevitably involves a range of other considerations and which is typically less transparent.

The HTA guidelines used were identified via the INAHTA website, the GEAR health economic evaluation guidelines database, and the ISPOR Outcomes Research Guidelines Index. These include the landmark report from the European Collaboration for HTA/Assessment of Health Interventions (ECHTA/ECAHI) project promoting

best practice in undertaking and reporting HTA [18], the Centre for Review and Dissemination (CRD)'s guidance for undertaking systematic reviews in health care [22], the WHO guide to cost-effectiveness analysis (CEA) [23] and the Gates Reference Case for Economic Evaluation [24]. Published methods guidelines from HTA agencies in low-, middle- and high-income countries (HICs) were also considered, such the Indonesian Health Technology Assessment Committee HTA guidelines [25], the guidelines for HTA in Thailand [26], and the NICE methods guide in England and Wales [20]. To date, INEAS has not published a methods or process guide for their assessments, and we did not identify any peer-reviewed guidelines tailored to the conduct of HTA within the region or specific to LMICs.

First, we summarise the clinical and economic evidence assessed by INEAS[1]. The critical review of the INEAS report is structured according to Busse *et al.* framework for HTA content and the key elements of HTA reporting, as presented in Table 1 [18]. Lastly, we provide recommendations for future practice drawing on lessons learnt from other HTA agencies in LMICs, and ongoing international research initiatives and collaborations to promote HTA methods worldwide.

Table 1. Content of a Health Technology Assessment

Policy question	
Background information on target group, target condition, technology (technical aspects, diffusing and current practice)	
Research questions	
Finding and Methodology	• Safety • Efficacy/effectiveness • Psychological, social and ethical considerations • Organizational and professional implications • Economic issues
Policy conclusions and recommendations	

Summary of trastuzumab clinical evidence

The review of the clinical literature performed by INEAS was two-fold. In a first instance, assessors identified all relevant clinical practice guidelines for the treatment of HER2 positive breast cancer to compare international recommendations on the use of trastuzumab; second, they summarised the risk-benefit profile of trastuzumab in the indicated population. Two clinical guidelines were included for comparison with the STOM—Société Tunisienne d'Oncologie Médicale—protocol for trastuzumab, the recently updated NICE guidance for early and locally advanced breast cancer and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines for the treatment of primary breast cancer [27–29]. The target population and treatment administration of trastuzumab across

[1] It should be noted that the full-text trastuzumab INEAS report is only available in French[15], the original report was used in the critical review as one of the authors is French native and could translate, as necessary.

the three guidelines aligned with the licensed indication, similar risks and contraindications were noted, and regular monitoring of cardiac function was recommended. Assessors presented the pooled results published in the Cochrane Systematic Review on trastuzumab containing regimens for early breast cancer, showing significant improvements in disease-free and overall survival for patients treated with trastuzumab as adjuvant therapy [30].

Summary of trastuzumab economic evidence

A systematic search of economic evaluations for trastuzumab in combination with standard chemotherapy compared with standard chemotherapy in early or locally advanced HER2 positive breast cancer was undertaken. The breadth of the search extended to six preferred online databases and the methodological quality of the included CEAs was assessed using two standard checklists: FLC 2.0 [lecturacritica.com] and Drummond's checklist for assessing economic evaluation [19].

No economic model, specific to the Tunisian health system perspective, was identified in the systematic review or developed *de novo* by INEAS or provided by the manufacturer. Instead, INEAS adapted a published Markov model by Pichon-Riviere *et al.* evaluating the cost-effectiveness, coverage, and accessibility of trastuzumab for patients with early HER2-positive breast cancer in seven Latin American countries [31(p)]. The modelling approach and input data used in the published CEA were summarised in the INEAS report. The safety and efficacy data, as well as the transition probabilities, were taken from the pivotal trastuzumab trial [32]; resource use and medical costs were informed by Latin American registries and hospital charges; and the quality of life valuation from two published utility studies [33,34]. The drug costs for both trastuzumab and standard chemotherapy were estimated by INEAS, based on the list prices of trastuzumab in Tunisian dinar before 2016 and following a price reduction per vial in 2018. The incremental cost-effectiveness ratio (ICER) for Tunisia was then calculated (using the Equation 1, translated from the INEAS HTA report [15]).

Equation 1. ICER calculation

$$ICER_{Tunisia} = \frac{\left(Total\ costs\ SC\ TZ - Cost\ TZ_{Reference\ country} + Cost\ TZ_{Tunisia}\right) - Total\ costs\ SC}{QALY_{Reference\ country}}$$

SC: standard chemotherapy; TZ: trastuzumab; SC TZ: standard chemotherapy + trastuzumab

INEAS found trastuzumab not cost-effective under the different pricing assumptions tested and based on their cost-effectiveness threshold calculations. Despite acknowledged caveats, INEAS described its conclusions as

robust in the scenarios tested and consistent with results from other published CEAs. Moreover, they estimated that in order to be cost-effective at an upper threshold of up to three times Tunisia's gross domestic product (GDP) per capita, a discount of 78% on the current list price of trastuzumab would be required [15].

4. Critical assessment

HTA protocol and research questions

The decision problem put forward by INEAS focused on a therapy already in common use in Tunisia, as opposed to a new health intervention. The stated rationale for this first assessment was the growing financial strain trastuzumab presented on the national health system and the need to explore the 'efficiency' of the drug in the given indication [15]. The report by INEAS clearly stated the policy question motivating the assessment and provided succinct, yet sufficient, background information on the condition and target population, technology, and current practice to contextualise the research questions posited. However, the report could have benefited from an *a priori* defined HTA protocol, describing explicitly how each stated objective was to be addressed, how and by whom [18,35]. In particular, which methodology was to be followed, based on which data were to be available, and how the retrieved evidence was to be synthesised. It should also be noted that despite the relatively high burden of disease and considerable percentage of health expenditure devoted to breast cancer in Tunisia [14,15]; at the time the assessment was published, the WHO had launched a pilot procedure for prequalification of biotherapeutic products including trastuzumab [36] and the market entry of biosimilars was likely to change the distribution and/or pricing of trastuzumab in the country.

Findings and methodology: safety, efficacy/effectiveness

In accordance with good practice guidelines, a systematic approach to identify relevant clinical evidence was presented by INEAS [18,20,22,37]. This included a pre-defined search strategy combining free-text and keywords, a stepwise study screening process by two independent reviewers, and a quality assessment of the included publications. Moreover, the reporting of the systematic search and review of clinical guidelines, demonstrated a willingness for transparency. The search strategies used by reviewers were included in an appendix and PRISMA diagrams were provided to illustrate the study selection process, as recommended by the CRD and NICE [20,22]. However, the inclusion and exclusion criteria used for study selection are not reported; a more detailed transcription of the search strategies annexed in the report—allowing for validation and/or replication by external reviewer—would have further improved transparency.

Additional data sources cited by assessors, e.g. published systematic reviews and HTA/appraisals produced by other countries, to demonstrate the net clinical benefit of trastuzumab vs. standard chemotherapy were not identified systematically, and recent publications appeared to be omitted. For example, the STOM protocol compliance with international recommendations was only based on a comparison with two UK guidelines. International practice guidelines such as those published by the American Society of Clinical Oncology (ASCO) or European Society for Medical Oncology (ESMO) were not included in the review [38–41].

The SIGN and NICE clinical guidelines formed the primary data source for the risk-benefit profile of trastuzumab and established its relative safety and efficacy compared with standard chemotherapy. However, it was unclear why the clinical literature review solely focused on identifying clinical practice guidelines. Drummond *et al.* suggest: "a comprehensive, well-conducted, [evidence-based medicine] review is a necessary first step in the HTA appraisal process" [35]; indeed, good practice principles favour systematic reviews and meta-analysis of randomised clinical trials (RCTs) often classified as the highest level of evidence to establish the relative safety, efficacy and effectiveness of technology compared to relevant comparators [18,20,22,37]. INEAS presented relative treatment effects for trastuzumab compared with standard chemotherapy in terms of disease free survival and overall survival; however, how the evidence transcribed from the trastuzumab Cochrane review and the patient populations in the included studies reflect that of the Tunisian context was not assessed [30]. The approach taken by INEAS is indeed more pragmatic, perhaps given time and/or resource constraints; however, this was not explicitly stated or justified by assessors and potential sources of bias in their approach were not reported.

Findings and methodology: economic issues

One of the key elements of the INEAS report was also acknowledged by assessors as its biggest limitation, that is the lack of a Tunisian-specific economic model and the absence of 'contextualised' data to inform a CEA. INEAS stated that despite an appeal to manufacturers to provide a CEA from the perspective of the Tunisian health system, an economic model was not submitted, and a *de novo* analysis could not be performed [15]. The conduct and reporting of the CEA search were more comprehensive than in the clinical section; PICO criteria were used to define the research question and inclusion/exclusion criteria were explicitly cited. The search methods used by INEAS were in line with CRD guidance on reviewing economic evaluations [22]. Some key search terms appeared to not have been used in the provided search strategy (e.g. economic evaluation or model, cost-benefit analysis), but this may have been a reporting issue with minimal impact on the search results. However, the review was restricted to CEAs performed in LMICs. This restriction was not substantively justified in the INEAS report and considerably

reduced the number of included CEAs. Somewhat counterintuitively, the assessors later referenced CEAs and technology appraisals from HICs in their discussion of the CEA results.

The CEA methods and results reported by INEAS may not have adequately reflected the Tunisian health system perspective, nor accounted for local resource utilisation, costing, or quality of life measure [23,35,42]. The comparability of direct medical costs between LMICs in Latin America and Tunisia was assumed by assessors, but no data were presented to validate this assumption [43]. Only the drug costs were adapted as per Equation 1. No sensitivity analysis or assessment of the uncertainty around the ICER could be performed beyond that published by Pichon-Riviere *et al.* [31]. The INEAS CEA raised the issue of the appropriateness of translating and transferring cost-effectiveness results across different jurisdictions. The Pichon-Riviere *et al.* model was selected by INEAS because it rated highly following the qualitative assessment of included CEAs; and assessors argued the direct medical costs included in the CEA for the five LMICs in Latin America were comparable to that of Tunisia [15,31]. The adaptation of economic models from other countries is relatively common in HTA practice; and can be much better use of limited resources and capacities compared to developing a local *de novo* model when one is not provided by the manufacturer or identified in the literature. However, some evidence can be considered more transferable across jurisdictions, such as treatment effects or utilities; a notable weakness here was the failure to adapt resource use and non-drug related costs to the Tunisian setting [43–45]. This probably would have required access to functional model. The economic evaluation of trastuzumab presented by INEAS would therefore be considered as weak evidence by most established HTA bodies, that is not to say non-informative for local health-decision makers [24,46].

Policy conclusions and recommendations

INEAS argued that drug costs were the key driver of trastuzumab's cost-effectiveness—or lack thereof—in Latin America and Tunisia. The price of trastuzumab in Tunisia was also tracked over time and internationally. Although the authors acknowledge the pricing of drugs in LMICs is important and timing, including the contentious price discrepancies between high- and LMICs and the healthcare funding dilemma often faced by the latter, a price comparison is not usually considered a key element of HTA. A budget impact model would have been more informative to address the research question of trastuzumab's 'efficiency' [15]; at least a presentation of the likely volume of patients who would be suitable for trastuzumab over time in Tunisia would have been useful.

Notwithstanding the methodological limitations and uncertainties surrounding the CEA, INEAS defended the relevance of their findings for Tunisia considering the magnitude of the 'inefficiency' of trastuzumab for the tested range of LMICs cost-effectiveness thresholds (CETs). The assessors did discuss the importance of how to

appropriately judge the implications of the estimated ICERs for medicines in LMICs and the relevance of different CETs. Although there is still much debate and ongoing research on how to best define CETs in LMICs; recent work by Woods *et al.* and Ochalek *et al.* suggest that calculations of CET, such as the use of one to three times GDP/capita, might be too high as they do not adequately capture the opportunity cost in terms of the health benefits foregone because of interventions not provided [47–49]. This work would further support the conclusions from INEAS, that despite stated limitations of the economic evidence presented for trastuzumab in Tunisia, the magnitude of the negative ICERs outweighed the inherent uncertainty of the 'naïve' model adaptation.

Lastly, it should be noted that wider psychological, social, and ethical considerations, the patient perspective, as well as organisational and professional implications referenced in a number of good practice guidelines, were not explicitly reported in the INEAS assessment but may have been discussed by appraisers[4,18].

5. Conclusions and recommendations

We find the first HTA by INEAS to be an encouraging example of evidence-based practice to inform decision-making in an LMIC. In fact, we commend INEAS for making their assessment publicly available, allowing this critique, and providing a unique opportunity for shared learning. Overall, the conduct and reporting of the assessment of trastuzumab's net clinical benefit for early and locally advanced HER2 positive breast cancer in Tunisia was well-structured and transparent. However, our review also highlighted important limitations in the assessment of the CEA of trastuzumab compared with standard chemotherapy for the Tunisian health system. We acknowledge the learnings from this case study are limited as only reflect a single HTA report by one emerging HTA agency in a LMIC; however, our recommendations are more far-reaching and could be generalisable to other LMICs. Following their survey of researchers who have experience in conducting economic evaluations in LMICs, Luz *et al.* find similar technical issues were reported across a number of assessments: "the lack of quality local clinical data, poor reporting, insufficient data to conduct the analysis from the chosen perspective (i.e. the lack of cost data), lack of context-relevant standards for economic evaluation, and lack of local health-related preference data, respectively."[10]

Adapting or borrowing evidence across countries and HTA agencies can be a practical and efficient 'shortcut' to conducting HTA in LMICs, but it may not provide sufficient context to answer the policy and research questions set out by local agencies [50]. It may be misleading to assume that relative treatment effects are transferable, as the majority of randomised clinical trials for a particular condition may not be undertaken in LMICs and case-mix might differ between HICs and LMICs [51]. However, it may be challenging to develop or identify evidence regarding relative treatment effects in the local context. More important, resource utilisation, unit costs and

quality of life data (and utilities using country-specific valuation sets) may differ substantially between LMICs for societal and cultural reasons; therefore care must be taken when comparing model inputs across jurisdictions, and ideally local data should be used [9,44,52].

The paucity of local data, or difficulties to obtain it, are well documented barriers to the implementation of HTA in LMICs [9,40]. Efforts to promote local data collection, especially through collaboration, should be prioritised. Considering the resource and time implications, obstacles to the gathering or sharing of data already being collected (e.g. cancer registries, medical cost data) could be removed; issues with missing or poor quality data should be addressed; or the use of technology (e.g. Electronic Health Records, especially in upper MICs) could generate local evidence both on clinical outcomes, resource use, etc. A number of LMICs are starting to develop frameworks for routine data collection and analysis of existing databases, such as medicines/healthcare utilisation and costs, following the example of countries such as Brazil or South Africa [53–57]. Gaining a better understanding of drug utilisation patterns and expenditures would also help prioritise key areas for HTA and resource allocation, which according to Jakupi *et al.* and Kivoto *et al.* is an essential first step before initiating HTAs [58,59].

The challenges of local data collection also raise an important question regarding the 'burden of proof' and who bears the cost of making the case for the funding of a new technology, in the broader sense of, generating relevant and generalisable evidence, capturing contextualised data and modelling. In certain countries, the manufacturer is responsible for submitting this case for newly developed technologies. The degree to which manufacturers will be willing to submit assessments will depend on their own local resources and their perceived return on investment in such submissions. One consideration will be how the local agencies proceed if manufacturers decide not to make a submission. In this case study, INEAS decided to pursue the assessment using published evidence. It should also be borne in mind that for many technologies, such as those that no longer enjoy patent protection, there may not be a single identifiable manufacturer with a strong incentive to develop a submission.

The WHO and iDSI promote multiple stakeholder engagement as a tool to build capacity to support HTA [1,60]. The HTA process should be viewed by all stakeholders as a learning continuum allowing for capacity building, resource training, and re-assessments of health technologies over time. Emerging and newly established HTA agencies could consider formalising HTA protocols to encourage stakeholder engagement, assign tasks and impose timelines [61,62]. As exemplified by this review and others, such as the Ghanaian HTA study of the cost-effectiveness of antihypertensive medicine; there are lessons to be learnt from the experiences and 'growing pains'

of emerging HTA bodies when implementing HTA frameworks, capacity building, and engaging with multiple stakeholders [62].

Improving communication and the sharing of information and resources could be a catalyst to the implementation of HTA in LMICs. Tantivess *et al.* reflect on the role NICE International and HITAP played in the HTA capacity development in Myanmar, finding: "[the] continuous support from international partners is indispensable for keeping the momentum of HTA introduction" [4]. Despite relying heavily on the Latin American experience and economic evaluation, INEAS disclosed a number of collaborations with other HTA agencies and a range of experts and stakeholders; in addition, to surveying international HTA bodies regarding previous assessments of trastuzumab in their respective jurisdictions [15].

Other examples of initiatives focusing on facilitating the development and dissemination of economic evaluations and HTAs across jurisdictions include: the CEA Registry by the Centre for the Evaluation of Value and Risk in health, GEAR, and Decide—Health Decision Hub. The publication of open access health economic models by HTA agencies could also help identify CEAs of interest or initiate more readily available model to be adapted and populated with local inputs. Another initiative is the Regional Database of Health Technology Assessment Reports in Americas (RedETSA) that publishes joint HTA reports for Latin America and the Caribbean [63]. From an evidence modelling perspective, such regional collaborations could lead to developing models which allow for a degree of similarity between countries when estimating both clinical and economic net benefit, as the health care systems are more likely to be comparable. The HTA guidance published by INEAS could be used as a steppingstone in the region, providing a useful reference case to neighbouring countries—e.g. Morocco, Algeria—wishing to implement similar HTA frameworks.

Moreover, a broader discussion on how to best incorporate issues of affordability and acceptability to health care providers and patients, especially for HTA agencies aiming to assess costly health interventions already in routine care, is warranted [64]. For example, the delivery of healthcare and the management of key diseases can be very different between LMICs and HICs, raising issues about patient co-payments and catastrophic out of pocket expenditures for households. Trastuzumab is an interesting case study to explore the use of HTA in LMICs; as the affordability of trastuzumab is highly topical and has recently been investigated in Iran, Latin America, and Sub Sahara Africa [31,65,66]. Work from Barrett *et al.* in the UK suggests the opportunity cost of trastuzumab could be considerable, as compared to other treatments for breast cancer; how this extends to other cancer medicines, or to other disease areas would merit further consideration [64,67]. However, the availability of trastuzumab biosimilars at

substantially lower costs is likely to not only impact the cost-effectiveness of trastuzumab but its use and marketing in Tunisia and other LMICs.

Lastly, better reporting is an efficient way of improving the methodological quality of an HTA without necessarily adding to the resource burden of such assessments. Similarly, pre-defining a HTA protocol, data requirements, and preferred methods for HTA in a tailored methods guide produced by local HTA agency would provide further clarity and consistency to future assessments. In our case study, we highlight a number of instances were HTA elements were not substantiated enough or not reported by INEAS. However, it is likely that these were captured or discussed and could have been included, even in Appendix, for completeness and in line with best HTA practice, such as search strategies and data extraction, psychological, social, and ethical considerations, or organizational and professional implications.

A stated caveat of our review is that specific issues surrounding the appraisal of new health technologies in LMICs, intrinsically linked to HTA, were not considered. Learnings from other countries demonstrate that understanding how evidence generated during the HTA process is translated into resource allocation decisions, and how HTA is implemented as part of a wider health policy change, particularly in LMICs, is critical [57]. Decision-making regarding resource allocation to specific healthcare technologies leads to inevitable 'trade-offs' and these may be contentious, if restricting funding and access to potentially useful, cost-effective treatments [68]. It is important that the process used to arrive at such decisions is seen as being socially just, otherwise both individual decisions and the evaluation process itself are likely to be contested. In this respect, although stakeholder engagement may be perceived as 'slowing down' and increasing the 'cost' of HTA, it is an important component of a socially just decision-making process and may contribute to the acceptance and increase the impact of HTA based decision-making [69]. The 2020 roadmap for systematic priority setting and HTA, developed by Management Sciences for Health (MSH) and the USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program, echoes a number of our recommendations for the implementation of HTA in LMICs. In addition to identifying key challenges for LMICs, this roadmap also provides tools and approaches to support HTA efforts and help navigate the process of institutionalising HTA—"from agenda setting through formulation, adoption/implementation to impact evaluation" [68].

Our critical review compared the approach and methods used by INEAS in their assessment of trastuzumab to a number of published HTA methods guidelines. However, using traditional HTA elements and methods, without consideration for capacity and resource constraints, as a benchmark for 'best practice' in LMICs is inconsistent. It may be more appropriate to focus on how useful an assessment is, given an agency's resource constraints. Luz *et al.* find that the lack of standard practice that is relevant to LMICs was frequently reported as an

issue by countries surveyed regarding the conduct, reporting and use of economic evaluations [10]. Despite challenges, it is promising that the core principles underpinning good HTA practice are endorsed by newly established HTA agencies such as INEAS [4,9,24]; and that ongoing research and global initiatives are continuously extending and adapting HTA guidelines to advance HTA practice in both HICs and LMICs [2,68,70].

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