iDSI Guide to Rapid Review of International HTA Reports

An Adaptive HTA Method

Lead Author
Daniel Ollendorf

Contributors
Pete Baker
Srobana Ghosh
Javier Guzman
Lieke Fleur Heupink
Cassandra Nemzoff
Andrés Pichon-Riviere
Shankar Prinja

Executive Summary

The use of health technology assessment (HTA) to inform which services are provided by publicly funded health systems has increased substantially in the past 20 years. Demand for HTA in low- and middle-income countries (LMICs) is strong, given the need to support national policies on universal health coverage and focus scarce resources on an essential package of services in these settings. However, LMICs face major challenges in conducting HTA, given the potential backlog of technologies to evaluate, an urgent need to make funding decisions, limited data, and lack of technical and/or institutional capacity to deploy a traditional, "full" HTA process.

One potential solution for these challenges is a process known as adaptive HTA (aHTA), which may take multiple forms but is a structured approach intended to reduce the time, capacity, and data required for HTA. This guide describes one such approach to aHTA developed by the International Decision Support Initiative (iDSI) network that maintains key features of a full HTA process but also allows for rapid interpretation of available international evidence and translation of the evidence to the local context. This *rapid review* approach to aHTA makes use of HTA reports available from other international settings as well as published cost-effectiveness analyses (CEAs). Utilising HTAs from other jurisdictions is a particularly powerful component of aHTA because it enables countries to leverage another countries' technical capacity in collating, synthesising, and appraising the quality of evidence on a topic.

The goal of this guide is therefore to provide a standardised and easy to implement aHTA method that enables the development of customised national aHTA processes that ultimately inform better decision making. This guide is organised according to the major steps in the process of rapid review aHTA, in chronological order. Of note, while selection of aHTA topics and deliberation on the results of aHTA—the typical starting and ending points of any HTA process—are included in the guide, they are not described in detail, as most settings will already have a topic selection and deliberation process that can be integrated into an aHTA initiative. Other core elements are described in detail, along with recommended sources of information, templates for collected data, and formulae for any key calculations to make. These elements include the following:

1) ***Scoping*—matching the scope of the decision problem to international evidence**

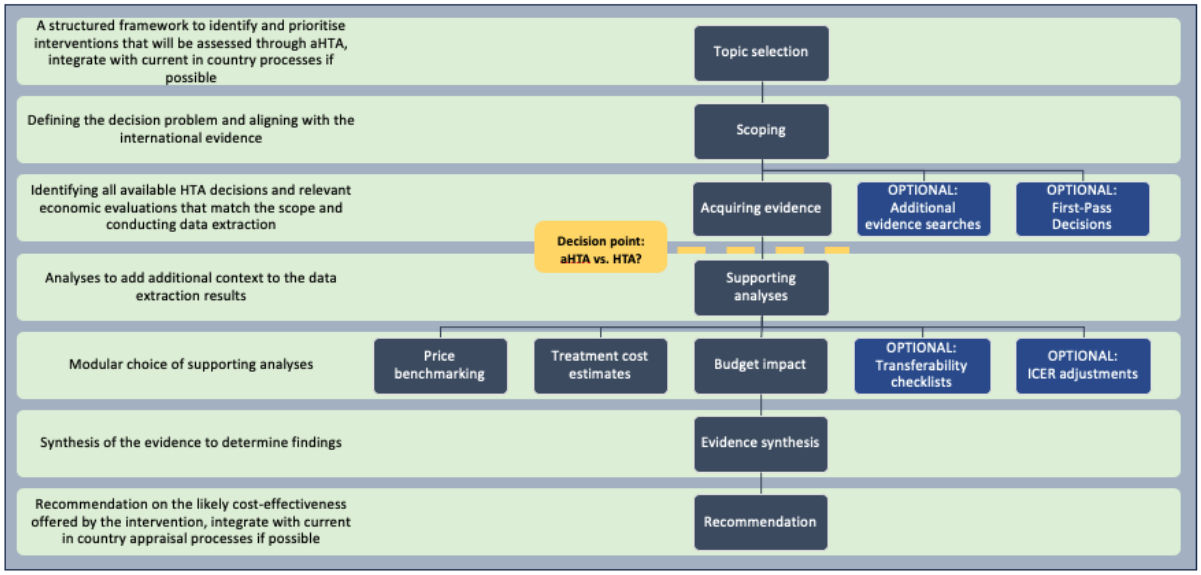
2) ***Acquiring Evidence*—identifying HTA reports and CEA studies, and completing templates for extraction of data**

3) ***Supporting Analyses*—price benchmarking, treatment cost calculation, and budget impact assessment**

4) ***Synthesising Results and Recommendations***

Optional modules are also described, should analysts and decision makers in the local setting wish to augment their efforts. These include acquiring additional evidence from systematic reviews and/or newer clinical studies, conducting a first-pass examination to determine if aHTA itself can be bypassed, using available checklists to determine if economic data are transferable between settings, and adjusting cost-effectiveness results for the local setting where feasible. All elements, including optional components in blue, are shown in Figure 1 below.

Figure 1. Overview of the Rapid Review of International HTAs approach



While the aHTA framework as described has its limitations, it is nonetheless a rapid, efficient, and pragmatic way of generating evidence for decision making and an important option in settings without the resources or political support to perform HTA on a large scale.

1. Introduction

1.1 Background

As countries progress in their efforts towards delivering universal health coverage, there is an urgent need for priority setting to ensure that they make optimal use of their limited health budgets to deliver the maximum health benefits possible to the population in the most efficient way. Health technology assessment (HTA) is an approach that many countries now use to carry out this prioritisation of health services.

A recent task force composed of HTA networks, professional societies, and global organisations defines HTA as "*a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision making in order to promote an equitable, efficient, and high-quality health system*."[1] The benefits of a well-functioning HTA process include identification and uptake of cost-effective or otherwise high-value interventions, disinvestment from interventions of doubtful value, consideration of implementation challenges, and monitoring of the use of technology in practice, all featuring an approach that engages and takes on board the views of patients, carers, clinicians, payers, technology manufacturers, and policymakers.

The use of HTA to inform policy and decision making has grown substantially in the past 20 years, such that nearly all high-income countries have one or more established agencies or affiliated organisations to serve this purpose. Demand for HTA in low- and middle-income countries (LMICs) has also grown, given the need to support national policies on universal health coverage and focus scarce resources on an essential "benefits package" of services in these settings.[2]

However, LMICs face major challenges in fully developing and efficiently conducting HTA. For one, the backlog of technology assessments and relevant decisions to be made may be massive, given that existing benefits packages are infrequently reviewed and become rapidly out of date.[3] This is in contrast to the political or financial urgency of sifting through these packages and identifying the most efficient interventions. Finally, LMICs have generally lacked data as well as sufficient technical and institutional capacity to carry out enough full HTA assessments to meet their decision needs.

One potential solution for these challenges is a process known as adaptive HTA (aHTA), characterised by Nemzoff and colleagues as "a *structured approach to selecting and conducting the optimal HTA analysis to produce efficient HTA results by adjusting for analytical time, data, capacity, and source of conduct*".[4] Thus, aHTA can increase efficiency primarily by leveraging information from other settings where possible.

This guide provides an overview of one such aHTA approach developed by the iDSI network that maintains key features of a traditional HTA process but also allows for rapid interpretation of available international evidence and translation of the evidence to the local context. It includes descriptions of core elements of this method, as well as optional additional components that countries may integrate should there be interest and capacity for doing so.

1.2 Approaches to Adaptive HTA

As the practice of aHTA is still emerging, there is no standardised nomenclature defining the process, nor are there any internationally agreed and standardised methods.[5] However, there is evidence that many countries are increasingly adapting the process or using some form of rapid HTA[5,6] to quickly gain a sense of the potential cost-effectiveness of an intervention. Methods employed have included rapid review,[7-9] model adaptations,[10] the use of transferability checklists,[11-13] "de facto" HTA (i.e.,

direct examination and/or use of foreign HTA reports, budget impact analysis, and reimbursement benchmarking),[14,15] or potentially adapting the in-country manufacturer submission process.[5]

Regardless of which of the approaches above are taken, the adjusted methods often save time or require less data or capacity than a full HTA and offer different levels of insight. Crucially, when selecting an aHTA method, it is important to ensure the process is systematic, transparent and replicable in order to build faith in the process and ensure the findings are credible, while acknowledging the naturally greater level of uncertainty with this method in comparison with a full HTA.

The focus of this guide is on a specific, systematic, and replicable aHTA method developed by iDSI following the network's experience in Romania, India, Indonesia, and Ghana over the last 10 years (see section 1.2). Further references to "aHTA" will be in reference to iDSI's "rapid review of international HTAs" method.

Table 1 below provides a comparison between full HTA processes and iDSI's approach to aHTA. In general, an aHTA operates on a shortened timeline given the synthesis and assessment of the evidence that has already been done internationally. A shortened timeline will not allow for a comprehensive assessment of all local concerns, but multiple recommendations and decisions can be taken in the time required to conduct one full HTA. Most importantly, aHTA will not rely on any de novo clinical or economic analyses, but instead draws on international evidence from other HTA settings with local adaptation, which may increase uncertainty but allows for an efficient process.

As Table 1 illustrates, most of the trade-offs for each HTA component involve some sacrifice of accuracy or increase in uncertainty for greater speed and efficiency. When the number of HTA decisions is significant, however, the benefits of aHTA are clear—an evidence-based process, even if abbreviated, is far superior to only being able to do a comprehensive assessment on a handful of technologies.

Table 1. Key differences between full and rapid review adaptive HTA

	Full HTA	Adaptive HTA	Benefits of aHTA	Limitations of aHTA
Timeline	12–24 months+	1–6 months	• Speed	• Level of comprehensiveness
Analysis	De novo clinical and economic evaluation (e.g., cost-effectiveness analysis)	Review of HTAs and other published cost-effectiveness evidence	• Requires less resources, staff time, and skills • Leverages high quality analysis and appraisal capacity from other HTAs	• Lower accuracy • (Un)certainty
Data sourcing	Local studies + primary data collection and systematic literature review	International HTA reports + targeted literature search for economic studies	• Speed of data sourcing • Leverages other HTA agencies' access to data	• Level of comprehensiveness • Reduced confidence in transferability to local context
Uses	• Adjustments to health benefits packages or essential medicines lists • Adoption of individual technologies • Price negotiations • Reimbursement decisions • Clinical guidelines • Quality standards	• Same as HTA	• Greater speed and quantity of decisions informed by aHTA may improve overall allocative efficiency of benefits package	• Lower precision of aHTA makes price negotiation less informed • Greater uncertainty of aHTA risks error in adjustment to packages • Not possible to do topics with no preexisting international HTAs

A key similarity between full HTA and aHTA, however, is the need to develop a comprehensive process, stating clearly what occurs at each stage for full transparency and accountability. Publishing the steps of such a process will legitimise an aHTA approach and the decisions made through it. Ideally, aHTA should complement and supplement existing in-country HTA frameworks for topic prioritisation, appraisal, communication of decisions, and other elements, with all interventions first being considered through aHTA so that full HTA is saved for the instances in which a complete de novo process is warranted, such as complex topics or those with significant local nuance.

1.4 Recent iDSI Work on aHTA

This guide is based on extensive practical experience of aHTA within the International Decision Support Initiative (iDSI) network. In 2020, iDSI[16] began substantial work on the development of an aHTA approach in India. Work initially began with the National Cancer Grid (NCG)[17,18] of India to pilot a new framework that could generate estimates of cost-effectiveness to inform oncology clinical guidelines, which was refined over the course of conducting 10 pilot aHTAs. This work further developed an approach originally designed by iDSI for the Romanian government in 2011.[14] The finalised framework was published by the NCG in their Process and Methods Guide.[19]

Work then continued with the Department of Health Research to institute a national aHTA method that could be used by India's National Health Authority (NHA) in conjunction with HTAIn, the national HTA body[20,21] to assess interventions for the health benefits package maintained by the PM-JAY public insurance scheme. A methods and operations guide developed for the NHA is currently in the final stages of production.

In 2022, there was interest in a national aHTA framework in Indonesia that could inform rapid evidence generation to enable the government to scale up its HTA informed decision-making capacity. iDSI worked with representatives from the Indonesian HTA committee, Ministry of Health, the National Formulary, and HTA departments from leading universities to carry out a pilot and develop a methods guideline that supplemented their existing HTA processes but could lead to faster evidence generation.

In Ghana in 2023, iDSI supported the University of Ghana and Ministry of Health to complete a pilot aHTA on selected diabetes medicines, to assess the suitability for inclusion on Ghana Standard Treatment Guidelines and National Health Insurance Reimbursement List. This work augmented preexisting guidelines that allowed for rapid reviews of secondarily collected data.

In the West Bank, the Palestinian National Institute of Public Health and the Norwegian Institute of Public Health, an iDSI partner, tested the feasibility of using an aHTA approach to coproduce an adaptive HTA report on breast cancer screening.[22]

Finally, in Argentina, the Institute for Clinical Effectiveness and Health Policy (IECS), an HTA research institute and iDSI partner, has developed a specific approach to evidence review for aHTA that is highlighted as an optional additional module in this guide (see page 29).

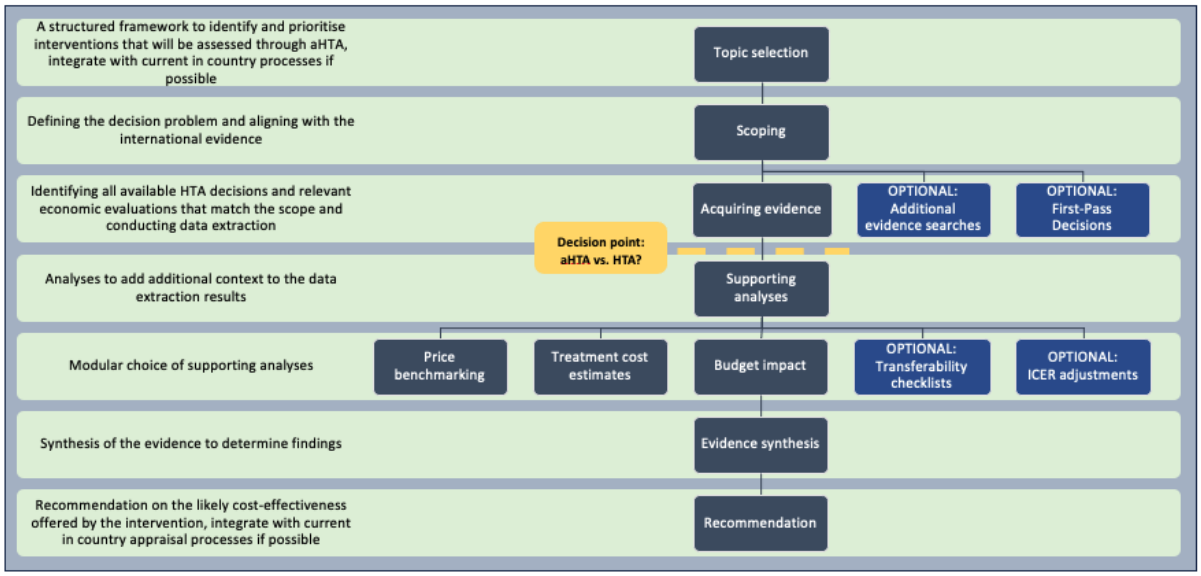
In addition to the de novo work mentioned above, it is also worth noting that several guidelines and procedures in LMICs already allow for rapid review of data collected in other contexts, including documentation in Kazakhstan, Malaysia, Moldova, and South Africa.

1.5 Orientation to the iDSI Guide and Overview of the aHTA Approach

The culmination of in-country experience of technical guidance on aHTA, as well as prior experiences with and procedures for rapid review, has contributed to the development of this *iDSI Guide for the Rapid Review of International HTAs*. In publishing this guidance, our goal is to provide a standardised method, alongside real-world examples of aHTA, and thereby encourage the development of in-country aHTA processes to lead to more rapid and pragmatic evidence generation, and ultimately to inform better decision making.

The intent is to provide a modular and flexible guide to integrating an appropriate aHTA approach in a given setting, as shown in Figure 1. There are core components considered essential for any aHTA program (in black) and optional components that a given country may find of interest given the level of available resources and capacity (in blue).

Figure 1. Overview of the Rapid Review of International HTAs approach



Note: ICER = incremental cost-effectiveness ratio.

The guide is structured chronologically, following the approach in Figure 1, and so begins with topic selection and prioritisation. The approach to determining the project scope is then described, using the Population, Intervention, Comparator(s), and Outcomes (PICO) rubric. This is followed by the approach and method for acquiring evidence and judging its quality; while the primary intent of aHTA is to make use of HTA reports and cost-effectiveness evaluations, an option for including published systematic reviews and individual clinical studies is also described. The "Acquiring Evidence" section also provides templates for clinical and economic data extraction as well as recording key uncertainties in the data. There are optional components for consideration of evidence beyond the required sources as well as conducting a first-pass examination to see if aHTA itself is necessary.

The next section describes supporting analyses that can be undertaken, including price benchmarking comparisons to similar countries, calculations of treatment cost, and assessment of potential budgetary impact. Optional components include methods to adjust cost-effectiveness findings to the local context and a checklist of considerations when transferring international economic evidence to local settings.

Concluding sections of the guide include how to do an overall assessment of the benefits, risks, and economic impact of the intervention, as well as best practices for judging the strength of evidence and comparing findings to existing thresholds for clinical benefit, cost-effectiveness, and other considerations.

2. Topic Selection and Prioritisation

2.1 Purpose

Regardless of whether full HTA or rapid review aHTA is considered, it is important to have a process by which topics are identified, selected, and prioritised. This is especially critical in low- and middle-income settings, given limitations on resources available for topic management. With regard to aHTA, the topic identification, selection, and prioritisation (TISP) process can help determine the order of operations for upcoming topics and to assess whether a given topic is a candidate for aHTA or full HTA (see Section 4.4 for further details).

In any given setting, an existing TISP process may already exist, in which case aHTA-related steps can simply be integrated into the existing TISP rather than being developed as a separate process. Global guidance on development and/or refinement of a TISP process should be followed and is publicly available.[23]

2.2 Rapid Review as the Default Option

One adaptation to existing TISP processes that we recommend is for resource-constrained systems to consider aHTA the *default* choice for every topic, with HTA reserved only for when the topic cannot be satisfactorily assessed through aHTA. This process allows for available resources to be directed to full HTA where it is most pressing or important (or where rapid review aHTA is infeasible), making the best use of time and capacity. Full HTA may be warranted, for example, when uncertainties in the evidence are too great for transfer to the local context, or governmental priorities are such that a full HTA should be done to provide the most comprehensive local assessment possible.

Importantly, the time to conduct the early phases of aHTA is not wasted—a considerable amount of information will be aggregated by aHTA, which will better inform any eventual HTA. The decision to supplement the aHTA with a full HTA is best made after surveying the international HTA landscape and is further described in Section 4.4.

3. Scoping

3.1 Purpose and Goal of aHTA Scoping

While a scoping effort for rapid review aHTA involves a similar technical approach to that of a full HTA, the rationale is quite different. For a full HTA, the scoping exercise is intended to ensure that questions to be answered by the assessment match the decision problem at hand. While this is also a goal of aHTA, there is a key additional consideration, which is to ensure that the evidence identified from international and/or published sources matches the local scope of interest, noting any differences that may complicate or preclude consideration of any of those sources. Therefore, an aHTA scoping exercise has two distinct goals: (1) to ensure the evidence accumulated matches the relevant local scope, and (2) to determine whether aHTA is a feasible approach given identified differences.

3.2 Population, Intervention, Comparator(s), Outcomes (PICO)

Once the topic has been appropriately prioritised, the scoping process will begin with a description of the decision problem as it relates to the local context and the definitions, comparisons, and outcomes that will define the evidence to be used in the assessment.

The PICO framework[24] is used widely in HTA settings and is employed here to determine if the project scope matches the available international evidence (see Table 2 and this can be recorded in the template spreadsheet). Importantly, an aHTA is only feasible if the PICO matches between current or anticipated clinical practice in the local setting and the defined scope for available international evidence.

Technology assessors should not undertake the scoping exercise in isolation. Rather, this represents a key opportunity to engage patients and caregivers, clinical experts, technology manufacturers, and others to refine the scope for anticipated local use and provide a basis for comparison to the international evidence.

Table 2. PICO definition of a project scope

Parameter	Definition	Example(s)
Population (and indication)	The definition of the population and indication should be very specific. While not exhaustive, elements to consider could include the following: • Disease category • Indication (e.g., stage or severity of disease and previous therapies attempted) • Age range	• Newly diagnosed type 2 adult-onset diabetes
Intervention	A full description of the intervention of interest should be given, including dose and route of administration as well as the details involved in delivering the treatment.	• Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (e.g., empagliflozin) for treatment of type 2 diabetes

Comparator	The comparator should be standard of care in clinical practice (with dose and route of administration specified) or a menu of alternatives recommended in clinical guidelines. More than one comparator can be included (this is often the case for established treatments). There should be a cost-effectiveness analysis, clinical trial data, or robust comparisons available comparing the intervention against the selected comparators for the target population.	• Metformin for treatment of type 2 diabetes
Outcomes	The key outcomes of interest for the technology should be listed. They should be patient-centred longer-term outcomes or intermediate measures that have been validated to predict longer-term outcomes.	• Survival/mortality • Cardiovascular events averted • Quality of life
Price or cost in local setting	Price or cost per unit should be provided for both the intervention and comparators. If there are additional costs associated with administration and/or monitoring, these should also be included.	• Listed or reimbursed drug price
Subgroups of interest	Specify if there is an interest for the results of a specific subgroup in addition to the overall population.	• Demographics (e.g., age, gender) • Comorbidities
Regulatory and safety evidence	Include in-country marketing indications and safety concerns from the Summary of Product Characteristics.	• Adults with adult-onset diabetes and known cardiovascular or kidney disease

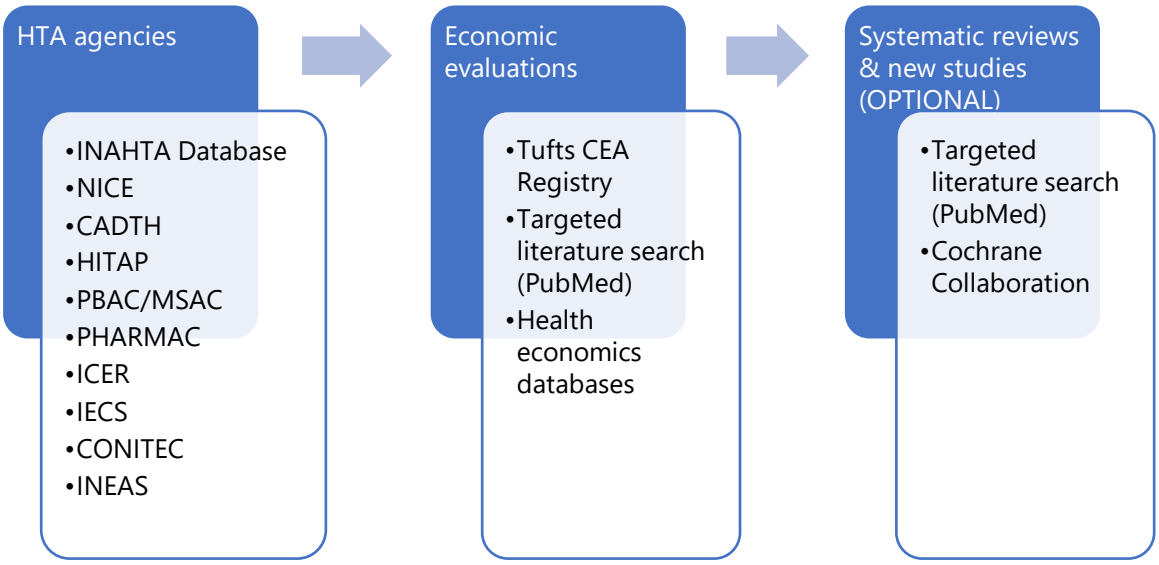
Note that in addition to the PICO elements, which are the critical elements for determining a match in project scope, we have added several items to ensure a relevant scope and potential connection to external evidence. Local prices are important local data to collect for price benchmarking, cost calculation, and (potentially) adjustment of cost-effectiveness evidence. Subgroups are often identified in HTA reports since the intervention might only be recommended for a subset of patients. Finally, regulators differ internationally with respect to the indication given for treatment, so it is important to define the regulatory indication within the local setting to ensure that the intervention can be prescribed for the indication specified.

4. Acquiring Evidence

Once the topic has been selected and the scope written, the next step is to collate the internationally available evidence on the topic. The set of evidence to be accessed is designed to be comprehensive yet pragmatic, and rapidly accessible. aHTA is generally structured to focus solely on (1) reports from HTA agencies, and (2) published cost-effectiveness analyses (CEAs) done in the local setting or internationally. HTAs from other jurisdictions is a particularly powerful component of this method because it enables countries to leverage other countries' technical capacity in collating, synthesising, and appraising the quality of evidence on a topic. Other possible data sources include published systematic reviews and clinical studies published more recently than the most up-to-date HTA report, but these are resource-intensive to identify and should be considered *optional* in any given setting (see optional module on Systematic Reviews and New Clinical Evidence later in this section).

Further details on the selection process can be found in the sections that follow. Representative sources and approaches for access are presented in Figure 2.

Figure 2: Hierarchical selection of potential sources of evidence



Note: CADTH = Canadian Agency for Drugs and Technologies in Health; CONITEC = Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde (Brazil); IECS = Instituto de Efectividad Clínica y Sanitaria (Argentina); ICER = Institute for Clinical and Economic Review; INAHTA = International Network of HTA Agencies; INEAS = National Authority for Assessment and Accreditation in Healthcare (Tunisia); HITAP = Health Intervention and Technology Assessment Program; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = The Pharmaceutical Management Agency (New Zealand).

4.1 HTA Reports

The International Network of HTA Agencies (INAHTA) maintains a searchable database to identify selected HTA reports: database.inahta.org. Figure 2 above lists a selection of the most influential HTA bodies worldwide, but the INAHTA database may be used to search for other reports that may be relevant to the local decision-making context. We recommend using this database as a complement to searching the individual websites of the HTA agencies of interest for your review.

4.2 First-Pass Examination of Evidence Base (OPTIONAL)

Once the scope has been defined and international HTA reports have been identified, there may be interest, particularly in settings that struggle to find sufficient resources even for aHTA, to pause for the purposes of determining if aHTA is necessary before proceeding further. There are two instances in which aHTA may be bypassed, each triggering a different pathway:

1) The available evidence consistently indicates that the intervention provides marginal or no benefit and is not cost-effective → exclude from consideration in health benefits package *without* conducting aHTA or any other form of HTA

2) The available evidence suggests significant clinical potential for the intervention, but there are key clinical and/or economic uncertainties that are known to be large and remain unresolved → consider full HTA

Note that the first-pass examination is *not* a detailed examination. Its purpose is to quickly survey authoritative sources on the technology in question to determine the level of consistency in findings and conclusions, not to actually synthesise the evidence. As such, this examination should focus only on a finite set of pre-approved HTA bodies with known rigorous methodologies and should not include assessment of the published literature or other grey literature sources. A diverse set of HTA organisations is recommended that vary in remit, operation, and country income to assess technology performance across a variety of settings. A sample list of organisations of interest might include:

- High-income: CADTH (Canada), ICER (USA), NICE (England/Wales), ZIN (Netherlands)
- Middle-income: HITAP (Thailand), CONITEC (Brazil), IECS (Argentina), INEAS (Tunisia)

It is entirely possible that the agencies listed above will not all have assessed a technology of interest; ***first-pass examination should only be conducted if at least 50 percent (four in the example above) have published an assessment (with representation from middle-income settings that are relevant to the local context).*** If these thresholds are not met, then the recommendation is to proceed with an aHTA.

1) Exclusion based on first-pass examination

Assuming that the characteristics of the population with disease and the severity of illness match the defined scope, HTA reports from the settings of interest are then reviewed for their principal findings, conclusions, and recommendation or decision. If the conclusions are consistently unfavorable toward the intervention, it could be excluded from consideration for the health benefits package without undergoing any HTA effort. Note that a similar approach is not recommended for consistently favorable findings, given the major health-system and cost differences that may persist across settings—in particular, what may be cost-effective or cost-saving in a high-income setting may not be so locally due to differences in the setting of care, alternative treatments, or other factors.

2) Referral for full HTA based on first-pass examination

In some cases, the clinical potential of a new intervention is consistently described, but there is a high level of uncertainty associated with assessment of the clinical and/or economic impact. This might arise from a limited evidence package for a technology that received expedited regulatory approval based on a small, single-arm study, for example, or for a new anticancer therapy with extremely limited survival follow-up. In these cases, it is likely advisable to conduct a full HTA based on the local context.

The overarching goal of the first-pass examination is to reduce the potential workload on topics for which the science is relatively settled. After scanning the conclusions and decisions of globally representative and authoritative institutions, analysts and policymakers will be able to focus resources on those topics requiring additional effort.

4.3 Published Cost-Effectiveness Analyses

In addition to HTA evidence, there may be published standalone CEAs that would be useful to consider. A full systematic review is unlikely to be feasible in the time available, and instead, a rapid and pragmatic search is recommended. Given the possibility that many such evaluations are available and the potential additions to the workload they may represent, it is recommended that priority be given to those CEAs conducted in middle-income settings that may be relevant to the local context (e.g., similarities in health systems and per capita income). CEAs evaluated in high-income settings may also be considered if the scope and perspective are a close match (e.g., a US-based evaluation using a Medicaid perspective, with similar demographics to the local target population).

It is important to note that economic evaluations can vary significantly in quality and may use inappropriate assumptions. They have rarely been through the same level of review and appraisal as an HTA report. It is therefore important to take time to appraise the quality and local applicability of these studies and use caution when interpreting their results.

There are a number of approaches to identify CEAs. First, the freely searchable PubMed database maintained by the National Library of Medicine in the United States (pubmed.ncbi.nlm.nih.gov), includes over 36 million citations and allows a filter to be set during searching to capture economic evaluation.

Economic evaluations may also be identified via the Tufts University CEA Registry (cear.tuftsmedicalcenter.org), an ongoing literature-based review of over 13,000 published CEAs that use the quality-adjusted life year (QALY) or disability-adjusted life year (DALY) as the measure of health gain of interest. A limited public search function is freely available; in addition, premium searching is available free of charge for LMIC researchers and institutions with the completion of a data use agreement.

4.4 Systematic Reviews & New Clinical Evidence (OPTIONAL)

If countries have more resources, they may wish to consider evaluating other published systematic reviews and meta-analyses, particularly if there are relatively few HTA reports available that represent a good match to the local context. These analyses may be identified in specifically curated databases, such as the library of systematic reviews maintained by the Cochrane Collaboration (cochrane.org). Studies published in peer-reviewed journals may be accessed through a targeted search of electronic literature databases. It is recommended that for pragmatic purposes the search be limited to PubMed, as the largest compilation that focuses on the English-language literature. Both databases include a search filter for systematic reviews.

It is also possible that available published HTA reports have not taken account of potentially important new clinical evidence. If the latest HTA report was published more than three years before the time frame of the aHTA, a limited search could be conducted to ascertain whether such evidence is available—for example, if there have been any updates to the underlying pivotal trial to see if the extrapolated outcomes can be validated. This should be an efficient process, conducted according to the following criteria:

- Limited time frame for publication, starting with the publication date of the most recent HTA or systematic review and ending with the current date
- Filtered to identify randomised controlled trials and prospective, comparative observational studies only

The purpose of this additional search is not to identify all new evidence but to highlight those studies that might make an important difference in the evaluation—for example, a direct comparison to an alternative of interest in a given country that was not a comparator in the original clinical trials. Importantly, for any new evidence, the quality of individual studies should be assessed. This will have been done already in HTA reports and published systematic reviews, but an appropriate tool should be used for any individual study identified.

An adaptive HTA effort was recently undertaken in Argentina that made use of these complementary sources of evidence, as described below.

In 2018, the Ministry of Health of Argentina commissioned the Institute for Clinical Effectiveness and Health Policy (IECS) to update its Health Benefits Package (PMO; Programa Médico Obligatorio in Spanish), which had not been revised since 2005. As part of this undertaking, 164 high-priority technologies were identified, for which prompt decisions regarding their adoption and coverage in the benefits package were imperative. Due to resource and time constraints (the project was required to be completed in less than a year), conducting full HTAs was not feasible. Therefore, an aHTA approach was employed.[25]

Rapid reports were generated in accordance with the IECS methodology for HTA documents[26] *within a time frame of six to eight weeks. The assessment and selection of studies were based on the PICO framework, with a specific search strategy for each technology, encompassing PubMed and supplemented by searches in Trip Database, INAHTA, LILACS database, health funders and scientific society websites, and generic Internet search engines. Priority was given to the inclusion of systematic reviews, randomised controlled clinical trials, HTA reports, economic evaluations, and clinical practice guidelines. A systematic search for coverage policies was carried out in public healthcare systems in*

Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay), Europe (France, Germany, and United Kingdom), Australia, and Canada, as well as a selection of public and private insurers in the United States.

These rapid HTAs focused on evaluating three key domains: the quality of evidence, net clinical benefit, and economic and organisational aspects (cost-effectiveness and budget impact). To assess the quality of evidence, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology was employed, while an adaptation from the German HTA agency (Institute for Quality and Efficiency in Health Care) was used for evaluating clinical benefit. The results were summarised using a five-category recommendation "traffic-light" scale, spanning from a strong recommendation in favor of technology inclusion in the health benefits package to a strong recommendation for exclusion.

Of the 164 technologies assessed, only 25 percent received a recommendation in favor of inclusion. The results of this work were intended to provide valuable input to the decision-making committee responsible for conducting a deliberative evidence-informed process and ultimately determining the final decisions regarding the benefits package update.

4.5 Data Extraction

Once the searches have been conducted and relevant documents have been selected for review, relevant background, clinical, and cost-effectiveness data should be extracted; templates for data extraction can be found in Tables 3-5 below and an Excel sheet is provided here to support this. The data extraction tables will be used to standardise the information aggregated to facilitate comparisons and provide consistency in reporting across selected documents.

4.5.1 Background information

Background information is used to identify and contextualise the studies and confirm that the information in the document under review matches the decision problem in the scope. Elements of interest can be found in Table 3 below.

Table 3. Data extraction: background information

Data point	Description
Country	The primary country of the document/analysis to help understand how generalisable the results are to the local context and the HTA agency if relevant
Analysis type	Whether the document is an HTA or stand-alone economic evaluation
Link	Web link to the document (and additional citation information if available)
Title	Full title of the document
Author	Names of the authors of the document, if appropriate
Date	Date of the report to contextualise when the recommendations were made
Population	The target population identified in the report
Indication	The disease area or subpopulation assessed to confirm that it matches the scope
Intervention	The name of the intervention in the report and its associated dose
Comparator(s)	The name of the comparator(s) in the report and their associated dose
Funding source	The type of entity funding the study or report (e.g., government, industry, foundation, etc.)

4.5.2 Clinical evidence

Clinical evidence can be extracted from the HTA reports or economic evaluations. This will provide the basis for the extrapolations used in the cost-effectiveness models, as well as how the benefits, risks, and uncertainties of treatment inform QALYs or other summary measures of health gain in the economic evaluations. Note that it is not necessary to conduct a separate search for detailed clinical evidence, as the summary data available in HTA reports or published CEAs will be sufficient.

The PICO exercise will determine what outcomes are most appropriate for the disease area and treatments under study. Regardless of the area of focus, however, there is consistent guidance regarding the type of information to extract, as listed below (and shown in Table 4):

- Absolute estimates of treatment effect (e.g., rates, means, medians, percentages, or months)
- Relative estimates of treatment effect (e.g., odds ratios, relative risks, or hazard ratios)

For each estimate, it is essential to include the following (where reported) to gain a sense of the potential uncertainty:

- Measures of variance, including standard deviation/error and others
- Sample size, p-values, and confidence intervals for all estimates
- For meta-analysis: number of contributing studies and weighting factors used

It is important that all relevant clinical outcomes and safety considerations are extracted and reported from each document in order to gain an understanding of all potential benefits that need to be considered. All data extracted should include both the point estimates to define the benefit and measures of variance with associated p-values and confidence intervals to understand the uncertainty around the benefit.

There may be additional nuances in the evidence base that should be described outside of the results of a given clinical study. For example, a placebo-controlled clinical trial conducted in patients who responded to prior therapy may overstate the benefit of a new treatment; this is a structural and design issue rather than a concern regarding reported results. Space should be allocated in data collection to describe these issues in further detail and identify if there are any potential limitations of the underlying clinical data.

Table 4. Data extraction: clinical evidence

Data point	Description
Study name	Title, author, year
Type of study	Study design, geographic settings, number of patients
Comments on clinical benefit	Note anything unusual or noteworthy about the findings
Duration of treatment and/or follow-up	Statistics (e.g., mean, standard deviation) on the duration of treatment with the intervention and comparator, length of study follow-up, or both
Outcomes	Point estimate and confidence intervals for each outcome of interest (e.g., %, mean), separately for intervention and comparator, and measures of between-group difference
Measures of variance	Standard deviation, standard error, 95% confidence interval, etc., for each outcome of interest
p-value	Measure of statistical significance of the comparison for each outcome of interest
Limitations, critiques, and residual uncertainties regarding the clinical evidence	Limitations on generalisability to the local context (e.g., differences in disease severity, subpopulation differences, bias in study design or sampling strategy); uncertainties from limited follow-up; major differences between study protocol and typical clinical practice, etc.
Safety evidence	Rate of serious adverse events for intervention and comparator; identification of any specific adverse event types that occur with more frequency in the intervention or comparator group; rate of discontinuation due to adverse events

Other considerations	Mention of other contextual issues, such as complex implementation or treatment delivery, specialised training required, etc.

4.5.3 Cost-effectiveness evidence

Cost-effectiveness evidence will also be extracted from HTA agency assessment reports or published economic evaluations from international jurisdictions. This evidence is typically based on the outputs of a simulation modeling exercise. The key data points which may be considered useful for decision making involve extracting information on costs, health-related quality of life, estimates of cost-effectiveness and budget impact, conclusions or recommendations based on findings, and an assessment of the quality of the evaluation (see Table 5 below for details on data extraction).

Table 5. Data extraction: cost-effectiveness analysis

Data point	Description
Study-level characteristics	Important study descriptors, including (1) perspective (e.g., health system, societal); (2) time horizon; (3) discount rate; (4) unit costs of intervention and comparator; (5) currency used; (6) currency year
Intervention costs	The costs associated with the intervention, disaggregated if available (e.g., treatment costs, resource use costs, adverse events, administration costs, other relevant costs)
Comparator costs	The costs associated with the comparator, disaggregated if available
Incremental costs	The difference in costs between the intervention and comparator
Intervention QALYs	The QALYs associated with the intervention
Comparator QALYs	The QALYs associated with the comparator
Incremental QALYs	The difference in QALYs between interventions
ICER	The incremental cost-effectiveness ratio (intervention vs. comparator)
Main drivers of cost-effectiveness	What were the most influential factors? Assessment of this will be important for considering the transferability to the local context
Cost-effectiveness threshold	The threshold to which the ICER was compared in the study publication or HTA assessment Note if this is adjusted in any way due to special conditions (e.g., rare disease, end of life, paediatric, etc.)
Price of intervention	The price of the pack and pack size in order to inform the additional analyses: price benchmarking, treatment cost estimates and budget impact
Price of comparator	Same as for the intervention

Likelihood of cost-effectiveness at the threshold	A metric that will be reported from the probabilistic sensitivity analysis that provides context on the uncertainty surrounding the ICER
Limitations, critiques, and residual uncertainties regarding the cost-effectiveness	Were there issues concerning model design, key assumptions, data sources, or other components of the evaluation that would improve or reduce confidence in the ICERs, or limit their transferability to the local context?
Recommendation or conclusion	Was the intervention recommended or did the study conclude that it was cost-effective? Were there any price discounts required? Additional restrictions on use?

Note: ICER = incremental cost-effectiveness ratio.

4.6 Pause to Determine Continuation of aHTA or Conversion to Full HTA

Once the evidence has been extracted, it is important to pause and reflect on whether the conditions are suitable to continue with rapid review aHTA or if a full HTA is warranted. While this is ultimately a judgment for the relevant decision makers, sample criteria for making the determination are provided in Table 6 below. For example, the relative comfort that comes from evidence generated by large, robust clinical trials may make aHTA a defensible choice, whereas limited evidence from small or uncontrolled studies may introduce enough uncertainty that full HTA is required. If most of the available data (e.g., estimated treatment effects) are felt to be transferable from settings in which the pivotal studies were conducted to the local setting, then aHTA is likely a feasible option. However, if detailed local data are required because of implementation issues, uncertainties in the evidence, or other concerns, full HTA may be the better option.

Finally, the impact of a decision compared to its urgency may need to be considered. If a given decision is felt to be impactful enough, then a careful, full HTA may be recommended to minimise the risk of an incorrect decision; however, if a high-priority topic also requires an urgent decision, aHTA should be employed at least as a first effort.

Table 6. Sample criteria for deciding to refer the aHTA topic for a full HTA

Criteria	Description	Examples of Potential Actions
Nature of the evidence	What are the types of study designs, outcomes measured, and size of the evidence base?	• Large randomised trials reporting patient-relevant outcomes → aHTA is acceptable • Small clinical studies reporting intermediate or surrogate outcomes → full HTA preferred
Local data	Are implementation concerns, uncertainties in the evidence, health system differences, or other criteria high enough to require local data?	• No → aHTA • Yes → full HTA

Timing of the decision	Is a decision on a technology urgent or less pressing?	• < 6 month time frame → aHTA • 6+ month time frame → full HTA
Exceptionally high impact decision	Is the burden of disease, budget impact, or political risk so high that it is critical to get the right decision?	• Normal impact level → aHTA • Exceptionally high impact → full HTA

These criteria may be deemed more or less important in any given setting, and other criteria not listed here might also play a role. For example, if the implementation of a given technology requires other activities for success (e.g., advanced training, a network of specialised centers, or a companion diagnostic test), full HTA may be warranted to explore these issues further.

4.7 Key Uncertainties

4.7.1 Uncertainties in translating the evidence to the local context

Before considering whether a particular technology may be cost-effective in the local setting, steps should be taken to document any uncertainties in the circumstances under which the technology is obtained, provided, and received in the international evidence, and how those circumstances might differ in the local setting. Key generalisability considerations are described further in Table 7 below;[27] local decision makers may wish to create additional categories as well. For example, a particular technology might require highly specialised training and have health professionals be certified in its use, a step that may not be feasible locally, or may require specialised equipment for delivery that is unattainable locally. The setting of treatment might also differ; a therapy that can be safely given in an outpatient setting in higher-income countries may require inpatient care locally, which may change the picture considerably for both clinical outcomes and costs. It could also be the case that the appropriate post-treatment monitoring recommended in higher-income settings cannot be achieved in LMICs because many patients do not have reliable transportation to the clinic. Inclusion of local clinical and health-system experts in the aHTA process is necessary to bring these sorts of uncertainties to light.

It is important to note that these examples largely would not be identified through the process to match the PICO between the local setting and the international reports, but instead represent areas of nuance and operational reality that must be considered. While some TISP processes can include feasibility-related criteria that may partly cover these concerns, TISP may not have fully covered all considerations relevant to this decision point. Therefore, it is still critically important to log these uncertainties separately in the Excel template.

Table 7. Key generalisability considerations

Domain	Description
Feasibility	Delivery of the intervention as reported in clinical studies should be possible in the local context, or variation by setting should be measurable (e.g., facilities with vs. without specialised training).

Coverage	Adequate coverage of the intervention is available or gaps in coverage are identifiable (e.g., urban vs. rural).
Acceptability	The intervention should be acceptable to patients, caregivers, and clinicians, and challenges to acceptability are identified (e.g., social norms for STD prevention).
Representativeness	Populations in clinical studies should be generally reflective of the target population for the intervention, or gaps in representation should be identified (e.g., underrepresentation of minority racial or ethnic groups).
Needs of future recipients	Support services necessary to ensure adherence to treatment in typical practice should be identified (e.g., educational materials or case management)
Impact on care pathway	Extent to which benefit extends beyond disease in trial vs. target population (e.g., spillover effects of treatment in high-risk individuals vs. a more general population)

Source: ***Bonnell C et al., 2006.***[27]

4.7.2 Uncertainty in incremental cost-effectiveness ratio estimates

As described above, most CEAs are the result of a simulation modeling effort that in many cases extrapolates short-term clinical data through a treatment pathway that has multiple decision points and is assessed over the very long term. As such, numerous assumptions must be made, and there are multiple uncertainties associated with these. It is therefore crucial to capture in the data extraction the level of uncertainty in the results.

The base-case cost-effectiveness results will typically rely on point estimates. These are often tested in multiple types of sensitivity analyses. It is important to characterise these results in detail, so there is understanding of how consistent the conclusions may be when parameters are varied and whether some parameters affect the results more than others. When set in context, there can also be understanding of whether the model sensitivities would be more or less pronounced when generalised to the local setting. Record in the Excel template any uncertainties that might change the results, and any concerns with the underlying assumptions and model structure.

4.7.3 Drivers of cost-effectiveness

In addition to documenting uncertainty, it is also important to record what the key underlying drivers of the results are, so there can be deliberation with experts regarding how the clinical effects and cost offsets might play out locally.

As an example, suppose a new treatment might become cost-effective if it would displace significant resource use involved in delivering the current standard of care. To use a UK example, the treatment might cost £10,000 more, but because patients are healthier for longer and do not require additional care, it could save the health system £15,000. However, this savings might not be generalisable to the local setting, which would change the results. Taking the same example, if the treatment costs 100,000 more Indonesian rupiah but due to the differences in clinical practice between Indonesia and the UK

the difference in resource use and associated costs might mean that it only saves 50,000 rupiah, then conclusions around cost-effectiveness might change.

Another common driver of cost-effectiveness is the comparability of the clinical benefits. If the clinical benefits are quite similar between a new treatment and the comparator, then even small differences in price can have a great impact on the cost-effectiveness. For example, if the QALY gain with a new treatment is 0.02 (about seven additional days of quality-adjusted life expectancy), a £250 increase in incremental costs from £500 to £750 would increase the incremental cost-effectiveness ratio (ICER) from £25,000 per QALY gained to £37,500, potentially changing conclusions about cost-effectiveness. However, if the QALY gain was 0.3 (a little more than three additional *months* of quality-adjusted life expectancy), the change in costs would change the ICER very slightly (from £1,667 to £2,500 per QALY gained) and wouldn't necessarily change the conclusions.

Another significant driver of cost-effectiveness is the expected duration of treatment. In cancer treatment, for example, many new therapies are prescribed on a "treat to progression" basis, where therapy continues until there is evidence that the disease has returned or progressed to a more severe level. In contrast, many older chemotherapy drugs, and even some newer specialised treatments, are given over a fixed number of cycles. These dynamics can greatly affect the incremental costs associated with treatment as patients progress through disease states. While keeping cancer in remission and avoidance of disease progression are desirable health outcomes, the expectations regarding duration of treatment are important to keep in mind when interpreting results and considering costs to the system.

Try to determine the main factors influencing the ICER (the cost offsets or the clinical benefits) and consider with experts whether they apply to the local context.

5. Supporting Analyses

Following consideration of the data extracted in Section 4, it is valuable to carry out additional analyses to inform decision makers. In this section we recommend three additional analyses: price benchmarking, treatment cost calculations, and budget impact analysis. We also propose two optional analyses that may be considered: ICER adjustments and a review using evidence transferability checklists.

5.1 Price Benchmarking

Commodity prices can be a key driver of cost-effectiveness and can vary substantially between countries. A price benchmarking analysis should therefore be done to compare the benchmark—meaning the list price in the country of the original HTA or cost-effectiveness analysis (CEA)—with the list price in the local setting, while adjusting for differences in country wealth.[15] While this is not a precise costing exercise, it can provide transparency and insight into the difference in price that the country of interest is paying and helps interpret decisions from other settings. Such efforts are commonplace in many European middle-income countries.

This analysis should be done for both the price of intervention and of the comparator. Are local drug prices similar to that of the benchmark countries relative to GDP? Are they higher or lower? Are prices similar for both the intervention and comparator, or is one more costly than the other?

If the local country is paying a similar amount for both drugs relative to GDP, then the results could be considered more transferable between settings. Alternatively, if local prices are higher for the intervention and lower for the comparator in relation to the benchmark country, then it is less likely that the intervention price would be considered a cost-effective investment.

The approach involves taking reported prices from HTA assessments or published CEAs of focus for the rapid review aHTA and comparing those prices to the current price in the local context. Prices are converted to a common currency and adjusted for gross domestic product per capita (GDPpc) to address different levels of affordability between settings. The prices paid for drugs in the local context may be similar to the prices paid abroad once adjusted for currency; however, a similar price could be perceived as being less affordable if per capita purchasing power (GDPpc) is lower than that of the benchmark country.

Therefore, the price in the benchmark country as a proportion of its GDPpc is compared to the price in the local country as a proportion of its GDPpc, creating a ratio that determines how much more or less is being paid for the same drug. A ratio greater than1 indicates that the price is higher than expected after taking GDP into account and therefore less likely to be cost-effective. A ratio less than 1 suggests it is lower than expected and more likely to be cost-effective. The exercise is repeated for all comparators as well. The detailed steps used to develop this benchmarking exercise can be found in the accompanying Excel template.

The value of the ratio is the most important consideration. Ratios less than 1 suggest that an HTA approval from the benchmark country, based on the reported price, can more reliably be transferred to the local context. Ratios much greater than 1 suggest that an HTA approval in the benchmark country may not be reliably transferred to the local context given the higher price paid locally.

It should be noted that the price analysis is merely meant to provide insight into potential pricing differences and should be considered one part of a broader package of analyses aimed at informing and supporting decisions. Additional analyses to adjust international cost-effectiveness estimates for local consideration are also available as an option and are summarised below.

5.2 Treatment Cost Calculation

While price benchmarking is an important exercise, it is also important to understand the overall cost of delivering the intervention (or comparator) of interest, given differences in dosing frequency, typical duration of treatment, and any monitoring or concomitant treatment necessary (e.g., complementary drugs to use with chemotherapy). Small differences in unit price (e.g., price per pack or injection) may grow larger when these other elements are considered. In order to fortify the aHTA, it is important to determine the treatment costs of all interventions and comparators being considered and include these figures in the final report.

As the difference in treatment cost grows larger, the clinical benefits or cost offsets would also need to increase for the intervention to be considered cost-effective. Knowing the difference will help anticipate the scale of benefits or cost offsets (i.e., costs avoided as a consequence of improvements in efficacy and/or safety, which offset a proportion of the additional cost of a new healthcare intervention) needed to render the intervention cost-effective; therefore, this analysis uses local price data to determine the difference.

It is also important to note that the larger the difference in costs, the more likely it will be that the intervention will have a large budget impact, as that difference will be multiplied by the number of patients expected to receive the treatment. A large budget impact may result in a refusal to recommend the intervention even if it appears to be cost-effective because it will not be financially sustainable to provide.

Treatment costs can be calculated with a degree of confidence based on the following:

- The unit price of the drug (e.g., per pill or syringe)
- Size of the pack (how many units)
- Frequency of dosing (e.g., three times per day or once per month)
- Duration of treatment cycle (e.g., daily chronic therapy or one chemotherapy treatment every 28 days)
- The number of cycles recommended (for anything other than chronic therapy)
- Any changes in dosing during treatment (e.g., a loading dose)

With this information, it is possible to calculate the treatment costs per year for the intervention and any comparator and then find the difference between the two to understand how much more or less money the health system is likely to spend, though it does not account for any costs offsets through displaced resource use. As noted above, the potential for cost offsets (i.e., reductions in the use of other resources from use of the drug) should be considered when large differences in treatment cost are observed. The Excel template can support you to carry out this analysis.

5.3 Estimated Budget Impact

If a given intervention appears to be cost-effective, this does not necessarily imply that it is affordable within the boundaries of the health system. Hence, an estimate of the budget impact of the new technology is essential to assess affordability. This generally involves estimating the current spending on the standard of care and calculating how much spending would change by introducing the new technology.

Estimating current spending is relatively simple—the size of the population that is currently receiving care is multiplied by the cost of standard treatment as calculated in Section 5.2. This is compared against the costs of care following the introduction of the new technology. Given that the new technology may not replace the existing technology completely, the new cost of care has two components—the costs related to the proportion who still receive standard treatment and the costs related to those who shift to the new technology. In addition, the new technology may increase access, so an adjustment must be made to include any new candidate patients for the technology.

As with treatment costs, this is a relatively simple approach and does not account for potential cost offsets because the data is normally not easily available.

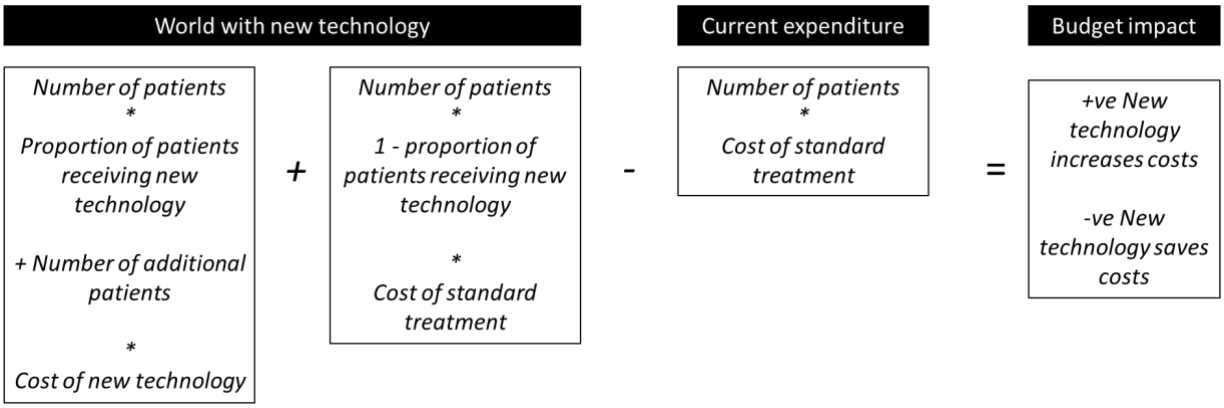
There are several components necessary to estimate a simple analysis of the budget impact of adopting a new technology:

A. Number of eligible patients
B. Cost of standard treatment (calculated as in Section 5.2)
C. Proportion of the population who will receive the new technology
D. Number of additional patients who will receive the new technology (e.g., subgroup that could not access standard care but can receive the new treatment)
E. Cost of the new technology (calculated as in Section 5.2)

The budget impact is then assessed using the formula, which is explained in Figure 3 below:

Budget impact = ((((A * C) + D) * E) + ((A * (1-C)) * B)) – (A*B)

Figure 3. Approach for estimating population budget impact



For example, suppose standard treatment is currently provided to 50,000 individuals and costs $1,000 per year. That would entail that current expenditure is $50 million.

Supposing the new treatment is expected to take 65 percent of the current market, be available to an additional 5,000 patients, and will cost $5,000 per year. Multiplying the size of the current population

by 65 percent yields a total of 32,500 individuals. Adding 5,000 new patients raises this figure to 37,500 and multiplying the resulting number by $5,000 yields a total of $187.5 million of costs introduced by the new treatment.

The size of the population that will continue to receive standard treatment is (50,000 multiplied by 0.35), or 17,500 individuals. Multiplying this figure by the annual cost of $1,000 yields total costs of $17.5 million.

Together, the total costs in a world with the new technology is $205 million. Subtracting the current expenditure of $50 million shows that there is a budget impact of $155 million of introducing the new technology in one year.

5.4 Optional Analyses

5.4.1 Adjusting Incremental Cost-Effectiveness Ratios to the Local Context

ICERs play a pivotal role in guiding resource allocation decisions for evidence-based decision making. The ICER is displayed as a ratio of the difference in costs between an intervention and comparator to the difference in health outcomes between these two treatments.[28] Outcomes are most frequently summarised as quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs), which reflect effects on both length and quality of life.

ICERs reported in studies published elsewhere offer valuable insights, but they may not always be directly applicable to local healthcare contexts due to contextual differences in patient populations, healthcare systems, and resource use. Decision makers need accurate information to allocate limited healthcare resources effectively. Local adjustments help bring the ICER closer to the local value of an intervention.

The adjustment of the components of ICERs for use in different healthcare contexts is a complex task that requires careful consideration of various factors. Methodologies for adjusting ICERs are still under development and include currency conversion, accounting for demographic and epidemiological differences, and considering variations in the costs of healthcare resources.

Adjusting ICERs may assist in interpreting evidence from other countries by removing the effects of some known parameters such as currency and relative wealth, but it is important to highlight that they are a crude calculation that should not be solely relied upon for decision making. International ICERs will be reflective of the difference in resource use and costs from a different country, and the same conditions may not apply to the local context. In addition, there is no internationally recognised standardised method of adjusting ICERs; these methods are exploratory and may add more uncertainty to results, which is why they are optional. It is therefore important to proceed with caution.

The following methods may be used to make separate adjustment to *incremental* costs and outcomes (i.e., the difference between intervention and comparator). Only after these adjustments are made should an "adjusted ICER" be calculated (see below).

5.4.2 Cost adjustments

Adjustment for differences in prices of healthcare

Healthcare costs can vary significantly between different countries and regions due to differences in the availability of resources, healthcare infrastructure, and economic conditions. For instance, the cost of medical personnel, medications, and medical equipment may differ substantially from one location to another. Applying an adjustment factor partly helps account for these differences and brings the cost estimates to a common baseline, although it cannot fully adjust for all potential cost differences.

This can be done by calculating the ratio of the GDPpc of the local country (country for which the decision has to be made using adapted estimates) to the GDPpc of a comparator country (country for which published estimates are available), and multiplying the resulting ratio by healthcare costs in the comparator country to generate a local estimate for incremental costs. The formula below can be used, where "l" indicates the local setting and "c" indicates the comparator country:

$$Cost\ (c) \times \frac{GDPpc\ (l)}{GDPpc\ (c)}$$

Adjustment for changes in price over time (inflation adjustment factor)

Healthcare costs, like other goods and services, are subject to inflation over time. Inflation causes the prices of healthcare resources to rise, which can have a significant impact on the cost-effectiveness of interventions. Failing to account for inflation can lead to inaccurate cost estimates, as the real value of money changes over time. This can be done by calculating an adjustment factor which accounts for inflation over time from the year of published estimates (base year) to the year of decision making for the local context (current year). The consumer price index (CPI) of the local country from the base year to current year should be used to adjust for inflation. This adjustment would account for the erosion of purchasing power due to inflation, allowing decision makers to make informed choices based on current economic conditions. The formula for this calculation is as follows:

$$Cost\ (base\ year) \times CPI\ \frac{current\ year}{base\ year}$$

Using both adjustments together will provide an insight into the ICER when adjusted for differences in country wealth and current year prices.

5.4.3 Health outcome adjustments

When considering CEAs from different healthcare contexts it may sometimes be a concern that health outcomes, as measured by QALYs and DALYs, are influenced by both the duration and quality of life. If there is a difference in life expectancy or health state preferences between contexts that may potentially influence the interpretation of results from abroad then there are two potential adjustment factors that are suggested that could assist with the interpretation of these estimates.

Adjustment for duration of life (life expectancy adjustment factor)

An adjustment factor that accounts for the variations in duration of life between the local and comparator countries can be used. This can be computed based on the ratio of the difference in country-specific life expectancy and the median age of onset of disease in the local country and the comparator country. This adjustment factor recognises that the age at which a disease occurs and its impact on life expectancy can vary between regions. Adjusting for this difference may better reflect the specific disease burden and life expectancy patterns of the local population, although it is still a crude adjustment. When disease-specific estimates of onset of disease are not available in both settings, life expectancy from birth may be substituted instead. Please see the formula below, where "l" indicates the local setting, "c" indicates the comparator country, "LE" indicates life expectancy, and "AD" indicates age of disease onset:

$$QALYs/DALYs\ (c) \times \frac{LE\ (l) - AD\ (l)}{LE\ (c) - AD\ (c)}$$

Adjustment for health state preferences (quality of life adjustment factor)

Preferences for health states, as measured by utility values, can vary among populations due to cultural, societal, and individual factors. An adjustment can be made to use utility values that better reflect the preferences of the local population. The intention of the adjustment is for the QALY component of the ICERs to better align with the values and priorities of the people being served by the healthcare system. QALYs can be multiplied by the mean of the ratios of tariff values of corresponding health states in the value set of the local country and comparator country. Note that

this adjustment is only relevant for QALY-based analyses and requires that tariff sets be available for both local and comparator settings. The step should be omitted if relevant information is not available. The formula for the calculation is below, where "l" indicates the local setting, "c" indicates the comparator country, and "UT" indicates the utility tariff:

$$QALYs/DALYs\ (c) \times \frac{UT\ (l)}{UT\ (c)}$$

5.4.4 Adjusted ICERs

Once any adjustments have been made to costs and QALYs or DALYs, an adjusted ICER can be calculated. This is simply the ratio of the adjusted costs to the adjusted QALYs or DALYs, using the formulae described above, and displayed as follows:

$$Adjusted\ ICER = \frac{Adjusted\ Incremental\ Costs}{Adjusted\ Incremental\ QALYs\ or\ DALYs}$$

As with any adjustments to original estimates that are complex themselves, there are pros and cons to this approach, as listed below.

Pros:

- Produces a rough estimate of local cost-effectiveness without the need to specify a full model
- Generates a quantitative estimate of local cost-effectiveness, which can be useful for negotiating prices with drug companies
- Adjusts for variables known to vary significantly by country

Cons:

- Does not reflect differences in health-system infrastructure or clinical practice that may drive the costs and/or effects of implementing a given intervention within the local country
- Uses simple multiplication and division, which does not reflect the uncertainty or instability in the original estimates
- Uses calculations that add significant uncertainty to the estimate
- Produces estimates that, by seeming precise, may provide a misleading sense of accuracy to decision makers

5.4.5 Price-adjusted ICERs

There may be situations in which it is clear that in all contexts (i.e., the settings where cost-effectiveness data will be both transferred *from* and transferred *to*) that the price of the technology is by far the most important driver of the results, such as with oncology drugs and treatments for rare diseases. In these cases, it may be possible to adjust the ICER itself from other jurisdictions to the local context using a simpler approach. The formula is shown below where $ICER_A$ is the ICER adjusted to the country of interest, $ICER_O$ and P_O are the ICER and price of the technology in the country of origin, and P_A is the price of the technology in the country to which the ICER is being adapted:

$$ICER_A = ICER_O * \frac{P_A}{P_O}$$

This approach is a component of a methodology published by the Inter-American Development Bank[29] that also includes analyses of coverage or inclusion in benefits packages of other countries and application of the treatment effects seen in clinical studies.

5.5 Checklists for Understanding the Transferability of Evidence

There is an important qualitative step to understanding the *transferability* of HTA reports to the local setting when the PICOs and key drivers and assumptions of an HTA are compared to the local context. An alternative option to guide this assessment is to use formal checklists to support this sort of transfer. Most HTA transfers follow a similar process, with the aim of determining if an HTA is applicable and generalisable or transferable to another context.

There are many checklists available for the assessment of transferability of HTAs.[30] There is no gold standard for these checklists, so in this section we provide a description of some of the commonly used methods that policymakers may wish to employ. If a full HTA report is identified (e.g., clinical evidence synthesis, economic evaluation, and implementation concerns), the EUnetHTA adaptation toolkit may be most relevant since it provides checklists for multiple HTA domains as well as assistance with searching for evidence, assessing applicability, and advice on transferability.[31] However, the toolkit is not very prescriptive and might best be considered a brainstorming tool for reflecting on current practices. For systematic reviews, the most detailed transferability checklist is the TRANSFER Approach.[32]

For rapid review aHTA, however, interest will primarily be in the transferability of economic evaluations. Checklists of interest include the Mullins checklist,[33] Welte's checklist,[34] and the Drummond-ISPOR checklist.[35] Each of these has specific features. The Mullins checklist, for example, provides detailed guidance on specific aspects of cost-effectiveness models to consider. Welte provides knock-out criteria for challenges to the general applicability and specific transferability of economic evaluations, while Drummond-ISPOR provides guidance for situations in which a study cannot be adapted or transferred. Each of these also has advantages and disadvantages, as outlined in Table 8 below.

When transferring HTAs, systematic reviews, or economic evaluations, it is important that the quality of the study is sufficient before consideration of transfer is made, to avoid erroneous decisions that arise from poorly constructed models. While there is no tool for rating the quality of HTA reports, the AMSTAR 2 rating system is available for systematic reviews.[36] There are multiple tools available for economic evaluations, but the most comprehensive and widely accepted tool is the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement, recently updated in 2022, which focuses on both completeness of description and methodological standards.[37]

Table 8 outlines the domains that can be considered for transfer, the applicable quality standards and transferability checklists, and the strengths and weaknesses of each option with regard to transferability. As noted, there is a general trade-off in the transferability checklists between the availability of specific and detailed guidance, and the complexity of the checklist itself.

Table 8. Summary of quality standards and transferability checklists

HTA domain(s)	Quality standards	Transferability checklist	Strength *transferability checklist*	Weakness *transferability checklist*

All domains in typical HTA reports	NA	EUnetHTA adaption toolkit	- Guidance from searching from studies to assessing transferability - Multiple domains	Reflective practice, guidance on adaptation less detailed
Safety and effectiveness	AMSTAR 2	TRANSFER Approach	- Detailed guidance on transfer - Framework to involve stakeholders	- Complex and lengthy
Costs and cost-effectiveness	CHEERS Statement (2022)	Welte's checklist	- General and specific knock-out criteria - Applies to model- and trial-based EEs	Limited guidance on adaptation of EE
		Drummond-ISPOR checklist	- Additional guidance if transfer not possible - Supported by ISPOR	Complex and lengthy
		Mullins checklist	- Detailed guidance on model elements	- Applicable to model-based EEs only

Note: EE = economic evaluation.

In addition to the specific advantages and disadvantages, there are general concerns with using transferability checklists that must be considered. First, a high-quality study that is poorly reported or documented may be excluded, while a study that has complete descriptions but major challenges in structure or data may be included.[37] In addition, even the most comprehensive checklist cannot reveal every element that may be of concern for transfer.[38]

We recommend that any agency conducting aHTA and using transferability checklists integrate safeguards into the process. For example, clinical experts, patient representatives, and others can provide an external *transferability review* to identify situations in which the transfer might be doubted because of differences in the conclusions of a transferred study relative to observations regarding clinical practice or care delivery in the local setting.

Nevertheless, the use of transferability checklists has the potential to screen in useful information and screen out data that may not be usable in the local setting. Careful use of these checklists can speed up aHTA processes and avoid duplication of effort.

Pros:

- Systematic measure of transferability
- Might increase confidence in using the results

Cons:

- Takes time to conduct and, depending on the level of detail of the checklist and need for prework, may not be as rapid
- Might miss certain crucial nuances since HTA evidence is bespoke and tailored to the decision problem

6. Synthesising Evidence and Making Recommendations

Once extraction of the information from HTA reports and cost-effectiveness studies is finished and interpreted, and supporting analyses of interest are completed, the full evidence package should be synthesised. The intent is to provide a comprehensive view on the accumulated information on the clinical benefits, risks, cost, cost-effectiveness, and potential budget impact of the intervention under review; any uncertainties that should be considered; and ultimately, a summary judgement regarding the appropriate decision on the intervention for the local setting. The sections below provide a step-by-step guide to the key elements of the assessment.

6.1 Background on Topic and Rationale for aHTA

The assessment should begin with background information on the disease in question, its epidemiology in the local setting, the current burden of the disease, and how the intervention of focus might address the burden. The rationale for aHTA should then be described in detail, including how the criteria set forth in Section 2 were fulfilled.

6.2 Summary of Findings from HTA Reports and Economic Evaluations

6.2.1 Clinical benefits and risks

Given the need for efficiency in a rapid review aHTA and the steps already taken to ensure a match in scope, there is no need to conduct an exhaustive review of the clinical evidence from available HTA reports. Instead, a brief summary should be generated from the HTA reports on the following elements:

- The main clinical benefits of the intervention relative to the comparator
- The main safety risks or concerns identified for the intervention
- The HTA conclusions regarding the magnitude of the clinical benefit to patients
- The level of confidence or certainty in the evidence available

Of these, the level of confidence or certainty may be the most difficult to estimate. Some HTA reports will explicitly describe this or provide guidance on it in the rating system they use for clinical effectiveness (e.g., evidence ratings in France and the United States).39,40 Others may not be as clear. State any concerns with the level of confidence in the estimates of clinical benefit and if it is anticipated that the potential changes could be meaningful. All concerns with the confidence of the results should be captured in the reporting.

6.2.2 Likely cost-effectiveness

Given that economic evidence will likely have been adjusted or transferred from the comparator studies to the local setting, summarising the economic evidence will be a more detailed exercise. The first step will be to summarise the conclusions from the available HTA reports that include a CEA as well as any published economic evaluations. These can be simply categorised as follows:

- Not cost-effective (at the price considered in the original HTA)
- Cost-effective (at the price considered in the original HTA)
- Insufficient data to determine cost-effectiveness

Next, the results of the price benchmarking and treatment cost analyses should be summarised. As described in the previous sections, the results of these analyses are reasonably straightforward and can be simply catalogued. For price benchmarking, the ratio should be provided and the two categories specified:

- Adjusted local price lower than or as expected (ratio less than or equal to1.0)
- Adjusted local price higher than expected (ratio greater than 1.0)

For treatment cost calculations, the focus is on the difference in estimated local costs between the treatment and comparator. While there is no clear threshold for this difference, it can be simply catalogued as:

- Small differences in cost between treatment and comparator
- Large differences in cost between treatment and comparator

As with a price benchmarking ratio of greater than 1.0, large differences in cost will make it difficult to achieve a cost-effective conclusion in the local context.

Finally, the results of any adjusted CEAs can be summarised. The details of the method selected should be provided, as well as the rationale for the decision to transfer (including checklist results if this option is taken). Original and adjusted ICERs should be included. Adjusted results can be compared to a local threshold (where available) that represents the willingness to pay for gains in health in the local context. ICERs close to or below the threshold can be considered to represent potentially cost-effective uses of the local budget and resources, while those above the threshold would likely not be. It should be noted, however, that the adjusted ICERs are all the result of some extrapolation and therefore likely not as precise as findings from a de novo model constructed for the local context.

If a standard threshold for health investments does not exist locally, there are resources available with country-specific threshold estimates. For example, researchers at the University of York used data on government expenditures, mortality, morbidity, epidemiology, and demographics to estimate improvements from health from a small increase in government expenditures across 120 LMICs and generated cost-effectiveness thresholds accordingly, ranging from near $0 per DALY averted to nearly $18,000.[41] A more recent effort tied thresholds in 174 countries to growth trends in health expenditures and life expectancy, and also found significant variability, from $87 per QALY gained in the Democratic Republic of the Congo to $95,958 in the United States.[42]

6.2.3 Budget impact

As described earlier, budget impact is also an important consideration that is related but clearly distinct from cost-effectiveness. A valuable therapy on an individual basis may be nevertheless unaffordable when made available to a large population. The local health system should determine a clear threshold for what would be considered an absorbable budget impact given the current status of budgets and other system constraints. Any estimate above this threshold should be labeled a significant budget challenge.

6.3 Key Uncertainties

Finally, a separate evaluation should be made of the key uncertainties presented by the available data. From a clinical perspective, challenges in study design and conduct such as small sample size, use of surrogate endpoints with an uncertain relationship to key outcomes, short-term follow-up, and

crossover trial design may all contribute to uncertainty in assessment of the results and conclusions. Other concerns, such as strong treatment effect observed in a placebo or standard care control group, may limit understanding of the magnitude of benefit.

From a cost-effectiveness standpoint, uncertainties may arise around the impact of drug prices, treatment effects, and other objectively defined parameters, and may also be manifested in assumptions required, such as the wrap-around services required for a technology, subsequent treatment in the case of lack of efficacy or adverse events, extrapolation of clinical trial endpoints to longer-term outcomes, and the like. Uncertainties may also arise from ICER adjustment. Cost offsets realised in the country of origin may not be feasible locally due to differences in clinical practice, for example. An oncology product may be followed in sequence by another agent that is not available in the local context, or the comparator's pricing may be different than expected. Such uncertainties should be noted in both general terms as well as in consideration of the adjusted ICERs.

A complete description of the uncertainties observed and their relation to the level of confidence in the conclusions, the need to monitor for new evidence and/or update the review in the short term, or other concerns should be documented.

A summary assessment of the generalisability of the findings to the local context should also be made. Along with strength of evidence, a generalisability assessment speaks to the likelihood that something close to the observed treatment effect will be realised locally. This summary should focus particularly on the key drivers of the CEA. If key drivers are strongly affected by generalisability concerns, concerns then the rapid translation of the HTA findings to a specific local context may not be possible, and a full HTA may be required.

6.4 Summary Table

To support decision makers, it may be helpful to summarise all the preceding evidence synthesis and analysis in a single table, including its implication for the local country in which the aHTA is being conducted. An example is given here from Indonesia in Table 9, focusing on the anticancer therapy pembrolizumab for non-small cell lung cancer.

Table 9. Summary of findings (edited example from Indonesia)

Analysis and theme	Finding	Implication for cost-effectiveness in Indonesia
Review of international HTA decisions	None of the HTA agencies recommended pembrolizumab at the initial submitted price.	Not likely to be cost-effective in Indonesia
Transferability of costs: staging	In Indonesia, approving pembrolizumab will require an introduction of staging tests. This change to current practice and resource use will drive up costs	Less likely to be cost-effective
Transferability of outcomes	The major driver of QALY gain was progression-free survival, and there is no reason to believe that the clinical benefits would not transfer to Indonesia.	Neutral

Major uncertainties Time on treatment	The likely average time on treatment is unknown and is a major cost driver. The impact of clinical management in Indonesia on the effect on time on treatment is unknown.	Unknown
General health of patients	It is possible that patients in Indonesia may present later and be less healthy than in the trial—and this could potentially reduce the predicted clinical benefit of pembrolizumab.	Less likely to be cost-effective
Economic evaluation results	The results of the economic evaluations appeared to broadly support the findings of the HTA agencies that pembrolizumab is unlikely to be cost-effective in Indonesia.	Less likely to be cost-effective
	Potentially, the incremental QALYs generated in Asian countries were slightly lower, but this could have been due to modelling assumptions, and the values were still in a similar range to those in Canada.	Less likely to be cost-effective / neutral
	The economic evaluation from Singapore found no evidence for a difference in pembrolizumab's effectiveness based on ethnicity, suggesting that the clinical outcomes are transferable to Indonesia.	Neutral
Price benchmarking	Indonesia is paying more for pembrolizumab than the list price of other countries relative to GDPpc.	Less likely to be cost-effective
	Indonesia is paying more for the comparator than the list price of other countries relative to GDPpc.	More likely to be cost-effective
Adapted budget impact	The additional cost of pembrolizumab per patient above each 6-cycle chemotherapy regimen would range as follows: • 12 cycles Rp. 299,978,699 to Rp. 311,619,765 • 35 cycles Rp. 926,429,734 to Rp. 938,070,799 2,748 patients are potentially eligible for pembrolizumab, but no data is available for market share of competitive agents.	-
Other considerations Feasibility of resource use	As patients take pembrolizumab for longer than the typical duration of chemotherapy, there will be additional use of facility and staff time.	Less likely to be cost-effective

6.5 Recommendations

Once all elements of the aHTA have been collated and summarised as described in the sections above, a summary recommendation should be made. In most settings this will be done by a committee tasked with reviewing the evidence and deliberating on the best path forward. While best practices for committee structure and the deliberative process are outside the scope of this guide, there should be consideration of committee composition and management of potential conflicts of interest, processes for stakeholder engagement and inclusion, the approach taken to deliberation (e.g., voting vs. consensus), transparency in documentation and communication, and a process for appeal of the decision or recommendation. Published guidance on the key elements of HTA deliberation is available.[43,44]

The form of the recommendation to a decision maker or an independent appraisal committee can vary. Most commonly, four possible recommendations are made, as shown below:

- **Adopt:** The treatment should be adopted without limitation.
- **Adopt with limitations:** The treatment should be adopted, conditional on limiting activities such as price negotiation, prioritisation for a subset of candidate patients, or other limitation.
- **Do not adopt:** The treatment should not be adopted.
- **Further research required:** There are too many uncertainties regarding implementation at this point, so the decision should be tabled without any recommendation until additional information is obtained or full HTA is commissioned.

A recommendation to adopt is typically made when there is confidence in the magnitude of clinical benefit and reasonable certainty in the available evidence, the intervention is likely to be cost-effective at the current price in the local context, and the budget impact is absorbable. A recommendation to adopt with limitations may be made when the budget impact is felt to be a challenge, the price is higher than expected, the clinical benefits seem to be concentrated in an identifiable subgroup of patients, or other concerns. A recommendation of “do not adopt” will most often occur when the treatment far exceeds any consideration of cost-effectiveness at current prices. Finally, the evidence base may be too small or contain significant uncertainty, in which case the decision may be postponed until additional evidence is generated or a full HTA is commissioned to provide definitive answers.

7. Limitations and Conclusion

There are a number of limitations of aHTA that should be noted.[4] For one, transferring cost-effectiveness results generated elsewhere adds uncertainty to an analysis that may already have key uncertainties associated with it. In addition, the process of adapting an international HTA to the local setting may require significant clinical and health-system expertise to understand how the results may or may not apply to the local setting, which may in turn raise implementation, equity, or other concerns. Finally, international evidence might have limited transparency due to the use of confidential data in HTA processes, publication bias favoring positive cost-effectiveness findings, or other concerns.

Despite these limitations, the aHTA framework is a rapid and pragmatic way of generating evidence for decision making and is an important option in settings without the resources or political support to perform HTA on a large scale. If HTA evidence cannot be generated within the necessary time frame, aHTA analysis provides an alternative to using no economic evidence at all. It should be considered a supplementary process, not a substitute. Ultimately, there is a trade-off between the need for evidence and the available capacity and time to generate said evidence that aHTA can assist with.

The framework collates the available international evidence on the potential clinical and economic impact of a new technology and presents it in a format that facilitates decision making, is transparent, and allows the wider public to understand the process followed as well as the context in which the decisions are made. This will allow for more evidence-based decision making that can lead to more efficient health systems.

References

1. O'Rourke B, Oortwijn W, Schuller T; International Joint Task Group. The new definition of health technology assessment: A milestone in international collaboration. Int J Technol Assess Health Care. 2020 Jun;36(3):187-190. doi: 10.1017/S0266462320000215. Epub 2020 May 13. PMID: 32398176.

2. Tantivess S, Chalkidou K, Tritasavit N, Teerawattananon Y. Health Technology Assessment capacity development in low- and middle-income countries: Experiences from the international units of HITAP and NICE. F1000Res. 2017 Dec 11;6:2119. doi: 10.12688/f1000research.13180.1. PMID: 29333249; PMCID: PMC5749126.

3. Joint Learning Network. Making Explicit Choices On The Path To UHC: The JLN Health Benefits Package Revision Guide. December 2022. Available at: https://jointlearningnetwork.org/wp-content/uploads/2022/12/Making-Explicit-choices.v4.pdf

4. Nemzoff C, Ruiz F, Chalkidou K, Mehndiratta A, Guinness L, Cluzeau F, Shah H. Adaptive health technology assessment to facilitate priority setting in low- and middle-income countries. BMJ Glob Health. 2021 Apr;6(4):e004549. doi: 10.1136/bmjgh-2020-004549. PMID: 33903175; PMCID: PMC8076924.

5. Nemzoff C, Shah HA, Heupink LF, Regan L, Ghosh S, Pincombe M, Guzman J, Sweeney S, Ruiz F, Vassall A. Adaptive health technology assessment: A scoping review of methods. Value Health. 2023 Oct;26(10):1549-1557. doi: 10.1016/j.jval.2023.05.017. Epub 2023 Jun 5. PMID: 37285917.

6. World Health Organization. The Global Survey on HTA and Health Benefit Packages: Interactive Databases and Findings, 2021. Available at: https://www.who.int/news-room/events/detail/2021/12/16/default-calendar/global-survey-on-hta-database-findings

7. Merlin T, Tamblyn D, Ellery B; INAHTA Quality Assurance Group. What's in a name? Developing definitions for common health technology assessment product types of the International Network of Agencies for Health Technology Assessment (inahta). Int J Technol Assess Health Care. 2014 Oct;30(4):430-7. doi: 10.1017/S0266462314000543. Epub 2014 Nov 14. PMID: 25397872.

8. Featherstone RM, Dryden DM, Foisy M, Guise JM, Mitchell MD, Paynter RA, Robinson KA, Umscheid CA, Hartling L. Advancing knowledge of rapid reviews: An analysis of results, conclusions and recommendations from published review articles examining rapid reviews. Syst Rev. 2015 Apr 17;4:50. doi: 10.1186/s13643-015-0040-4. PMID: 25925676; PMCID: PMC4415284.

9. Hamel C, Michaud A, Thuku M, Skidmore B, Stevens A, Nussbaumer-Streit B, Garritty C. Defining rapid reviews: A systematic scoping review and thematic analysis of definitions and defining characteristics of rapid reviews. J Clin Epidemiol. 2021 Jan;129:74-85. doi: 10.1016/j.jclinepi.2020.09.041. Epub 2020 Oct 8. PMID: 33038541.

10. PHARMAC. Prescription for Pharmacoeconomic Analysis. Last updated May 2020. Available at: https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-

manuals-and-processes/economic-analysis/prescription-for-pharmacoeconomic-analysis-methods-for-cost-utility-analysis

11. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride JE. Transferability of economic evaluations: Approaches and factors to consider when using results from one geographic area for another. Curr Med Res Opin. 2007 Apr;23(4):671-82. doi: 10.1185/030079906x167327. PMID: 17407623.13.

12. Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, Reed SD, Sculpher M, Severens JL; ISPOR Good Research Practices Economic Data Transferability Task Force. What do international pharmacoeconomic guidelines say about economic data transferability? Value Health. 2010 Dec;13(8):1028-37. doi: 10.1111/j.1524-4733.2010.00771.x. PMID: 20667054.

13. Drummond M, Augustovski F, Kaló Z, Yang BM, Pichon-Riviere A, Bae EY, Kamal-Bahl S. Challenges faced in transferring economic evaluations to middle-income countries. Int J Technol Assess Health Care. 2015;31(6):442-8. doi: 10.1017/S0266462315000604. Epub 2016 Feb 1. PMID: 26831815.

14. Lopert R, Ruiz F, Chalkidou K. Applying rapid 'de-facto' HTA in resource-limited settings: Experience from Romania. Health Policy. 2013 Oct;112(3):202-8. doi: 10.1016/j.healthpol.2013.07.019. Epub 2013 Aug 14. PMID: 23953877.

15. Radu CP, Chiriac ND, Pravat AM. The development of the Romanian Scorecard HTA System. Value Health Reg Issues. 2016 Sep;10:41-47. doi: 10.1016/j.vhri.2016.07.006. Epub 2016 Sep 2. PMID: 27881276.

16. International Decision Support Initiative (iDSI). Available at: https://www.idsihealth.org/.

17. Pramesh CS, Badwe RA, Sinha RK. The national cancer grid of India. Indian J Med Paediatr Oncol. 2014 Jul;35(3):226-7. doi: 10.4103/0971-5851.142040. PMID: 25336795; PMCID: PMC4202620.

18. Sengar M. National Cancer Grid: A model for collaboration in cancer care and research. Ann Oncol 2019;30(12) Supplement 6: doi:10.1093/annonc/mdz309.

19. National Cancer Grid. NCG AHTA Process and Methods Guide National Cancer Grid. 2022. Available at: https://www.ncgindia.org/assets/ahta-process-guidelines/ahta-process-guidelines.pdf.

20. Prinja S, Rajsekhar K, Gauba VK. Health technology assessment in India: Reflection & future roadmap. Indian J Med Res. 2020 Nov;152(5):444-447. doi: 10.4103/ijmr.IJMR_115_19. PMID: 33707385; PMCID: PMC8157896.

21. National Health System Cost Database for India. Health Care Economic Evaluation Studies from India. Available at: https://www.healtheconomics.pgisph.in/costing_web/index.php?action=pblctn_economics_studies.

22. Isbeih M, Heupink LF, Qaddomi S, Salman R, Chola L. Conducting a health technology assessment in the West Bank, occupied Palestinian territory: Lessons from a feasibility

project. International Journal of Technology Assessment in Health Care. 2024;40(1):e12. doi:10.1017/S0266462324000084

23. Norwegian Institute of Public Health. Technical Guidance for Health Technology Assessment in Low- and Middle-Income Countries. 2023. Available at: https://www.fhi.no/contentassets/0f548deb25244305a1bab513f6f5f0e2/hta-guidance-document-final.pdf.
24. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: A key to evidence-based decisions. ACP J Club. 1995 Nov-Dec;123(3):A12-3. PMID: 7582737.

25. Alcaraz A, Alfie V, Gonzalez L, Virgilio S, Garcia-Marti S, Augustovski F, Pichon-Riviere A. Evidence-informed update of Argentina's health benefit package: Application of a rapid review methodology. Int J Technol Assess Health Care. 2022 Mar 11;38(1):e24. doi: 10.1017/S0266462322000034. PMID: 35274604.

26. Institute of Clinical and Health Effectiveness (IECS). Reporting Methodology. Available at: https://www.iecs.org.ar/metodosets2/.

27. Bonell C, Oakley A, Hargreaves J, Strange V, Rees R. Assessment of generalisability in trials of health interventions: Suggested framework and systematic review. BMJ. 2006 Aug 12;333(7563):346-9. doi: 10.1136/bmj.333.7563.346. PMID: 16902217; PMCID: PMC1539056.

28. York Health Economics Consortium. Incremental Cost-Effectiveness Ratio. Available at: https://yhec.co.uk/glossary/incremental-cost-effectiveness-ratio-icer/.

29. Pichon-Riviere A, Drummond M, García-Marti S, Augustovski F. Application of economic evidence in health technology assessment and decision-making for the allocation of health resources in Latin America: Seven key topics and a preliminary proposal for implementation. Inter-American Development Bank (IDB). Technical Note IDB-TN-2286. July 2021. DOI http://dx.doi.org/10.18235/0003649

30. Heupink LF, Peacocke EF, Sæterdal I, Chola L, Frønsdal K. Considerations for transferability of health technology assessments: A scoping review of tools, methods, and practices. Int J Technol Assess Health Care. 2022 Nov 2;38(1):e78. doi: 10.1017/S026646232200321X. PMID: 36321421.

31. Guegan, E., Milne, R., & Pordage, A. EUnetHTA HTA Adaptation Toolkit & Glossary: Revised Version 5. 2011. Available at: https://www.eunethta.eu/wp-content/uploads/2011/01/EUnetHTA_adptation_toolkit_2011_version_5.pdf.

32. Munthe-Kaas H, Nøkleby H, Lewin S, Glenton C. The TRANSFER Approach for assessing the transferability of systematic review findings. BMC Med Res Methodol. 2020 Jan 17;20(1):11. doi: 10.1186/s12874-019-0834-5. PMID: 31952495; PMCID: PMC6967089.

33. Daniel Mullins C, Onwudiwe NC, Branco de Araújo GT, Chen W, Xuan J, Tichopád A, Hu S. Guidance document: Global pharmacoeconomic model adaption strategies. Value Health Reg Issues. 2014 Dec;5:7-13. doi: 10.1016/j.vhri.2014.02.006. Epub 2014 May 16. PMID: 29702790.

34. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics. 2004;22(13):857-76. doi: 10.2165/00019053-200422130-00004. PMID: 15329031.

35. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009 Jun;12(4):409-18. doi: 10.1111/j.1524-4733.2008.00489.x. Epub 2009 Jan 12. PMID: 19900249.

36. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008. PMID: 28935701; PMCID: PMC5833365.

37. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. Value Health. 2022 Jan;25(1):3-9. doi: 10.1016/j.jval.2021.11.1351. PMID: 35031096.

38. Frederix GWJ. Check your checklist: The danger of over- and underestimating the quality of economic evaluations. Pharmacoecon Open. 2019 Dec;3(4):433-435. doi: 10.1007/s41669-019-0118-3. PMID: 30680675; PMCID: PMC6861398.

39. Rodwin MA, Mancini J, Duran S, Jalbert AC, Viens P, Maraninchi D, Gonçalves A, Marino P. The use of 'added benefit' to determine the price of new anti-cancer drugs in France, 2004-2017. Eur J Cancer. 2021 Mar;145:11-18. doi: 10.1016/j.ejca.2020.11.031. Epub 2021 Jan 4. Erratum in: Eur J Cancer. 2021 Jul;152:259-261. PMID: 33412466.

40. Ollendorf DA, Pearson SD. ICER Evidence Rating Matrix: A User's Guide. 2017. Available at: https://icer.org/wp-content/uploads/2020/10/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf.

41. Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: A novel approach and evidence from cross-country data. BMJ Glob Health. 2018 Nov 5;3(6):e000964. doi: 10.1136/bmjgh-2018-000964. Erratum in: BMJ Glob Health. 2019 Jun 4;4(3):e000964corr1. PMID: 30483412; PMCID: PMC6231096.

42. Pichon-Riviere A, Drummond M, Palacios A, Garcia-Marti S, Augustovski F. Determining the efficiency path to universal health coverage: Cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. Lancet Glob Health. 2023 Jun;11(6):e833-e842. doi: 10.1016/S2214-109X(23)00162-6. PMID: 37202020.

43. Oortwijn W, Husereau D, Abelson J, Barasa E, Bayani DD, Santos VC, Culyer A, Facey K, Grainger D, Kieslich K, Ollendorf D, Pichon-Riviere A, Sandman L, Strammiello V, Teerawattananon Y. Designing and implementing deliberative processes for health technology assessment: A good practices report of a joint HTAi/ISPOR task force. Int J Technol Assess Health Care. 2022 Jun 3;38(1):e37. doi: 10.1017/S0266462322000198. PMID: 35656641; PMCID: PMC7613549.

44. Oortwijn W, Jansen M, Baltussen B. Evidence-informed deliberative processes: A practical guide for HTA bodies for legitimate benefit package design. Version 2.0. Radboud University Medical Center, Nijmegen, the Netherlands, 2021.

Further Resources

General:

- Adaptive Health Technology Assessment (video).
- Adaptive Health Technology Assessment to Facilitate Priority Setting in Low- and Middle-Income Countries by Nemzoff et al.
- Assessment of Generalisability in Trials of Health Interventions: Suggested Framework and Systematic Review by Bonnell et al.
- Considerations for Transferability of Health Technology Assessments: A Scoping Review of Tools, Methods, and Practices by Heupink et al.
- Evidence-Informed Update of Argentina's Health Benefit Package: Application of a Rapid Review Methodology by Alcarez et al.
- Limitations of HTA (Avoiding Health Technology Assessment: A Global Survey of Reasons for Not Using Health Technology Assessment in Decision Making by Teerawattananon et al.)
- Rapid Priority Setting in Low- and Middle-Income Countries (CGD blog).
- Technical Document on Transferability of Cost-Effectiveness Methods and Evidence (working draft) by WHO DECIDE Network Cost-Effectiveness Data Across Settings (CEDAS) Working Group.
- WHO's recent survey on HTA and health benefits packages

Country specific:

- Canada: https://www.cadth.ca/about-cadth/what-we-do/products-services/rapid-response-service
- England/Wales: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation
- EUNetHTA adaptation toolkit- https://www.eunethta.eu/wp-content/uploads/2011/01/EUnetHTA_adptation_toolkit_2011_version_5.pdf
- Ireland: https://www.ncpe.ie/submission-process/process-flochart/
- Netherlands: https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/evaluatie-effecten-producten-zorginstituut
- Philippines: https://hta.dost.gov.ph/philippine-hta-methods-guide/
- Romania: https://linkinghub.elsevier.com/retrieve/pii/S016885101300208X or full report: https://media.hotnews.ro/media_server1/document-2012-03-15-11748944-0-raportul-institutului-nice-engleza.pdf
- South Africa https://knowledgehub.health.gov.za/elibrary/health-technology-assessment-hta-methods-guide-inform-selection-medicines-national
- Thailand: https://www.hitap.net/en/documents/165667
- Tunisia: https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines/pe-guideline-detail/tunisia
- United States: https://icer.org/our-approach/methods-process/

Economic evaluation methods

- Methods for the Economic Evaluation of Health Care Programmes (textbook) by Drummond et al.
- Decision Modelling for Health Economic Evaluation (textbook) by Briggs et al.
- Guide to Economic Analysis and Research (GEAR) Database, HITAP

- Plant-A-Tree (open-source Microsoft® Excel Add-In), Saw Swee Hock School of Public Health at the National University of Singapore and HITA
- The iDSI Reference Case for Economic Evaluation, by iDSI