NATIONAL CANCER GRID

COLLABORATION FOR CANCER CARE

2022

NCG AHTA Process and Methods Guide

NATIONAL CANCER GRID

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Published by National Cancer Grid, Mumbai, India

Contributors

Apurva Ashok
Pete Baker
Pramesh CS
Srobana Ghosh
Javier Guzman
Cassandra Nemzoff
Abha Mehndiratta
Prakash Nayak
Priya Ranganathan
Francis Ruiz
Manju Sengar
Hiral Shah
Jayahree Thorat
Tabassum Wahid

Acknowledgement

Center for Global Development, International Decision Support Initiative, Great College St., SW1P 3SE, London, UK

ATHA Process and Method Guide

National Cancer Grid (NCG)

Published Online: https://tmc.gov.in/ncg/index.php/guidelines/
Release Date – May 2022

National Cancer Grid
TMC Mumbai,
Dr. E Borges Road,
Parel, Mumbai 400012
Maharashtra, India
Email - ncg@tmc.gov.in

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Executive summary

There is a need to consider whether treatments included in health benefits packages (HBPs) are cost-effective in order to run an efficient health system, improve the financial sustainability of said HBPs and increase the chances of equitable access to healthcare.

Cancer care in particular is often associated with exorbitant treatment costs, and it can be unclear whether the associated benefits are expected to be affordable. This is particularly important considering that patients, hospital providers, insurance systems and national level healthcare payers have limited resources yet need to know which treatments provide the highest value for money. Knowing this information will improve the equitable access to medicines which will ultimately assist India on its path to deliver universal health coverage (UHC).

Whether a treatment provides value for money can be ascertained through health technology assessment (HTA) which is a systematic evaluation of a treatment to determine whether it is a cost-effective use of resources. Whilst there is a burgeoning system of HTA in India, limited resources entail that only a finite number of HTAs that can be completed at a given time. In addition, conducting HTA in the Indian context is particularly challenging given the lack of resources, data, time and capacity. There is therefore a need to conduct a large volume of HTAs rapidly in a setting with limited capacity and information.

Adaptive HTA (AHTA) is a means of leveraging or adapting available evidence from international contexts on the potential safety, effectiveness and cost-effectiveness of a technology to inform policy and could be a potential solution to this problem, however it should be noted that there is no internationally recognized definition or framework of AHTA.

A working group at the National Cancer Grid of India (NCG) has piloted a scheme of using AHTA to assess whether a treatment is potentially cost-effective or not. The results help give context to the Guideline Development Group (GDG) when determining their recommendation for inclusion, exclusion or updating of the treatment in health benefits packages and clinical guidelines.

This process and methods guide, provides the reader with a comprehensive overview of the existing AHTA process and methodology used by the NCG working group to assess the potential cost-effectiveness of treatments.

1. Introduction

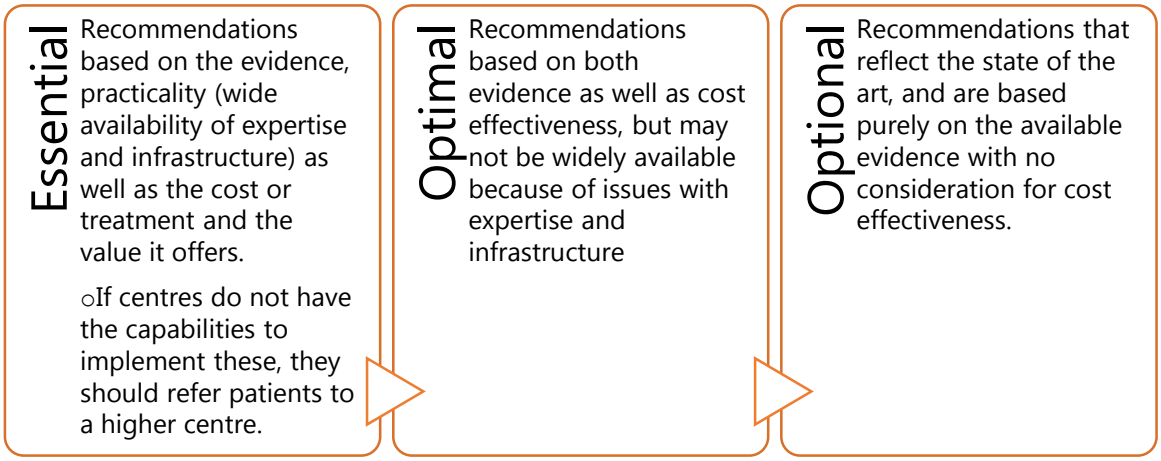
1.1 Background

The Global Cancer Observatory estimated cancer incidence in India as 1.3 million new cases in 2020, with 2.7 million 5-year prevalence cases. Cancer management includes multiple therapeutics, medical technologies, and diagnostics which are costly. This is compounded further by limited public funding for diagnosis and treatment and majority seeking treatment in private healthcare systems.,. This has resulted in cancer becoming the leading cause of catastrophic health spending, distress financing, and increasing expenditure in India.

The National Cancer Grid (NCG), a large network cancer centres, research institutes, patient groups and charitable institutions across India was established in 2012 with the mandate to establish uniform standards of patient care for the prevention, diagnosis, and treatment of cancer, whilst providing specialized training and education in oncology and facilitating collaborative basic, translational and clinical research in cancer. The NCG members provide the care for an estimated 60% of all patients with cancer across India. NCG has developed resource stratified guidelines for management of cancers. (Figure 1) The purpose of these guidelines (essential, optimal and optional) is to ensure uniform delivery of care based on the infrastructure and resources without compromising the quality.

In 2019, the NCG and the National Health Authority (NHA) signed a memorandum of understanding to link the optimal category of NCG guidelines with reimbursement of oncology health benefit packages (HBP) under the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (AB-PMJAY). AB-PMJAY, the largest Government funded health assurance scheme in the world which provides a cover of 5 lakh INR to the vulnerable entitled families at the point of care for approved HBP. Given the potential impact of NCG guidelines in ensuring quality through HPB utilization, it is highly relevant to develop and modify the NCG guidelines based on best available evidence on safety, efficacy and cost-effectiveness. However, there are very limited resources and expertise in comparison to the number of interventions which require cost-effectiveness assessment. Use of full health technology assessment (HTA) seems impractical for timely evaluation of these intervention which can feed into guidelines. Therefore, there is a need to identify alternative methods like adaptive HTA (AHTA) which can provide evidence in relatively shorter time-period.

Figure 1: Resource stratified guidelines



Source: NCG Guidelines Manual (2021).

However, there are limited formalised methods to guide the effective use of limited health spending and inform the resource stratified STGs. Using more objective assessments could promote the effective use of limited health budgets and deliver value-based care to the maximum number of beneficiaries. This can lead to the creation of health benefit packages that are more sustainable to deliver and assist India in its goal to deliver universal healthcare (UHC).

1.2 Document objective

Given the mandate of the NCG and the collaboration between the NCG and NHA, there is an urgent need to update existing NCG STGs to incorporate evidence on the cost-effectiveness of existing and new interventions to inform the resource stratified guidelines.

A working group at the NCG has piloted a scheme of using AHTA to assess whether a treatment is potentially cost-effective. This information can then be used by the GDG when determining their recommendation for inclusion of the intervention in clinical guidelines and can increase transparency over the decisions on inclusions.

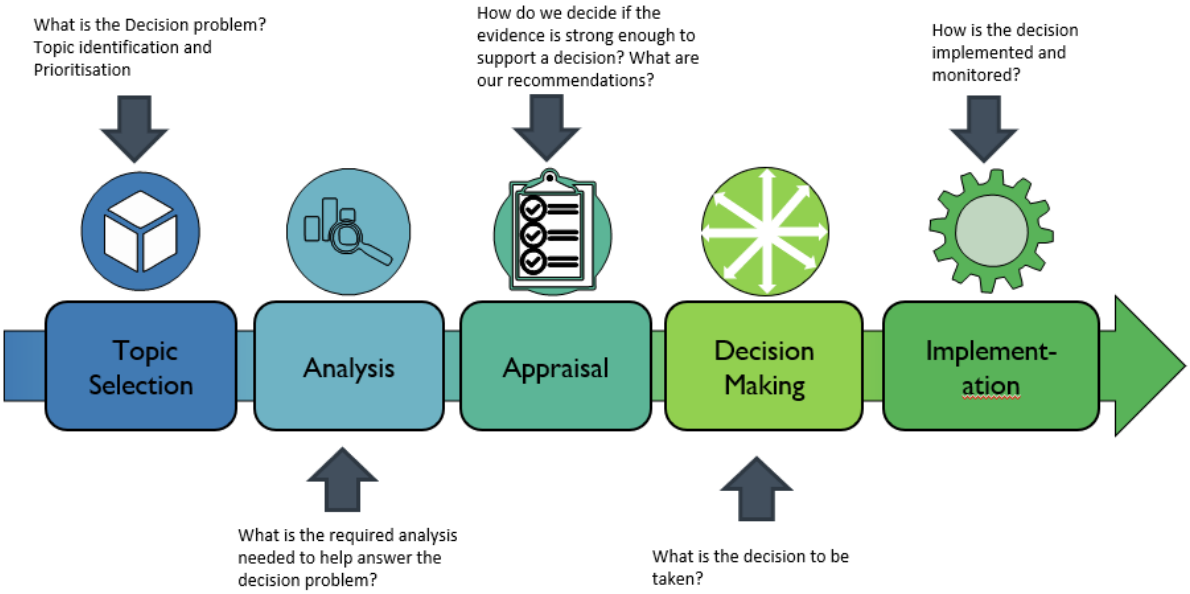
This guide will provide the reader with an overview of the AHTA methods used by the NCG in their assessment of the potential cost-effectiveness of treatments that may be included in the STGs.

1.3 Overview of HTA

Whether a treatment provides value for money can be established through HTA. HTA is the systematic evaluation of properties, effects and/or impacts of health technologies and interventions. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system. HTA is used to assess the added value of a given

health technology over and above existing interventions. It aims to inform the formulation of safe, effective health policies that achieve the best value for money. The HTA process involves five steps (**Error! Reference source not found.**) including topic selection, data analysis, evidence appraisal, decision making and implementation.

Figure 2: The traditional HTA process



The data analysis for HTA is a multidisciplinary process, that includes multiple forms of evidence generation including systematic reviews, clinical studies and economic evaluation. Economic evaluation considers the clinical benefits, costs and cost offsets of the adoption of a particular treatment and summarizes this information into an assessment of its cost-effectiveness.

In some countries, health interventions have to go through an HTA process before they are approved for use or funding (e.g. a non-exhaustive list includes Australia's PBAC, Canada's CADTH, England's NICE, New Zealand's PHARMAC, Thailand's HITAP). Information on the likely cost-effectiveness helps inform decision making. If the estimated clinical benefit is found to cost an amount within the country's threshold of what is affordable then the treatment will be approved. Conversely, treatments that have insufficient benefits that are deemed too expensive will not be recommended unless there are important considerations outside of cost-effectiveness.

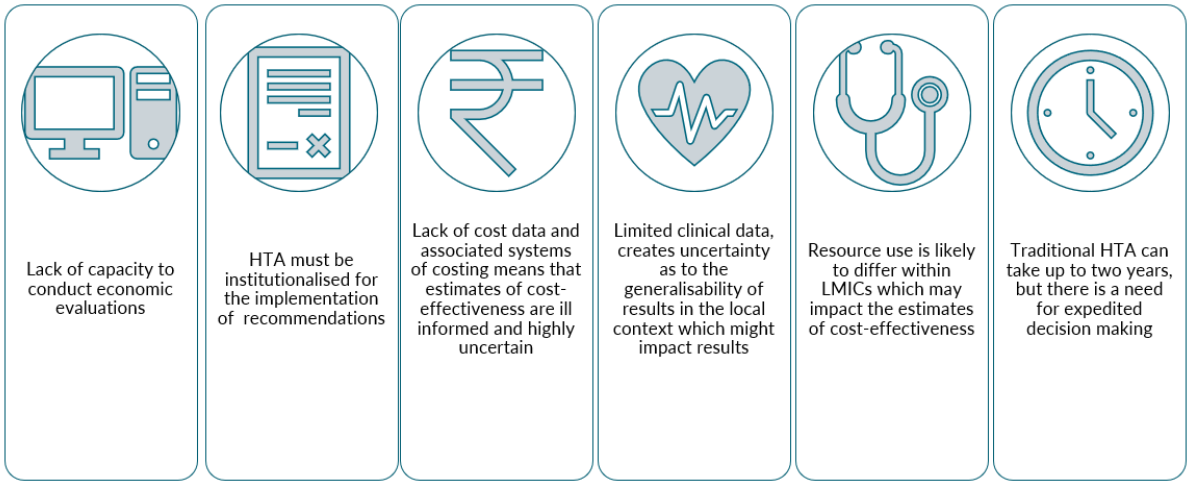
The government of India has created an institutional arrangement called the Health Technology Assessment in India (HTAIn) under the Department of Health Research (DHR) to collate and generate HTA evidence related to the clinical effectiveness, cost-effectiveness, and safety of medicines, devices and health programs. There is also a growing body of economic evaluation work currently being conducted by universities and regional resource centres across the country.

However, there are many limitations to conducting economic evaluation in India including but not limited to the following (Figure 3);

- a need for greater local capacity to conduct evaluations
- absence of a formalized process for getting HTA recommendations into decision making/clinical practice
- dearth of cost data available which can make it challenging for models to truly capture the economic impact of an intervention
- the outcomes based on clinical data from the trials conducted in high or upper middle-income countries could potentially not be generalizable to the Indian population, and high-quality local data might not be available
- local resource use must be estimated as estimates from the clinical trials might not apply to the Indian context
- the need for many HTAs to be conducted, whilst there is not enough capacity to conduct them all at once
    - there is an urgent need to ensure that HBPs are financially sustainable however HTA for a single intervention can take months or years. AHTA can take a few weeks and will expedite and facilitate the process of getting evidence into decision making

delays in conducting HTA might lead to packages becoming unsustainable to provide or adverse patient outcomes

Figure 3: Challenges to conducting HTA in India

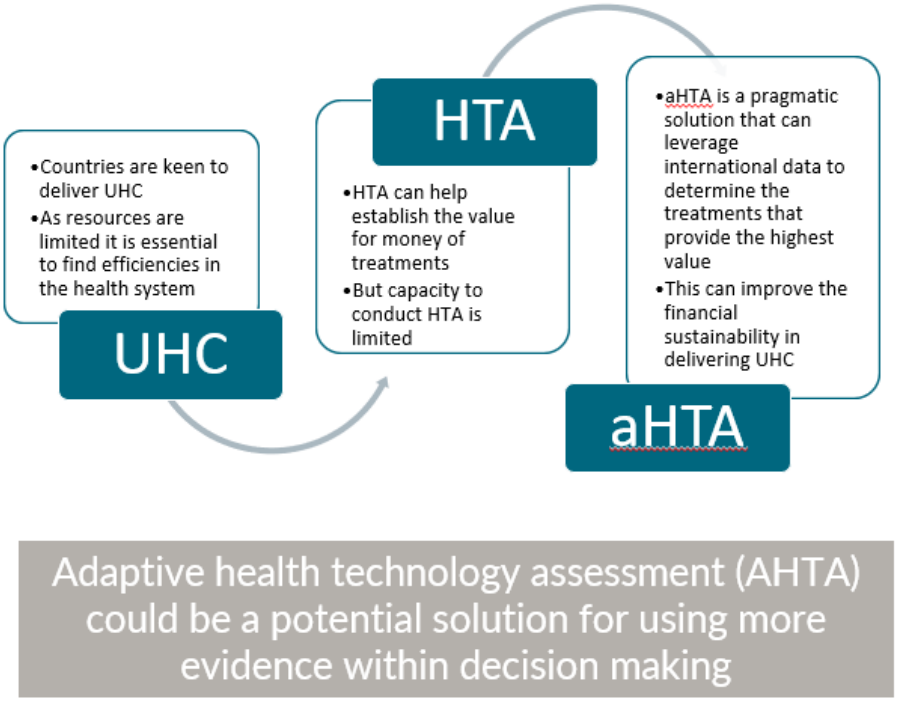


Abbreviations: HTA, Health Technology Assessment; LMICs, Low and middle-income countries

1.4 AHTA overview

Given the lack of feasibility to conduct a full HTA for all interventions in the Indian context, adaptive HTA (AHTA) may be a possible solution to ensure that health economic evidence is used to inform healthcare decisions (Figure 4).

Figure 4: AHTA as a potential solution



AHTA is defined as a broad term for modifying HTA methods and processes to be fit-for-purpose and pragmatically address practicality constraints to get an understanding of the cost-effectiveness of a treatment based on global findings. Hence, AHTA can leverage or adapt available international data, economic evaluations, models and/or decisions from the published literature or established HTA agencies to inform policy decisions, whilst accounting for uncertainty considerations and allow for the inclusion of factors specific to the local context.

AHTA can provide important context as to whether a treatment should be included in an HBP through identifying interventions that are very clearly cost-effective and those that should not be recommended because they are very clearly too expensive. Where it is unclear if an intervention is cost-effective, a full HTA is more appropriate.

AHTA does not necessarily need to be a totally separate parallel process to full HTA and could potentially share many of the same steps, but is often conducted in a more pragmatic fashion (**Error! Reference source not found.**).

Whilst AHTA is still a growing discipline that does not have a set process yet, an increasing number of HTA agencies are using adaptive or rapid methods to assess whether a full HTA is needed thereby shortening the time it takes to gain an insight into the cost-effectiveness of a technology (See Section **Error! Reference source not found.**).

Recently, the working group at the NCG has established an AHTA process to review the available international evidence to assess whether the treatment is likely to be cost-effective in India, when local prices, resource use and efficacy are considered.

Table 1: Differences between the traditional HTA process and AHTA

	Traditional HTA	Adaptive HTA in LMICs	Trade offs
Timeline	8–12 months+	1–6 months	• Level of comprehensiveness • Speed
Topic selection	Detailed topic selection process with established criteria and fits government priorities.	Shortened process. Might have an abbreviated criteria and/or opportunistic process. Can be triggered by urgent local or national need	• Identifies low hanging fruit • Local relevance • Range of topics
Analysis	De novo economic evaluation (eg. cost-effectiveness analysis).	Price benchmarking or literature reviews or adapted economic evaluation.	• Accuracy • Quality • (Un)certainty • Builds capacity • Leverages available data
Data sourcing	Local studies + primary data collection and systematic literature review/meta-analyses as needed.	Pragmatic/sources known to authors. No additional data collection needed.	• Level of comprehensiveness
Appraisal	Multistakeholder group guided by agreed principles appraises evidence and makes policy recommendations.	Might have an abbreviated appraisal process.	• (Sub)optimal decisions • Level of HTA system improvement and health system strengthening
Implementation	Wide ranging policy changes could include adjustment to health benefits packages, essential medicines lists (including appropriate indications), price negotiations, reimbursement decisions, clinical guidelines, care pathways and quality standards.		• (Sub)optimal allocation of resources • Mobilises HTA institutionalisation

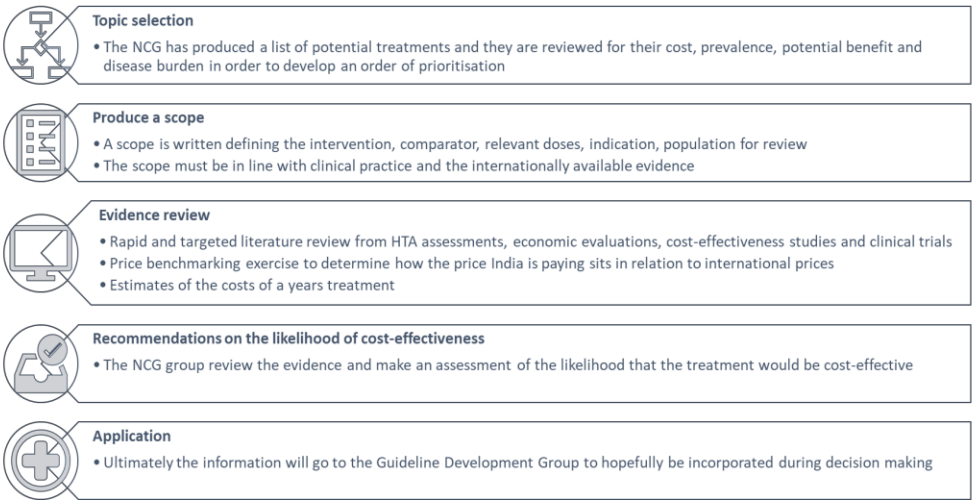
Source: Nemzoff et al. 2021

2. The NCG AHTA process and methodology

To initially formulate the AHTA process in the NCG, a technical AHTA working group was convened consisting of health economists from the International Decision Support Initiative (iDSI) and oncologists from the NCG who are familiar with HTA processes and methods. This working group was formed to scope, review and analyse existing evidence using an adapted HTA approach to indicate whether a potential intervention is likely to be considered cost-effective or not. Below we provide a step-by-step guide on how the NCG has been conducting its adaptive HTA's for cancer technologies.

The AHTA framework developed for the NCG was based on the traditional HTA process described in **Error! Reference source not found.**, however it was adapted to suit the needs and resources of the NCG as can be seen in **Error! Reference source not found.**.

Figure 5: The NCG AHTA process



The main requirement was speed, therefore most processes were expedited and the timeframe was shortened considerably, such as topic selection and producing a scope.

The analysis stage was modified into an evidence review as no original analysis was conducted. Instead, this stage is focussed on collating and understanding the existing evidence available.

A formal appraisal process could not be conducted but the results of the evidence review were considered to make a recommendation on the likely cost-effectiveness of the treatment.

Whilst in a formal HTA appraisal decision makers decide whether a treatment is recommended and then that decision is implemented, within the AHTA process, an assessment is made of the likely cost-effectiveness of the treatment, and then reported. This information can be sent to the GDG and they can include the evidence as part of their decision-making process.

3. Step 1: Topic selection

3.1 Topic selection

As part of the traditional HTA or AHTA approaches, it is important to have a process of identifying and selecting potential topics for review in order to facilitate prioritization so that technologies that have the highest impact can be assessed first. Topic prioritisation is rarely based on one criteria; rather, it is based on multiple criteria balanced together. **Error! Reference source not found.** provides insight on the potential aspects that should be considered and weighed when prioritizing topics for the NCG, the reasons why they are important and where this data can be taken from. Due to constraints, it is likely that some of this data will be from international jurisdictions.

Table 2: Factors influencing topic selection

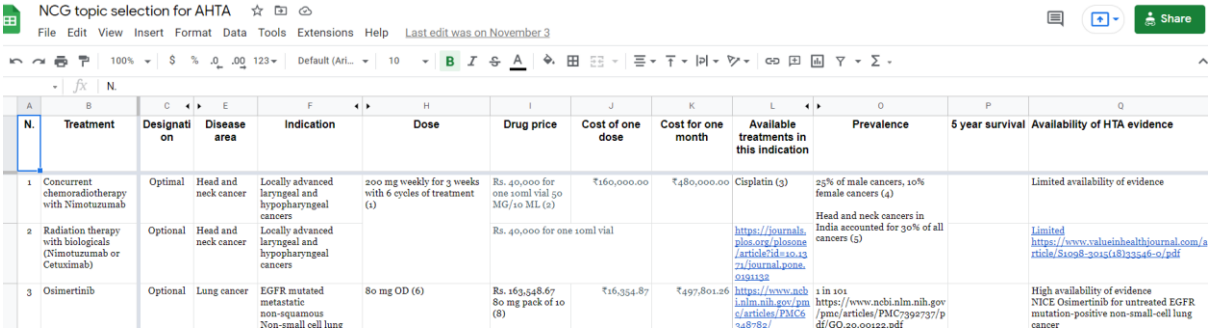
Criteria	Description	Data sources
Clinical impact	If the technology has a very clear benefit that is greater than the current standard of treatment then there is a strong justification for the technology to become the new standard of care, therefore it is important for the cost-effectiveness to be known	• Clinical studies with head-to-head comparisons • Previous economic evaluations that demonstrate clinical benefit
Treatment landscape	If there are limited comparators in this indication then the prioritization for the AHTA increases due to the greater need for approved treatments. Conversely if there are many approved treatments then the prioritization for conducting an AHTA on this technology is lower. However, if disease prevalence is very high then there might be a greater need for more treatments to become available.	• Marketing authorisations for other treatments in this indication • Clinical guidelines
Disease severity	Treatment for an illness with high disease burden can increase prioritization	• Estimates of survival (1 year, 5 years etc), utilities, QALYS, from clinical studies
Prevalence	Conversely even if there is a low disease burden, but there are many people requiring the intervention then	• Estimates from the literature of disease prevalence in India

	it is highly important to determine the cost-effectiveness of a treatment to ensure the financial sustainability of the package	
Treatment cost	Estimating the anticipated cost of a year on treatment can help inform the cost impact of the intervention (is it fairly low or high?)	• List price, dose and likely number of treatment cycles
Budget impact:	Combining the above two, any technology that is expected to have a high budget impact associated with its introduction should be assessed for cost-effectiveness	• Cost of one year of treatment multiplied by the potential number of patients • This could also be done for the comparators to ascertain the likely difference
System capacity	If the introduction of a technology is anticipated to change system capacity in any way it should be reviewed	• Advice from clinical experts
Available HTA data and estimates of cost-effectiveness	If there is an abundance of international evidence available then this will assist the conducting of an AHTA, conversely if there is limited evidence available then the intervention should be deprioritized as there will be limited capacity to conduct an AHTA. Consider whether a full HTA would be beneficial.	• Review HTA agencies for previously made decisions • Check the literature for any economic evaluations • Check the Tufts database
Source of Request:	Requests may come from clinicians, the guideline development group or elsewhere. It is important to note the amount of interest in the drug and where the interest is coming from	-

3.2 Topic selection sheet

In order to facilitate transparency in topic selection and decision making, it is useful to ensure that the topic selection process is tracked so that the evidence base considered in the topic prioritization is clear. This was done by the NCG through the construction of a spreadsheet (**Error! Reference source not found.**).

Figure 6: Example topic selection sheet



NCG topic selection for AHTA

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N.	Treatment	Designation	Disease area	Indication	Dose	Drug price	Cost of one dose	Cost for one month	Available treatments in this indication	Prevalence	5 year survival	Availability of HTA evidence
1	Concurrent chemoradiotherapy with Nimotuzumab	Optimal	Head and neck cancer	Locally advanced laryngeal and hypopharyngeal cancers	200 mg weekly for 3 weeks with 6 cycles of treatment (1)	Rs. 40,000 for one 10ml vial 50 MG/10 ML (2)	₹160,000.00	₹480,000.00	Cisplatin (3)	25% of male cancers, 10% female cancers (4) Head and neck cancers in India accounted for 30% of all cancers (5)		Limited availability of evidence
2	Radiation therapy with biologicals (Nimotuzumab or Cetuximab)	Optional	Head and neck cancer	Locally advanced laryngeal and hypopharyngeal cancers		Rs. 40,000 for one 10ml vial			https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0191132			Limited https://www.valueinhealthjournal.com/article/S1098-3015(18)33546-0/pdf
3	Osimertinib	Optional	Lung cancer	EGFR mutated metastatic non-squamous Non-small cell lung	80 mg OD (6)	Rs. 163,548.67 80 mg pack of 10 (8)	₹16,354.87	₹497,801.26	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6248782/	1 in 101 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7392737/pdf/GO.20.00122.pdf		High availability of evidence NICE Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer

All potential interventions of interest that had been submitted to the NCG were added to the spreadsheet alongside their background characteristics to facilitate prioritization. **Error! Reference source not found.** details the datapoints extracted to provide the background information that was considered in the topic selection process by the NCG.

Table 3: Topic selection sheet data points

Item	Description	Example
Treatment	Full name of the treatment plus any concomitant treatments	Concurrent chemoradiotherapy with Nimotuzumab
Designation	Designation as per the NCG guideline	• Essential • Optimal • Optional
Disease area	The specialized area of oncology and name of disease	Head and neck cancer
Indication	The full indication and population, including previous treatment status, mutations, contraindications, resectability status	Nimotuzumab in the treatment of newly diagnosed, treatment-naïve adult patients with stage iii or iv locally advanced head and neck squamous cell carcinomas (LAHNSCC) who were fit for radical chemoradiation
Dose	Expected daily dose. This should align with the marketing indication, scope and international evidence.	200 mg weekly for 3 weeks with 6 cycles of treatment
Drug price	Price per pack, number of units in the pack and size of units	Rs. 163,548.67 80 mg pack of 10
Cost per dose	If available include the cost of an average dose to facilitate comparison	Rs. 163,548
Cost per month /cycle	Cost per dose multiplied by number of doses in an average cycle or month for comparability	Rs. 497,801

Available treatments	List any other treatments that patients can take in this indication	Palliative care
Prevalence	To help determine the disease burden enter the prevalence from a trusted source	25% of male cancers, 10% female cancers. Head and neck cancers in India accounted for 30% of all cancers
Availability of HTA evidence	Do a quick search and check if there is any international evidence available to inform prioritization	Limited availability of international evidence
Clinical benefit	Include any estimates of how beneficial the treatment is expected to be	12m OS was 75.1% for the nimotuzumab plus CRT group and 54.4% for the CRT group.

Upon completion of the table, the treatments were compared against each other in terms of price, disease burden and potential benefit and prioritization took place. Clinicians then reviewed the completed spreadsheet and agreed a ranking system of the most important treatments to review based on the above criteria.

4. Step 2: Scope

4.1 Produce a scope for the AHTA

Once a topic is selected, it is necessary to develop the scope of the AHTA which will be based on a review of the evidence available and the question that needs to be answered.

The scope of the AHTA defines the question being considered. Here the PICO (Population, Intervention, Comparator, Outcome) framework is used to develop all scopes within the NCG AHTA process. Hence, all scopes are structured as an intervention within a specific indication assessed against a specific comparator in the same indication, although more than one comparator can be specified if there are multiple in clinical practice.

AHTA can only be done if the population, indication, comparator and intervention match up to the approval for the intervention, the available international evidence and clinical practice in India, otherwise the results will not apply.

It is important to be specific when defining the scope to ensure that the correct question is being answered, otherwise there is a risk that international data or evidence which does not match up to the scope will not sufficiently answer the question. If there is no international evidence available for the research question, then AHTA cannot be used and a full HTA including primary data analysis is required.

Error! Reference source not found. provides an overview of what the scope should comprise of.

Table 4: Producing a scope

Parameter	Definition	Example
Population	The definition of the population and indication must be very specific. In oncology it is important to specify the disease area, the line of therapy, whether it is metastatic, if it is adjuvant or neo-adjuvant, and any further information such as mutation. Always specify if it is the adult population or whether there is an age restriction.	• EGFR mutated metastatic non-squamous non-small cell lung cancer (NSCLC)- as first line therapy • the first-line treatment of adult patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
Intervention	• The name of the intervention and the dose. This should be reflective of the dose prescribed in clinical practice in India as per its license.	• Osimertinib (3rd generation TKI)

	• The international evidence used should aim to also be the same as the intervention and dose.	
Comparator	• As with the intervention, the comparator must be the standard of care in clinical practice, the dose must be specified and the international evidence should aim to use the same comparator and dose. • There should be cost-effectiveness analysis or clinical trial data available comparing the intervention against the selected comparators in this indication, otherwise it will be challenging to conduct the AHTA.	• Gefitinib (1st generation TKI) • Erlotinib (2nd generation TKI)
Cost in India	• Include the price per dosing unit, e.g., pack or vial size, and amount per unit to inform cost estimates for the treatment and the comparators. Specify any known administration costs.	• Dose: 80mg once daily • Pack 80 mg tablets, 10 tablets per pack, 3 packs in a box • Cost of the box 439,478 INR
Subgroups of interest	• Specify if there is an interest for the results of a specific subgroup in addition to the main group	None
Regulatory and Safety Evidence	• Indication that received marketing authorisation • Authorised dose and route	•
Justifications for selection as high priority	• This will be added to the background section of the briefs, therefore add anything that comprises part of the disease burden such as prevalence, higher rates of a mutation in India, or any other aspect of unmet need • Include the justification for why this topic was selected	• High prevalence and incidence rates of lung cancer in India • 30-40% are metastatic at diagnosis • 20-50% of EGFR positive • Osimertinib has the clinical advantage of also being given when resistance develops to first and second generation TKI • Biosimilars not available

5. Step 3: Evidence review

Once the topic had been selected and the scope written, the next step is to collate the internationally available evidence on the topic.

There is no single definitive internationally recognised framework for conducting AHTA. Generally, assessments are made based on the capacity and data available.

AHTA approaches can involve a variety of methods such as conducting rapid or targeted literature reviews, adapting existing cost-effectiveness models, benchmarking against publicly available prices in other countries, conducting local costing, making use of international data sets (e.g., Tufts Database), international priority setting tools (HIP Tool) or adopting a scorecard approach using qualitative judgement.

As part of the NCG AHTA approach we employ the use of the following methods to generate useful information on potential cost-effectiveness:

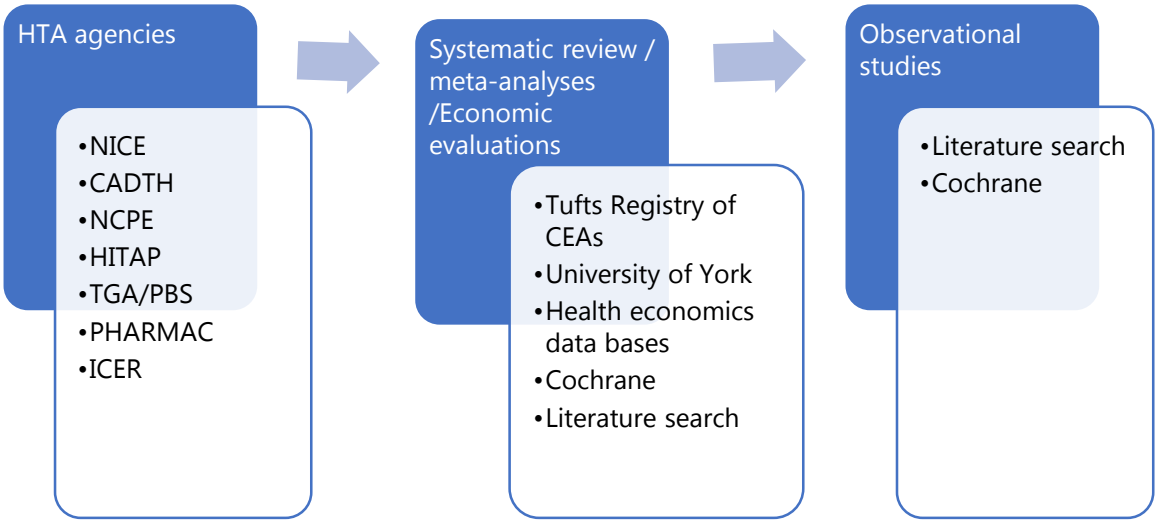
- Rapid and targeted literature reviews
- Price benchmarking analysis
- Treatment cost estimates

5.1 Rapid and targeted literature reviews

The first component of the evidence review is a rapid and targeted literature review for economic evaluations and studies that report on the cost-effectiveness of the treatments. In order to expedite the process a formal search strategy was not conducted; however, a systematic process was followed and a process of double extraction was implemented.

The process of data collection and sources of evidence are summarised in **Error! Reference source not found.**. First, an online search was conducted for any relevant HTA, through review of the websites of select HTA agencies. To supplement this a search was conducted for any systematic review or meta-analyses of economic evaluations or cost-effectiveness analysis studies or rapid reviews that have addressed the exact same decision problem. This is done through a search of international data sets, health economic databases and a general search of the literature and Google. If no CEA information was found, then observational studies that showed the clinical benefits could be included as well. It is useful to highlight the underlying study that shows the clinical benefits, however if only clinical studies are available then AHTA might not be suitable. If no data is available on the cost-effectiveness, clinical or safety benefits then the AHTA cannot proceed.

Figure 7: Sources of evidence



Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; ICER, Institute for Clinical and Economic Review; HiTAP, Health Intervention and Technology Assessment Program; NICE, National Institute for Health and Care Excellence; NCPE, National Centre for Pharmacoeconomics; PBS, Pharmaceutical Benefits Scheme (Australia); PHARMAC, The Pharmaceutical Management Agency (New Zealand); TGA, Therapeutic Goods Administration (Australia).

The region of the data should be considered. Most HTA agencies are based in high income countries therefore there are difficulties with the generalizability of the results. Data from India should be searched for, as well as data from a non-high-income setting.

Once the search has been conducted and relevant documents have been selected for review, a data extraction template is used to standardize the information aggregated to facilitate comparisons and provide consistency in reporting across selected documents (**Error! Reference source not found.**). The data extraction template consists of three sections with associated data points:

- Background information
- Clinical evidence on efficacy and safety
- Cost-effectiveness evidence

Figure 8: Sample data extraction sheet

	A	B	C	D	E	F	G	H
1	**Country**	England	International 1	Singapore	Ireland	International 2	India	Canada
2	**Analysis type**	HTA	Study	CEA (modelling)	HTA	Evaluation	Clinical outcomes	HTA
3	**Body**	NICE	INAHTA	Agency for Care Effectiveness, Ministry of Health, Singapore	NCPE	WHO [in association with European Society for Medical Oncology (ESMO)]	Single insittute	CADTH
4	**Link**	https://www.nice.org.uk/guidance/TA654	https://database.inahta.org/article/18724	https://www.tandfonline.com/doi/full/10.1080/13696998.2020.1819822	http://www.ncpe.ie/drugs/osimertinib-tagrisso-for-the-first-line-treatment-of-metastatic-nsclc/	https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.29_osimertinib.pdf?sfvrsn=59353ob5_4	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5763619/	https://cadth.ca/tagrisso-non-small-cell-lung-cancer-first-line-details
5	**Title**	TA654	Osimertinib (Tagrisso®) for the initial treatment of EGFR-mutated advanced non-small-cell lung cancer (NSCLC)	Cost-effectiveness analysis of osimertinib for first-line treatment of locally advanced or metastatic EGFR mutation positive non-small cell lung cancer in Singapore		Application for the inclusion of Osimertinib in the WHO Model List of ESSENTIAL MEDICINES for the 1st Line Treatment of EGFR mutated locally advanced or metastatic non-small cell lung cancer.	Osimertinib in Indian patients with T790M-positive advanced nonsmall cell lung cancer	Tagrisso for Non-Small Cell Lung Cancer (first line)
6	**Reviewer**	Srobana	Prakash Nayak	Priya	Srobana	Malkeet, Srobana	Manju	
7	**Date of report**	14 October 2020	10 Aug 2021	21-Sep 2020	August 2019 (approved october 2020)	Nov 2020 (Proxy Date)	2017	Jan 2019
8	**Intervention**	Osimertinib	osemertinib	Osimertinib	Osimertinib	Osimertinib	Osimertinib	Osimertinib
9	**Comparator**	SoC second EGFR-TKI erlotinib or gefitinib	SOC 250 mg gefitinib or 150 erlotinib	erlotinib (150 mg daily) or gefinitib (250 mg daily)	Model compared against erlotinib 150mg and afatinib(gefitinib market share considered too low). Trial included gefitinib	Gefitinib, Erlotinib and Afatinib	Single arm -13 patients	Gefitinib 250 mg once a day, Erlotinib 150mg once a day(Afatinib was also considered for economic evlauation)

5.1.1 Background information

The data extraction sheet begins with a section on background information to identify and contextualize the studies within the hierarchy of evidence and determine that the information in the document under review matches the decision problem in the scope (**Error! Reference source not found.**,**Error! Reference source not found.**). If during data extraction it is clear that the document is addressing a different decision problem to the scope, it should not be included.

Table 5: Data extraction sheet data points; Background information

Data point	Description
Country	The primary country of the document/analysis to help understand how generalizable the results are to the Indian context
Analysis type	Detail whether the document is an HTA, CEA, study or other to determine where it lies in the hierarchy of evidence
Link	Weblink to the document
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
Intervention	The name of the intervention in the report
Comparator	The name of the comparator in the report
Indication	The indication under review, please be detailed to ensure that the correct indication is being compared
Dose	The dose of the intervention and comparator to ensure that these are same as in the scope

Figure 9: Data extraction sheet; background information

	A	B	C	D	E	F	G	H
1	**Country**	England	International 1	Singapore	Ireland	International 2	India	Canada
2	**Analysis type**	HTA	Study	CEA (modelling)	HTA	Evaluation	Clinical outcomes	HTA
3	**Body**	NICE	INAHTA	Agency for Care Effectiveness, Ministry of Health, Singapore	NCPE	WHO [in association with European Society for Medical Oncology (ESMO)]	Single insittute	CADTH
4	**Link**	https://www.nice.org.uk/guidance/TA654	https://database.inahta.org/article/18#24	https://www.tandfonline.com/doi/full/10.1080/13696998.2020.1849822	http://www.ncpe.ie/drugs/osimertinib-tagrisso-for-the-first-line-treatment-of-metastatic-nsclc/	https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.23_osimertinib.pdf?sfvrsn=59353ob5_4	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5763619/	https://cadth.ca/tagrisso-non-small-cell-lung-cancer-first-line-details
5	**Title**	TA654	Osimertinib (Tagrisso®) for the initial treatment of EGFR-mutated advanced non-small-cell lung cancer (NSCLC)	Cost-effectiveness analysis of osimertinib for first-line treatment of locally advanced or metastatic EGFR mutation positive non-small cell lung cancer in Singapore		Application for the inclusion of Osimertinib in the WHO Model List of ESSENTIAL MEDICINES for the 1st Line Treatment of EGFR mutated locally advanced or metastatic non-small cell lung cancer.	Osimertinib in Indian patients with T790M-positive advanced nonsmall cell lung cancer	Tagrisso for Non-Small Cell Lung Cancer (first line)
6	**Reviewer**	Srobana	Prakash Nayak	Priya	Srobana	Malkeet, Srobana	Manju	
7	**Date of report**	14 October 2020	10 Aug 2021	21-Sep 2020	August 2019 (approved october 2020)	Nov 2020 (Proxy Date)	2017	Jan 2019
8	**Intervention**	Osimertinib	osemertinib	Osimertinib	Osimertinib	Osimertinib	Osimertinib	Osimertinib
9	**Comparator**	SoC second EGFR-TKI erlotinib or gefitinib	SOC 250 mg gefitinib or 150 erlotinib	erlotinib (150 mg daily) or gefinitib (250 mg daily)	Model compared against erlotinib 150mg and afatinib(gefitinib market share considered too low). Trial included gefitinib 250mg once daily or erlotinib 150mg once daily. (In clinical practice erlotinib, afatinib and gefitinib)	Gefitinib, Erlotinib and Afatinib	Single arm -13 patients	Gefitinib 250 mg once a day, Erlotinib 150mg once a day(Afatinib was also considered for economic evlauation)
10	**Indication**	First line untreated locally advanced or metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC)	untreated EGFRm (19 del or 21 substitution)advanced NSCLC	first line treatment in locally advanced or metastatic NSCLC patients with EGFR mutation.	first-line treatment of adult patient with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.	1. Frontline treatment for metastatic NSCLC with EGFR sensitizing exon 19 and L858R mutations, detected by validated molecular test 2. T790M EGFR resistance mutation-bearing NSCLC that progressed to 1ST or 2nd generation EGFR TKI directed therapy, also detected by validated molecular test	T790M mutated EGFR psoitive metastatic NSCLC -relapsed	First line,locall advanced, metatstatic exon 19, exon 21-L858R mutation, PS-0-2, stable or asymptomatic CNS mets
11	**Dose**	80 mg OD oral	80 mg OD oral	80 mg OD oral	80 mg OD oral	Oral - 80 mg tablet, once daily	80 mg OD	80 mg OD

5.1.2 Clinical evidence

Clinical evidence is necessary in order to determine the anticipated benefit and potential harms of the treatment. Clinical evidence includes but is not limited to the expected improvement in overall survival, progression-free survival, mortality rates and any other clinical outcome. All economic analysis will include clinical outcomes; therefore, it is useful to state which values were used in the model and the source of the data which will most likely be from a clinical trial or an indirect analysis. It is useful to gather all mentions of clinical benefit if there are other sources, particularly if multiple sources were used in the analysis.

It is important that all clinical outcomes 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 confidence intervals with associated p values to understand the uncertainty around the benefit. In addition, it is equally important to note down any issues with the quality of the study or potential for bias to help the reader interpret how robust the findings are.

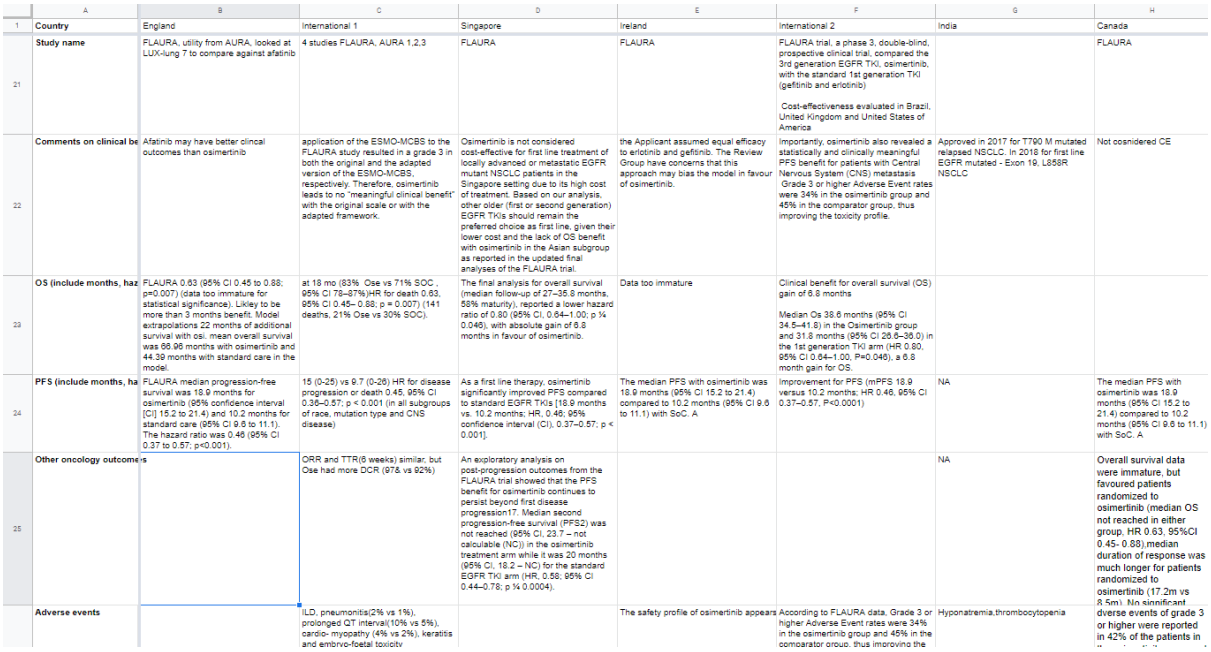
Although no formal assessment of quality was done, it was important to flag any study that appears flawed and detail any potential concerns with how these values were generated as the results are unlikely to be replicated in India and it is important that clinicians do not rely on these findings.

Error! Reference source not found. below shows the data points that should be extracted to collate the evidence for the clinical benefit. **Error! Reference source not found.** is an example of the data sheet.

Table 6:

Data point	Description
Study name	Title, author, year
Type of study	Study design, geographic range, number of patients
Comments on clinical benefit	Note anything unusual or noteworthy about the findings
OS	Detail all outcomes such as months, hazard ratios and % at median. Specify the point estimates, the confidence interval and the p value
PFS	
Other oncology outcomes	Detail any other outcomes specified (e.g., the hazard ratio, difference between comparators in months, time in health state, % alive or progression-free at the end of the time period, median survival or time in PFS)/
Limitations and critiques of the clinical evidence	Specify any limitations of the study that may prevent the results from being generalizable to the Indian population such as e.g., small sample size, bias, inappropriate dose, different population or subgroup, flaws in the study design
Safety evidence	It is important to know whether the treatments can be tolerated equally and are comparable. Instead of extracting all adverse events, it is particularly important to extract any significant differences in adverse events, particularly adverse events that incur a high cost of care or cause great disease burden Serious adverse events are above grade 3

Figure 10: Data extraction sheet data points; Clinical evidence



	A	B	C	D	E	F	G	H
1	Country	England	International 1	Singapore	Ireland	International 2	India	Canada
21	Study name	FLAURA, utility from AURA, looked at LUX-lung 7 to compare against afatinib	4 studies FLAURA, AURA 1,2,3	FLAURA	FLAURA	FLAURA trial, a phase 3, double-blind, prospective clinical trial, compared the 3rd generation EGFR TKI, osimertinib, with the standard 1st generation TKI (gefitinib and erlotinib) Cost-effectiveness evaluated in Brazil, United Kingdom and United States of America		FLAURA
22	Comments on clinical be	Afatinib may have better clincal outcomes than osimertinib	application of the ESMO-MCBS to the FLAURA study resulted in a grade 3 in both the original and the adapted version of the ESMO-MCBS, respectively. Therefore, osimertinib leads to no "meaningful clinical benefit" with the original scale or with the adapted framework.	Osimertinib is not considered cost-effective for first line treatment of locally advanced or metastatic EGFR mutant NSCLC patients in the Singapore setting due to its high cost of treatment. Based on our analysis, other older (first or second generation) EGFR TKIs should remain the preferred choice as first line, given their lower cost and the lack of OS benefit with osimertinib in the Asian subgroup as reported in the updated final analyses of the FLAURA trial.	the Applicant assumed equal efficacy to erlotinib and gefitinib. The Review Group have concerns that this approach may bias the model in favour of osimertinib.	Importantly, osimertinib also revealed a statistically and clinically meaningful PFS benefit for patients with Central Nervous System (CNS) metastasis Grade 3 or higher Adverse Event rates were 34% in the osimertinib group and 45% in the comparator group, thus improving the toxicity profile.	Approved in 2017 for T790 M mutated relapsed NSCLC. In 2018 for first line EGFR mutated - Exon 19, L858R NSCLC	Not cosnidered CE
23	OS (include months, haz	FLAURA 0.63 (95% CI 0.45 to 0.88; p=0.007) (data too immature for statistical significance). Likley to be more than 3 months benefit. Model extrapolations 22 months of additional survival with osi. mean overall survival was 66.96 months with osimertinib and 44.39 months with standard care in the model.	at 18 mo (83% Ose vs 71% SOC , 95% CI 78–87%)HR for death 0.63, 95% CI 0.45– 0.88; p = 0.007) (141 deaths, 21% Ose vs 30% SOC).	The final analysis for overall survival (median follow-up of 27–35.8 months, 58% maturity), reported a lower hazard ratio of 0.80 (95% CI, 0.64–1.00; p ¼ 0.046), with absolute gain of 6.8 months in favour of osimertinib.	Data too immature	Clinical benefit for overall survival (OS) gain of 6.8 months Median Os 38.6 months (95% CI 34.5–41.8) in the Osimertinib group and 31.8 months (95% CI 26.6–36.0) in the 1st generation TKI arm (HR 0.80, 95% CI 0.64–1.00, P=0.046), a 6.8 month gain for OS.		
24	PFS (include months, ha	FLAURA median progression-free survival was 18.9 months for osimertinib (95% confidence interval [CI] 15.2 to 21.4) and 10.2 months for standard care (95% CI 9.6 to 11.1). The hazard ratio was 0.46 (95% CI 0.37 to 0.57; p<0.001).	15 (0-25) vs 9.7 (0-26) HR for disease progression or death 0.45, 95% CI 0.36–0.57; p < 0.001 (in all subgroups of race, mutation type and CNS disease)	As a first line therapy, osimertinib significantly improved PFS compared to standard EGFR TKIs [18.9 months vs. 10.2 months; HR, 0.46; 95% confidence interval (CI), 0.37–0.57; p < 0.001].	The median PFS with osimertinib was 18.9 months (95% CI 15.2 to 21.4) compared to 10.2 months (95% CI 9.6 to 11.1) with SoC. A	Improvement for PFS (mPFS 18.9 versus 10.2 months; HR 0.46, 95% CI 0.37–0.57, P<0.0001)	NA	The median PFS with osimertinib was 18.9 months (95% CI 15.2 to 21.4) compared to 10.2 months (95% CI 9.6 to 11.1) with SoC. A
25	Other oncology outcome	s	ORR and TTR(6 weeks) similar, but Ose had more DCR (97& vs 92%)	An exploratory analysis on post-progression outcomes from the FLAURA trial showed that the PFS benefit for osimertinib continues to persist beyond first disease progression17. Median second progression-free survival (PFS2) was not reached (95% CI, 23.7 – not calculable (NC)) in the osimertinib treatment arm while it was 20 months (95% CI, 18.2 – NC) for the standard EGFR TKI arm (HR, 0.58; 95% CI 0.44–0.78; p ¼ 0.0004).			NA	Overall survival data were immature, but favoured patients randomized to osimertinib (median OS not reached in either group, HR 0.63, 95%CI 0.45- 0.88),median duration of response was much longer for patients randomized to osimertinib (17.2m vs 8.5m). No significant
	Adverse events		ILD, pneumonitis(2% vs 1%), prolonged QT interval(10% vs 5%), cardio- myopathy (4% vs 2%), keratitis and embryo-foetal toxicity		The safety profile of osimertinib appears	According to FLAURA data, Grade 3 or higher Adverse Event rates were 34% in the osimertinib group and 45% in the comparator group, thus improving the	Hyponatremia,thrombocytopenia	diverse events of grade 3 or higher were reported in 42% of the patients in

5.1.3 Cost-effectiveness evidence

Cost-effectiveness or costing evidence will primarily be extracted from HTA agency assessment reports, systematic reviews of economic evaluations or economic evaluations from international jurisdictions. This evidence will be reported as the results of a modelling analysis. The key data points which may be considered useful for decision making involve extracting information on costs, health-related quality of life and cost-effectiveness.

Data points for costs include information on direct costs borne by the healthcare system mainly comprising of treatment costs, resource use, and adverse event costs. Costs are calculated for each intervention included in the model.

Data points for health-related quality of life captures the health benefits gained. This might be an increased in overall survival or progression free survival or a better quality of life. This will be calculated for each intervention and presented as a quality adjusted life year (QALY) or an estimate of increase in life expectancy shown in units of time (months, years etc.) or as a percentage of patients who have survived.

Data points for cost-effectiveness include the incremental cost-effectiveness ratio (ICER) which is defined as the incremental cost divided by the incremental QALY gain for the healthcare intervention of interest versus its comparator (typically a new intervention versus current standard of care). Incremental costs and QALYs are the difference in the costs and health benefits respectively associated with a treatment in relation to its comparator. This

helps to determine how much it will cost the health system for the additional benefits associated with the treatment.

The ICER is a ratio of the two data points and provides insight on the affordability of the treatment.

An ICER from another country might not be generalizable to India as there might be too many differences in the setting, however it is useful to know whether other countries consider the treatment to be cost-effective and what the level of uncertainty is.

The ICER is driven by clinical benefits and costs. A drug might be cost-effective in another setting due to there being a significant discount, therefore it is important to check if a discount has been applied when considering whether the treatment was reimbursed as it is unlikely that India will be paying a similar price therefore the drug might not be cost-effective in India.

Error! Reference source not found. identifies the data points for the cost-effectiveness data and **Error! Reference source not found.** is an example of a completed data extraction sheet.

Table 7: Data extraction sheet data points; Cost-effectiveness analysis

Data point	Description
ICER	This is the incremental cost-effectiveness ratio If reported it will be stated explicitly It will be presented as a monetary figure per QALY e.g., £30,000/QALY
Incremental costs	The difference in costs between interventions
Incremental QALYs	The difference in QALYs between interventions
Total costs	The costs of each intervention (includes treatment costs, resource use costs, costs of adverse events, administration costs, plus any other costs considered to be relevant)
Total QALYs	The total predicted clinical benefit of each in intervention
Time to treatment discontinuation	The average number of cycles the patient receives treatment for and the cycle length This is used to determine the costs of treatments in the calculator
End of life	State whether any end-of-life criteria applied, as this will influence the decision

	Treatments that are considered to be end of life in England will have a higher willingness to pay threshold, therefore they will be considered to be cost-effective at a higher ICER (£50,000 per QALY) This needs to be considered when reviewing the recommendation as £50,000 per QALY might be too high for the NCG
Reimbursement status	Was the intervention recommended? Yes or no and if there was a discount applied that reduced the cost of treatment or if any restrictions were put in use

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Figure 11: Data extraction sheet – cost-effectiveness evidence

	A	B	C	D	E	F	G	H
1	Country	England	International 1	Singapore	Ireland	International 2	India	Canada
12	ICER	Within the WTP	pending mature OS data	base-case ICER of SG$418,839 (US$304,277) per quality-adjusted life year gained.	The resultant NCPE preferred base case ICERs are €115,912 per QALY (incremental cost/incremental QALY €78,556/0.678) vs. erlotinib and €113,162 per QALY (incremental cost/incremental QALY €76,693/0.678) vs. afatinib. In the Applicant base case, the incremental cost-effectiveness ratio (ICER) was €78,914 per QALY (incremental cost/ incremental QALY €75,818/0.961) vs. erlotinib and	JAMA Study United States- $226,527 (erlotinib), $231,123 (gefitinib) $219,874 (afatinib) Threshold: $190,248 Brazil- $162 329 (erlotinib), $180,804 (gefitinib), and $175,432 (afatinib) Threshold: $20349	NA	50,000-100,000
13	Incremental costs	Redacted		incremental cost of SG$133,633 (97984 USD)		the incremental cost per 1 life-year save	NA	NA
14	Incremental QALYS	Redacted		increased 0.319 QALYs		0.594 QALY Gain (Using FLAURA Trial Results) Incremental life-years gained- 1.01	NA	NA
15	Total costs intervention	Redacted		207440 SGD		£5,770 f/pack containing 80 mg of osimertinib	NA	osimertinib costs $294.68 per d
16	Total costs comparator	Redacted	afatinib (40 mg) at € 2,176.13, gefitinib (250 mg) at € 2,300.00, and erlotinib (150 mg) at € 1,809.77.	48039 SGD (standard TKI)			NA	Geftinib -$2,052.40 per 28-day course., Erlotinib - $1,904.00 per 28-day course, Afatinib-$2,052.40 per 28-day course.
17	QALYs intervention	Redacted		1.253			NA	NA
18	QALYs comparator	Redacted		0.75			NA	NA
19	Drug price	List price: 30 tablets of 40mg or 80mg £5770	€6132 for 30 tab, €98120 for 16 months.€ 35,764,740.00–53,647,110.00 annually , € 165.00) per Cobas® EGFR Mutation Test v2	Osimetinib 2042 SGD per cycle. Erlotinib 507 SGD and Gefitinib 637 SGD per cycle	€6,200 for 30 tablets			osimertinib costs $294.68 per d

5.1.3.1 Uncertainty

With all the evidence synthesised there will always be an element of uncertainty. Whilst this cannot be avoided, it is vital that it is recorded so that anyone who is using the evidence can make an informed decision on how robust, translatable and generalizable the evidence is and how reproducible the results are.

One of the most crucial aspects to capture in the data extraction is the level of uncertainty in the results. The base-case cost-effectiveness results will rely on point estimates but it is important to capture the range of ICERs reported which state the ICER if the analysis was run with parameters at the full range of their confidence intervals. This range will help understand if the ICER is relatively consistent or if it is possible for it vary wildly, and potentially to an unaffordable amount for India.

Many HTA agencies and peer-reviewed articles will provide information on why the ICER value varies so much and why the ICER may change. Therefore, documenting this information is important to aid the guidelines development group know why there is so much uncertainty surrounding the cost-effectiveness of an intervention and whether the same uncertainty is generalizable or translatable to India.

5.1.3.2 Drivers of cost-effectiveness

In addition to documenting uncertainty, it is also important to note down what is driving the results. This is slightly different to uncertainty. The drivers of cost-effectiveness will be either from the cost offsets or the potential clinical benefits which are the biggest factor in making the treatment either cost-effective or not cost-effective. Whichever they are, it is important to document the main reason for the results.

When using international evidence, it is important to note what the drivers are in case they do not apply to India which could potentially change the result. For example, a treatment might become cost-effective because it might displace significant resource use. To use a UK example, the treatment might cost £10,000 more but because patients are healthier for longer and don't require additional care it could save the health system £15,000. However, this saving might potentially not be generalizable to India and then the results would change. Taking the same example, if the treatment costs □10,000 more but due to the differences in clinical practice between India and the UK the difference in resource use might mean that it only saves □5,000 then the results will not apply and it might not be cost-effective in India.

Another common driver of cost-effectiveness is the comparability of the clinical benefits. If the clinical benefits are quite similar then even small differences in price can have a great impact on the cost-effectiveness, as a similar benefit can be clearly be achieved from the cheaper intervention. For example, with robotic surgery any additional clinical benefit appeared to be highly uncertain and at best it was non-inferior to open surgery, however the cost of robotic surgery was thousands of rupees higher. To become cost-effective robotic surgery would have had to have had substantial clinical benefits which could not be proven therefore it was very unlikely to be considered cost-effective in India.

One of the most significant drivers of cost-effectiveness is the duration of treatment. Treatment costs are expensive and the longer a patient takes a drug, the higher the intervention costs become. Therefore, if a patient spends longer in a progression-free state then they will take the treatment for longer which increases the costs. This is a desirable outcome; however, it is important to note that this is why the treatment is so expensive and the duration of treatment should be noted to assist with cost calculations.

5.1.3.3 Factors other than cost-effectiveness affecting reimbursement status

It is also important to note down if the economic evaluation approved the intervention due to any considerations outside of cost-effectiveness.
AHTA is only used to determine whether an intervention is likely to be cost-effective or not, however there are many other factors that could influence why a treatment should be recommended.

E.g., there might not be any other treatments in this indication, delivery might be easier, there might be other clinical benefits that are not captured, there might be a higher disease burden in the country rendering the need for more treatments.

Whilst AHTA is not able to capture such additional considerations, if they are mentioned in any HTA agency document or peer reviewed publication they should be included in the extraction table to provide additional insight and context around the decision.

5.2 Price benchmarking analysis

A price benchmarking analysis is done to assess value for money and identify potential opportunity costs. It compares the list price in India with the list price in other countries whilst controlling for gross domestic product (GDP) adjusted purchasing power parity (PPP). Whilst this is not a precise costing exercise, it can provide transparency and insight into the difference in price that India is paying.

The approach involves selecting a region which has conducted an HTA process where outcomes are available, and assumes that the treatment would not be cost-effective at a higher price paid than that of the reference country. The price India is paying is adjusted for currency and PPP adjusted GDP and then compared to the price paid in the benchmarked country to see how the price India is paying compares to the price in the benchmarked country and whether this is likely to be cost-effective (**Error! Reference source not found.**).

Figure 12: Price benchmarking analysis example

A	B	C	D	E	F	G	H	I	J	K	L
Drug price in Ind	India GDP per c	Benchmarked C	Benchmarked Pr	Benchmarked G	Adjustment Fact	Currency Conve	Currency Conve	Converted Indiar	Pro-rata Price	Pro Rata Curren	Price Ratio
439478	6,454.00	Singapore	2042	98,526.00	0.02072549378	0.018	INR TO SGD	7910.604	42.3214583	SGD	187
439478	6,454.00	Ireland	6200	93,612.20	0.06623068361	0.012	INR TO EUR	5273.736	410.6302384	EUR	13
439478	6,454.00	England	5770	44,916.20	0.128461446	0.0098	INR TO GBP	4306.8844	741.2225433	GBP	6

A	Cost of the drug in India
B	India GDP per capita adjusted for purchasing power parity. Source: World Bank https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD
C	Name of comparison country
D	Cost of the drug in comparison country
E	Comparison country GDP per capita adjusted for PPP
F	The ratio of the India GDP divided by the benchmarked country GDP to adjust for differing PPP
G	Currency converter rate - this should be aligned with the time frame of the GDP rates (e.g. do not use 2021 daily price conversaions with 2020 GDP data)
H	Currencies in the conversaion
I	The Indian price converted to the currency of the comparator country to show the price paid based on a straight up currecy swap
J	The comparator country price multiplied by the adjustment factor to determine what the price in India should be if PPP was taken into account
K	Comparator currency
L	The price in India converted into the comparator currency divided by the comparator country price multipled by the adjustment factor to determine how much more India is paying

To find out if India is paying more, the price India is paying is adjusted for currency and PPP adjusted GDP and then divided by the price the benchmarking country is paying to determine any price discrepancies.

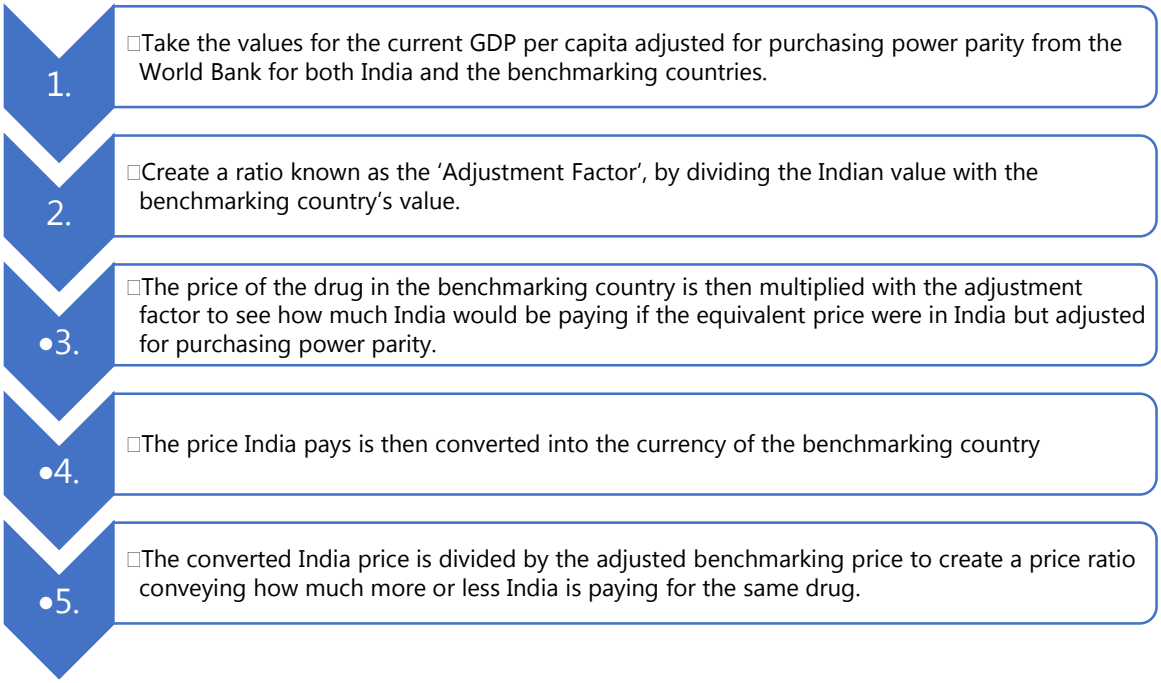
The formula is described in **Error! Reference source not found.**.

Figure 13: Method of de facto price determination

$$\text{'Cost Effective' Price in India} = Country\ A\ price\ x\ \frac{\text{India PPP} - \text{adjusted per capita GDP}}{\text{Country A PPP} - \text{adjusted per capita GDP}}$$

Conducting a price benchmarking analysis is one of the methods used in the NCG AHTA process. The steps involved in doing so are set out in **Error! Reference source not found.**.

Figure 14: 5 steps of how to conduct a pricing analysis



It should be noted that the price analysis is merely meant to provide insight into potential pricing differences and should be considered as but one part of a broader package of interventions aimed at strengthening overall health system performance.

5.3 Drug cost estimates

In a full HTA it is important include as much local cost data as possible to ascertain the cost impact of the intervention, yet it can be difficult for this to be consistently achieved in India which is why there are not many costing methods included in the framework.

However, it is possible to estimate the likely drug costs with a fair degree of accuracy, therefore the calculation of drug costs is included as a method in the NCG AHTA process.

To do so, it is necessary to know: the price of the drug, size of the pack, how many units are in the pack, how many milligrams are in the units, the dose, the number of days administered per cycle, the cycle length and how many cycles the treatment is taken for.

With this information it is possible to calculate the drug costs per year for the intervention and any comparator, and the difference between the two to understand how much more money the treatment will cost the healthcare system which can be balanced against the anticipated clinical benefit.

This information should **not** be considered a budget impact analysis because it does not consider any other cost offsets.

6. Step 4: Recommendations on cost-effectiveness

6.1 Assessment process

After data extraction, the evidence should be reviewed and collated to determine whether it appears that the drug is expected to be a cost-effective use of resources or not in India and whether this finding is considered to be robust and convincing.

There are many ways this can be conducted such as group consensus, quantitative survey or through nominal group exercises. The approach taken so far by the NCG has been through the use of an anonymous polling process.

Questions asked in the poll include but are not limited to the following:

- Based on the evidence do you believe that the intervention provides a sufficient clinical benefit in comparison to the standard regimen or is non-inferior?
- Do you think the estimates of clinical benefit are generalizable to the Indian context?
- Do you think the estimates of costs are generalizable to India?
- How do you think the drivers of cost-effectiveness would differ in India?
- Do you believe that the intervention would be considered to be cost-effective in India based on the evidence presented?
- If the treatment was approved and included in the HBP, how would you designate the recommendation?
- Do you have any other concerns or points that you would like to raise? (e.g., equity, epidemiology unmet need)

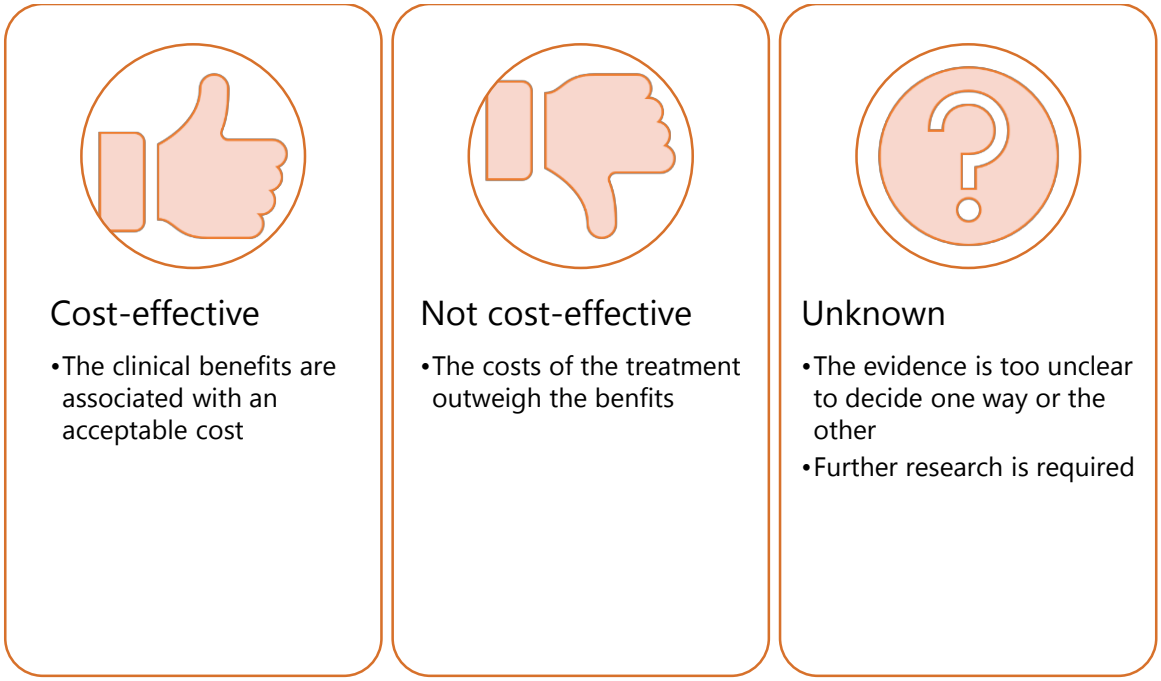
Once the working group have completed the poll, the answers are reviewed to determine the areas of consensus and discussion. Once all concerns and queries are discussed in full, a decision is reached on whether the intervention is considered to be potentially cost-effective or not or whether full HTA is required.

6.2 What the decisions means

Error! Reference source not found. demonstrates that there are three potential decisions that could be made after the assessment process. That the treatment is:

- Likely to be cost-effective
- Not likely to be cost-effective
- The potential cost-effectiveness is too unclear

Figure 15: Potential decisions



If a treatment is found to be cost-effective then it means that the cost of the clinical benefits is considered to be an acceptable amount.

If the treatment is not found to be cost-effective then it means that the costs considerably outweigh the benefits and other options are likely to provide a similar clinical benefit at a more sustainable cost, unless a discount can be negotiated

As AHTA relies on international data it is possible that the likely cost-effectiveness of the drug in India cannot be decided through the evidence available. In this instance it would be best to conduct a full HTA on the treatment. (See Section **Error! Reference source not found.**.)

It is very important to note that the decision is not a recommendation of whether the treatment should go into the guideline. The assessment of whether the treatment is potentially cost-effective is only one component of whether the treatment should be made available and where it sits in the resource stratified guidelines. There are multiple factors that inform whether a treatment should be included in a standard treatment guideline and the decision is made on a balance of them. However, the benefit of AHTA is that this information helps the GDG to objectively evaluate the intervention for inclusion in the guidelines and the category of inclusion

6.2.1.1 What if further information is needed?

If there is no clear indication as to whether the drug is cost-effective or not or the results are inconclusive then a full HTA might be necessary to determine the likely cost-effectiveness.

If this is the case the policy brief will state the evidence available but will designate that the treatment should be assessed through full HTA as further evidence will be required and the treatment will be assessed externally through a partnership with a university or regional resource center to conduct the review, or perhaps HTAIN.

It should be noted however that for the full HTA to be completed there will need to be clinical outcomes, utility data, cost data and resource use which may be challenging to obtain.

7. Step 5: Reporting of findings

The final output of the process is a policy brief for each intervention within its scope. This policy brief presents all underlying evidence that was extracted to support a final decision on whether an intervention is potentially cost-effective or not covering the background, clinical and safety evidence, cost-effectiveness evidence, price analysis and treatment cost estimation.

There is a standardised template for the policy brief that informs how the evidence will be presented and discussed attached as an appendix.

The policy briefs will be hosted by the NCG alongside the supporting evidence.

7.1 Methodology

Once the policy briefs are completed, they are then sent to the GDG as part of their consideration process when drawing up guidelines,

The GDG are a group of clinical cancer experts from the NCG that include a fair regional representation. Each of these groups is responsible for specific cancer guidelines (for example, urological malignancies, head and neck cancer etc..). Each GDG has a chair and two coordinators: one from the Tata Memorial Centre (TMC), the other from the NCG centres.

The guideline development process is covered in the NCG Guidelines Manual, but there is a similar framework involved where the GDG define the scope and research question and understand the key clinical issues which need to be addressed in the guideline. The GDG review existing international guidelines and consider what can be adapted to the Indian context, then consider if additional reviews or data are necessary that are India specific, including economic analyses.

The GDG members can then make a collective decision after reviewing and interpreting the evidence to develop the recommendation.

As mentioned earlier the strength of recommendations may be represented as “resource stratified recommendations” that take into account the clinical evidence, equity, costs and also implementation considerations.

The AHTA policy briefs can help to inform the designations of treatments that are part of the resource stratified guidelines of:

- Essential
- Optimal
- Optional

This decision will ultimately help determine which treatments should be made available in the national health insurance scheme health benefits package

8. Limitations of using AHTA

Adaptive HTA is a pragmatic solution but leveraging international data will never achieve the nuance of detail of local estimates.

As AHTA makes use of leveraging international evidence, it is difficult to conduct an AHTA on any technologies that have not been through a formal HTA process in an international jurisdiction. In this instance we recommend collating as much quality evidence possible on the clinical and economic benefits, however the lack of HTA evidence is strong limitation.

It is important to note that AHTA is most insightful when assessing the cost-effectiveness of pharmaceutical drugs given the substantial evidence base available. There are greater challenges in using AHTA to assess other interventions, particularly non-pharmaceutical interventions (NPI's).

HTA is predominantly used to assess drugs but not NPIs which are assessed in slightly different ways, therefore there tends to be less international evidence available which means that there is less available evidence to conduct an AHTA on.

In addition, NPIs have more unclear and variable costs. There are no treatment costs to compare therefore differences in costs are highly driven by changes in resource use which requires cost data to ascertain. Without accurate cost data, it is very difficult to determine the cost difference with non-pharmaceutical interventions. It can be unclear what is the true comparator for NPIs, whereas drugs tend to be highly fungible and more easily compared.

Generally, the only information available to compare is likely to be safety and efficacy. If efficacy is comparable then the main driver of cost-effectiveness will be differences in resource use. If a technology is associated with high costs, then it is very unlikely to be cost-effective as the same clinical benefit can be found with a cheaper intervention. However, if the safety and efficacy is highly improved, it can be difficult to determine whether this additional benefit is cost-effective.

Finally, AHTA is intended to inform decision making, but it is only meant to be one component in the process. Estimates of cost-effectiveness should be considered alongside the broader needs of patients and the health system.

9. Conclusion

The AHTA framework developed by the NCG is a rapid and pragmatic way of generating evidence for decision making. The framework collates the available international evidence on the potential cost-effectiveness of a treatment and presents it in a format that allows for easy comparison. All international evidence should be considered with its generalisability to the Indian context in mind. However, the policy briefs developed for each intervention should be an informative collation of the available evidence for a treatment's cost-effectiveness, clinical benefits, safety and treatment costs.

10. Further resources

General:

- Nemzoff C, Ruiz F, Chalkidou K, et al, Adaptive health technology assessment to facilitate priority setting in low- and middle-income countries BMJ Global Health 2021;6:e004549.
- Cochrane guide on rapid reviews: https://pubmed.ncbi.nlm.nih.gov/33068715/
- Limitations of HTA: https://resource-allocation.biomedcentral.com/articles/10.1186/s12962-021-00308-1
- WHO's recent survey on HTA and HBPs: https://app.powerbi.com/view?r=eyJrIjoiYzMyZDY4NDEtY2VmOC00YjNhLTgzZWUtMDU0MTlhODNlZmMyIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9&pageName=ReportSection6010075c0d83085bc926

Country specific:

- Canada: https://www.cadth.ca/about-cadth/what-we-do/products-services/rapid-response-service.
- 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/
- Philippines - https://hta.doh.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://www.knowledgehub.org.za/system/files/elibdownloads/2021-07/3.%20HTA%20Methods%20Guide_draft_v1.2_14Jun21.pdf

Economic evaluation methods

- Methods for the Economic Evaluation of Health Care Programmes
  Drummond et al., 2015
  Textbook
- **Decision Modelling for Health Economic Evaluation**
  Briggs et al.
  Textbook
- **Guide to Economic Analysis and Research (GEAR) Database**
  HITAP
  Database
- Plant-A-Tree
  Saw Swee Hock School of Public Health at the National University of Singapore and HITAP
  Open-source Microsoft® Excel Add-In that you can use to make decision trees for use in economic evaluations or any decision problem you are facing
- The iDSI Reference Case for Economic Evaluation
  by iDSI
- Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development
  Robinson et al.
- Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses
  by Second Panel on Cost-Effectiveness in Health and Medicine

Priority setting and HTA

- HTA Glossary by International Network of Agencies for Health Technology Assessment (INAHTA), Health Technology Assessment international (HTAi)
- HTA 101 by Goodman (NIH Library of Medicine)

  Comprehensive introduction to HTA, from definition of concepts to

  recommendations.
- HTA toolbox for emerging settings by Advance HTA
- HTA toolkit by iDSI
- **Multiple Criteria Decision Analysis for Health Care Decision Making – An Introduction: Report 1** by IPSOR
- Multiple Criteria Decision Analysis for Health Care Decision Making – Emerging Good Practices by IPSOR
- **Multicriteria Decision Analysis to Support Health Technology Assessment Agencies: Benefits, Limitations, and the Way Forward** (methods paper by Balthussen et al.)
- An Introduction to the Main Types of Economic Evaluations Used for Informing Priority Setting and Resource Allocation in Healthcare: Key Features, Uses, and Limitations
  Turner et al 2021