



Health Technology Assessment in India

A Manual

Department of Health Research
Ministry of Health & Family Welfare
Government of India

Health Technology Assessment in India (HTAI_n)



The logo of Health Technology Assessment in India (HTAI_n) is in the form of a shield which represents the protecting role of HTAIn towards its citizens from the financial hardships arising out of health care seeking. The top of the shield is marked with Ashok Chakra, depicting the allegiance of HTAIn towards the constitutional values and the nation. The Rod of Asclepius and the symbol of the Indian Rupee are placed side by side below the National Emblem; as while making a decision about the cost-effectiveness of an intervention, HTAIn gives due consideration to both public health potential and the costs associated with the intervention. “सर्वे: सन्तु निरामयाः” is scripted in Devnagri script on a ribbon, which means “Let all be healthy”, and expresses the devotion of HTAIn towards the values of Universal Health Coverage (UHC).

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A Manual

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Compiled by

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Disclaimer

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Preface

To facilitate the process of transparent and evidence informed decision making in the field of health, Government of India decided to set up *Health Technology Assessment in India (HTAI)*. HTAI will generate and compile evidences related to cost-effectiveness, clinical-effectiveness and safety of medicines, devices and health programmes by means of Health Technology Assessment (HTA) studies. It will evaluate appropriateness and cost effectiveness of the available and new health technologies in India, so that maximum people can have access to quality healthcare at minimum cost in the country to ensure the best value gained from the health budget.

Establishment of HTAI may prove to be a watershed in achieving Universal Health Coverage (UHC) as it aims to encourage the process of standardizing cost effective interventions that will reduce the cost of variation in patient care by optimizing expenditure, bringing down overall cost of medical treatment and thereby reducing out-of-pocket expenditures on the part of patients. This may also facilitate streamlining the medical reimbursement procedures and improvement in quality of care for government-funded health insurance schemes, such as the National Health Protection Scheme (NHPS) under Ayushman Bharat Yojana and other state insurance schemes.

This short manual seeks to familiarize readers with the concepts of HTA, to build capacity regarding the many facets of it to increase their knowledge base on the essentials on how to conduct HTA studies in our country's settings. It also highlights the various potentials of HTA as its role in evidence based decision-making and policy formulation for deployment of effective health interventions in India.



Prof. Balram Bhargava

Secretary



MESSAGE

Health Technology Assessment in India (HTAI) has been set up under the Department of Health Research (DHR), Ministry of Health & Family Welfare (MoHFW) with the responsibility to analyse evidence on cost-effectiveness, clinical-effectiveness, socio-cultural and equity related issues in the implementation of health technologies. These can be medicines, devices and health programmes and by means of Health Technology Assessment (HTA), we can arrive at informed decision making for an efficient use of a finite resource pool. The primary aim of HTAI is to maximize health, minimize out-of-pocket expenditures and counter inequities.

This manual provides a description about the significance of HTA in evidence informed decision making in healthcare and on how to conduct one in our settings. It also gives an outline of how HTAI functions – its vision and mission and how HTAI can play an important role in prioritization and allocation of health budget, procuring health interventions and strategic purchasing. HTAI is an important milestone for the Indian Healthcare System and has the potential to improve the mobilization of resources towards healthcare, taking our country one more step forward towards the goal of Universal Health Coverage.

I congratulate the editorial team and all those who have contributed and have been involved in the compilation of this manual.

Well done!

Balram Bhargava

(Prof. Balram Bhargava)

Secretary, DHR & Director General, ICMR

V. K. Gauba

Joint Secretary to the Government of India
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वी. के. गाबा

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Message

Health Technology Assessment, a touchstone of health policy formulation in several countries – be they developed or developing – will become a bedrock for better healthcare provisioning in India, through the establishment of Health Technology Assessment in India (HTAI). It is a robust system instilling confidence in health policy makers in having evidence on the most appropriate, safe and effective technologies be it related to drugs, devices, treatment protocol or a whole treatment programme. This lays the cornerstone for moving towards Universal Health Coverage (UHC) by optimizing and improving the existing healthcare system in India.

HTAI, in its advisory role will provide findings based on evidence based HTA outcomes to the Department of Health & Family Welfare and State Governments as crucial input at the time of formulation of policy or implementation. The participatory and all-inclusive approach of technology assessment is the strength of HTAI. Though HTA is in its developing stages today, it is expected that it will take deeper roots tomorrow with assistance from national and international partners that have valuable experience in this field.

This HTA manual gives an overview about the importance of HTA and how HTAI is taking it forward. It mentions how HTA can help in efficient allocation of budget in healthcare increasing the health coverage and in reducing the out of pocket expenditure. It also acts as a guide on how to go about conducting HTA studies in our country's settings. The amount of effort and hard work put in compiling this manual is well commended.

(V.K. Gauba)

Joint Secretary, DHR & Sr DDG, ICMR



Message

The Health technology assessment (HTA) is systematic evaluation and assessment of health interventions and/or technologies. The main purpose of establishing HTAIn in Department of Health Research, Ministry of Health & Family Welfare is to inform policy decision making and develop a system to better tackle health problems and improve the quality of life of the general population. The HTAIn is an advisory body that will provide the recommendations based on evidence, through HTA studies, for the user Departments to help in the formulation and implementation of better and effective health policies.

The HTA is the internationally accepted tool for utilizing health economic principles to assess evidence for cost effectiveness, clinical effectiveness, safety and equity to provide for investment and disinvestment answers within a given health system and to assist in the prioritization of health resources. The HTAIn has the potential to play a key role in Government's commitment towards Universal Health Coverage.

This Manual gives a concise overview about the HTA activities going on in India under HTAIn and its collaborating partners. The HTAIn will play an important role in reducing out-of-pocket expenditure and maximise the coverage of health services. I congratulate and appreciate the work done by the HTAIn Team and look forward to more outcomes coming from HTA studies that may be adopted by the Government while formulating its health policies. I congratulate and express thankfulness to the editorial Team in HTAIn Secretariat, along with all the contributors, on their effort in compiling this Manual.

(Om Parkash)
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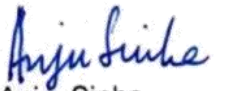


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Health Technology Assessment is an emerging concept, which can spearhead the enhancement of the existing healthcare system by providing a framework for systematic assessment and analysis of the various health interventions and technologies. This would mean that an efficient process would be there which can then be used for generating evidence on any new health intervention that needs to be adopted by the policy and decision makers for moving towards Universal Health Coverage.

For this purpose, the setting up of HTAIn is a landmark that establishes our first foundation of moving towards efficient and effective implementation via evidence based decision-making. A structure that is both comprehensive and inclusive is what defines HTAIn. In addition, systematic reviews and assessment can act as a core fundamental pillar of HTA as well. Though HTA is in its infancy today, it can be a strong pillar for healthcare delivery in the near future.

This manual briefly describes what the scenario of HTA is in India and abroad, and how we can formulate effective HTA studies in Indian settings. This can act as a guide for its readers for starting with the foundation of building on existing data and evidences for conducting HTA studies in India.


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Dr. Ashoo Grover
Scientist 'E'



MESSAGE

In many Countries the demand of the health care services goes beyond the resources. In that scenario, we need to decide upon the interventions for a given disease, between treating a disease or preventing it in the first place, or between treating one disease as opposed to another. These decisions require interpretation of evidence in a systematic manner. Hence, the call for Health Technology Assessment (HTA) as a systematic, unbiased and transparent method of assessing healthcare interventions is an important tool for bridging the gap between evidence and rational decision making.

Health Technology Assessment India (HTAI) has been set up under Department of Health Research, Govt. of India to undertake the various approaches to HTA, which is dealing with safety, efficacy / effectiveness, economic, organizational, ethics, social, and legal aspects; that are key issues in the HTA process.

This manual is the first manual relating to Health Technology Assessment (HTA) in Indian context which has been designed as a tool for HTA practitioners and presents updated new scientific methods. With in short span of experience in conducting HTA in India, the development of this manual is very useful as a guide for health professionals, political and administrative decision-makers, interest groups, researchers and others who want to adopt an HTA approach in conducting assessment of health technologies.

I would like to congratulate team of HTAI for their commitment in developing this manual and sincerely hope that this HTA manual will further improve the quality of HTA work in India.

(Dr Ashoo Grover)

Chapter 1
Priority setting for
Universal Health Coverage

In most countries, health service delivery is undertaken by health organizations that take it upon themselves to meet the requirements of the population as best they can, with a finite resource pool. In essence, if there are more stakes on the resources than the resources available, some form of prioritization needs to take place. This means that from a funder's perspective, which in our case means the central or state governments, regardless of how many resources are available in total, choices need to be made on what to and what not to fund. To do this, either the health services can be commissioned (as done in the UK) or the pool of resources can be divided up among the regional health authorities as a kind of a decentralized approach towards the management of the healthcare delivery (as is the case in parts of Canada and Australia).

What is Priority Setting?

The task of determining the priority to be assigned to a service, a service development or an individual patient at a given point in time. Prioritisation is needed because claims (be it for needs or demands) for healthcare are greater than the resources available for providing them. To prioritize a process may also refer to allocate resources to it with the goal of maximizing its health impact within a defined budgetary constraint (the major hurdle in our system). Another way for prioritization is to rank order interventions with an aim to inform decision-makers on all the pros and cons of implementation of the ranked health interventions.

When we talk of setting priorities, it may differ according to requirements of the population in question for which the health intervention is being implemented or the overall disease burden that needs to be targeted; some of the reasons why we need to prioritize. So the levels of prioritizing can be broadly categorized as:

- Macro-level : e.g. national
- Meso-level : e.g. state/ provincial
- Micro-level : e.g. local community level

Other than this categorization based on the scale of the impact of the healthcare interventions/services being targeted, prioritization is of two types, i.e., either explicit or implicit. As a broad explanation, explicit priorities are well defined and precise with clear cut boundaries of action while the implicit ones are usually more flexible in its scope of action.

Explicit Prioritization

- The decision makers are clearly defined; who makes which decision
- Has a defined criteria and if it was met or not with reasons
- What evidences were considered and their sources
- Can be challenged

Implicit Prioritization

- It may be ad-hoc, or rely on semi-explicit strategies like peer benchmarking or oversight
- Decentralization of the responsibility may be done to the local providers either via budgetary or some regulatory methods

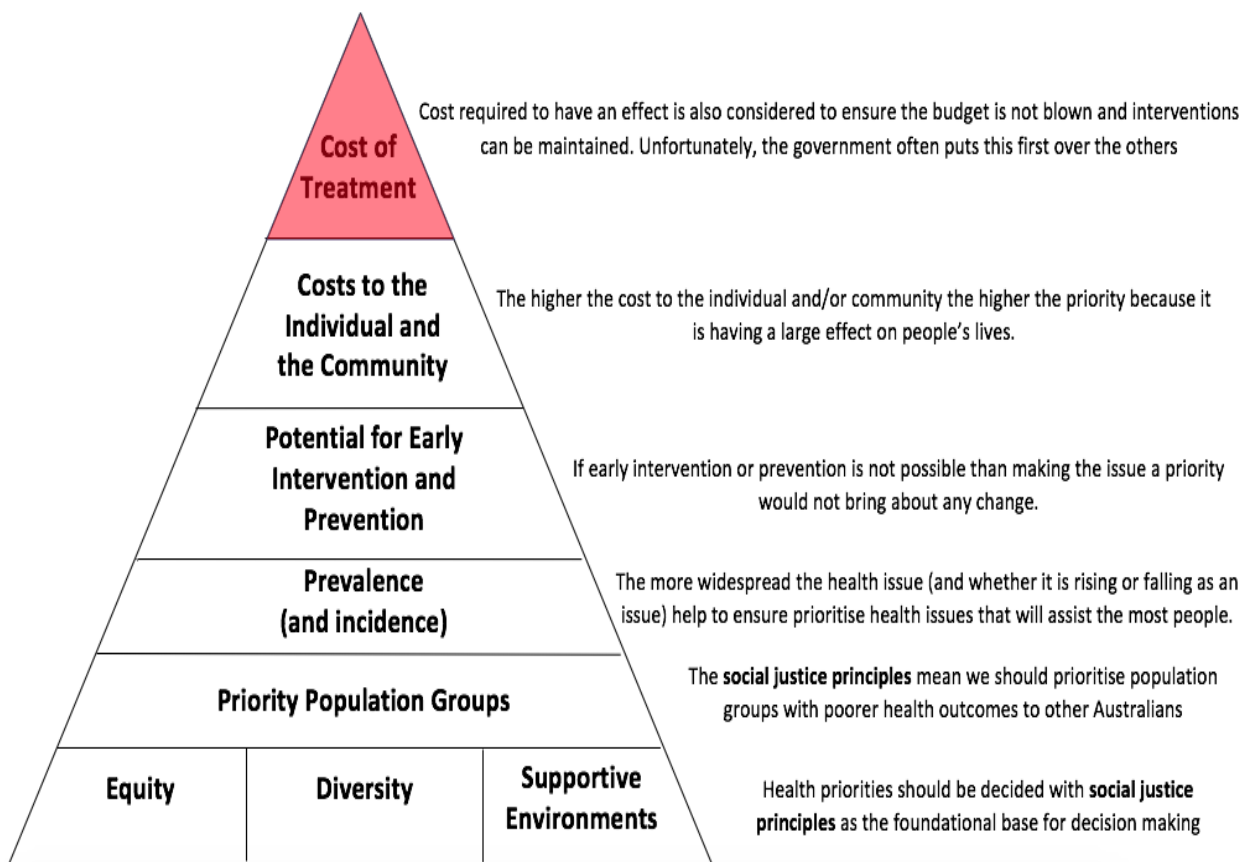


Figure 1: How to identify priority issues as per Australia's Health Pyramid

The process for prioritizing needs in healthcare varies due to a number of factors; sociodemographics, geography, disease burden, resources available, etc. to name a few. For example, figure 1 illustrates how priority setting for healthcare moves up in the form of a pyramid and what all things are considered while making in a healthcare decision.

Universal Health Coverage (UHC) and Priority Setting

UHC has been defined as “all people receiving quality health services that meet their needs without exposing them to financial hardship in paying for them” (figure 2 illustrates the 3 core dimensions considered when moving towards UHC).

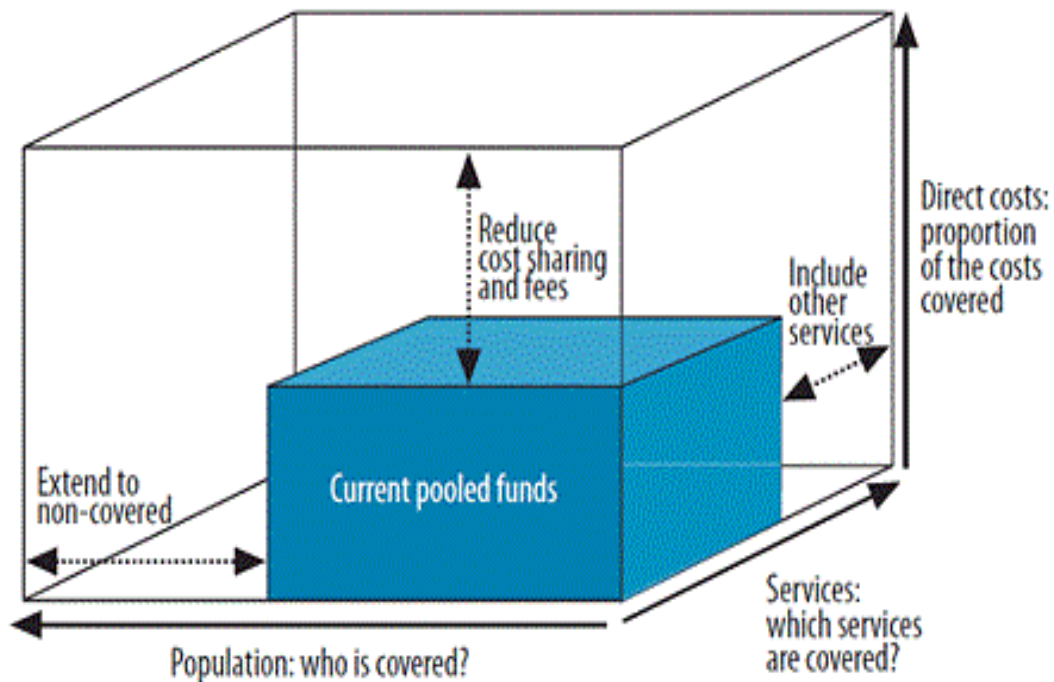


Figure 2: Three dimensions when moving towards Universal Health Coverage

However, scarcity of resources and a paucity of funds in most developing countries ensure that not everyone gets all the beneficial health services at affordable prices. UHC has three dimensions in terms of three axes of a cube – the population covered, the services delivered and the financial cover provided to the population. Depending the resources and programmes covered in a country the size of the cube varies according to how much of each axis has been tended to. Also, countries trying to move forward with UHC will face at least one bottleneck regarding fairness and equity issues in each dimension. So while pursuing an approach to adjust for these issues, some trade-offs come to mind that are generally unacceptable:

1. To reduce out-of-pocket expenditures for low or medium priority services before eliminating out-of-pocket expenditures for high-priority services.

2. To prioritize high cost services whose coverage will provide substantial financial protection when the health benefits are very small compared to better or balanced alternatives.
3. To expand coverage for population of the higher socio-economic strata before doing so for those of the lower socio-economic strata or those below the poverty line (BPL population) when the costs and benefits do not vary much.
4. To include only those with the ability to pay for services (both low and high end) and not include people from the informal sector (most of whom fall in the impoverished category) even if it is achievable in the UHC approach.
5. To move from out-of-pocket expenditures to a mandatory pre-payment approach in a way that compromises the whole healthcare financing system.

Thus, there needs to be taken a clear approach while deciding our priorities, keeping in mind the UHC concept, and for as to how the decision-making process would follow. A skeleton framework guided by certain key factors is then structured starting with the scope of the whole process till the implementation and the monitoring of the end implementation. These factors are listed below.

- Defining the overall scope
- Listing out issues under defined scope
- Ordering of priority issues
- Evidence generation/synthesis for the same
- Collation of pooled results
- Making a decision
- Implementation
- Monitoring and evaluation

Lastly, we come to why and where we might need to set up priorities for health interventions. Figure 3 illustrates the various reasons why we need to prioritize health interventions.

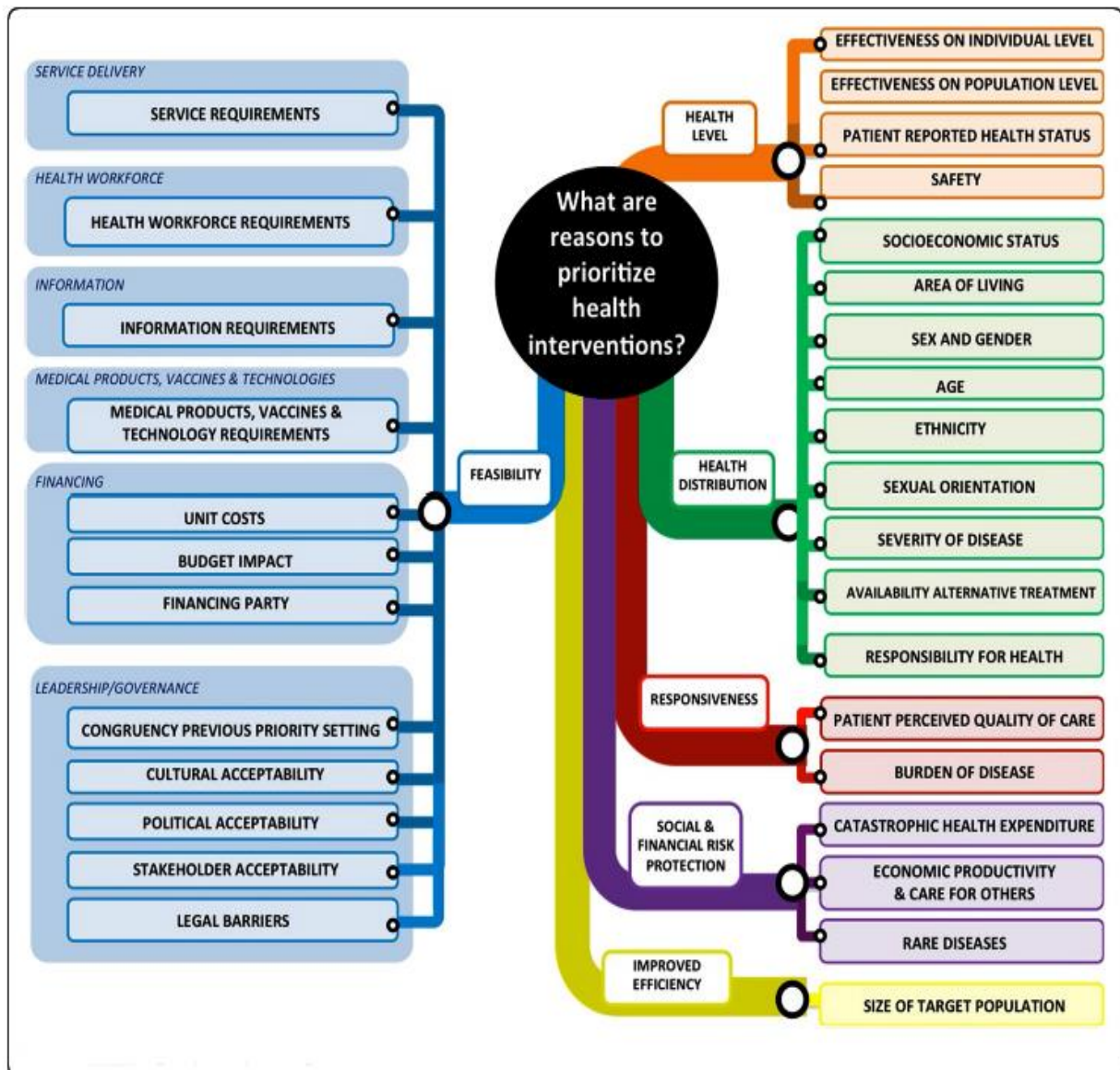


Figure 3: What are the reasons to prioritize health interventions

Conclusion

To conclude, a conceptually and practically feasible priority setting process would be one that takes care of all trade-offs, while being transparent, precise and fully accountable of the use of the resource pool set out for the healthcare service. While the importance of preferentially subsidizing health interventions and products for UHC is recognized globally, there is still a lack of national capacity on the concept of prioritization and its amalgamation with UHC to have a holistic approach for a better healthcare system. A better priority setting mechanism can be a constructive channel for the growing and competing demands and calls for action in health.

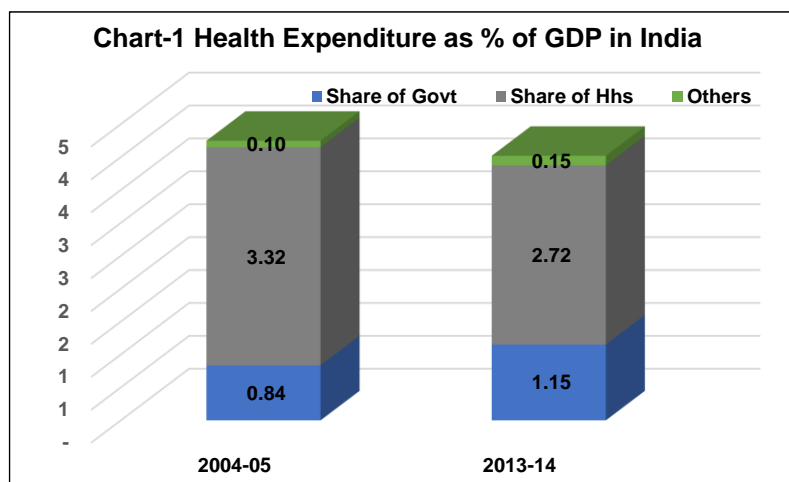
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*Chapter 2:
Financing Health
Care in India*

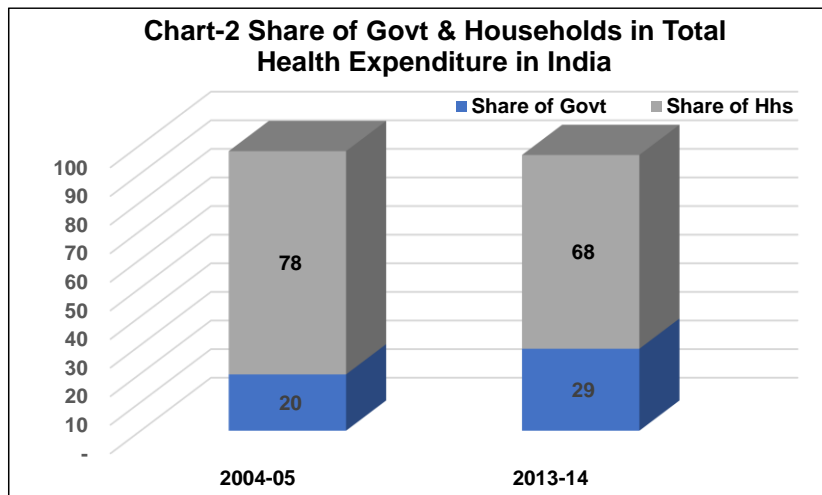
Financing health care in India has assumed critical importance both for the government and for households. In spite of sustained efforts and recommendations by various committees and commissions, allocation to health sector by the government remained abysmally low. The National Health Policy-2002 aimed to increase the public health spending to about 3 per cent of GDP. Even after a decade later since the recommendation of NHP-2002, the public spending on healthcare remains around 1.1 per cent of GDP as revealed through the National Health Accounts-2014-15. Further, the commitment of governments in terms of allocation of resources to health sector by government has also been shrinking and down to a level of 3.9 per cent of total government expenditure at present from more than 5 percent during early 2000. Over the last decade, total health care spending in the country has declined from 4.25 percent to 3.9 percent of GDP.

In the expanding health care markets, any reduction in the government spending is borne by the households due to the near absence of pooling mechanism. While access to public health care services have improved considerably



over the last decade, particularly after the initiation of National Rural Health Mission (NRHM), they remain financially inaccessible for a majority of the population. Private health care providers continue to dominate the market because of their easy access in spite of higher cost of care. Of the total per-capita expenditure on health of Rs.3,826 in 2014-15, nearly Rs.2,400 was spent by households as out-of-pocket expenditure. Such high costs often impoverish households, particularly the vulnerable and rural households.

One of the objectives of NRHM was to reduce financial hardships and impoverishments of households on account of healthcare access by improving public health services through



focussed investments. Targeted approach and non-lapsing budgets for certain areas under NRHM, not only improved the access but also the quality of a number of primary care services. As a result, there is a considerable change in the composition of government and household health expenditures as revealed through respective national health account reports 2004 and 2014 (Chart-2)

Recent Initiatives

Pooling of health risks is suggested as one of the mechanisms to mitigate the household burden. As of now, a very negligible size of the population is covered through insurance programs for health care in the country. While the publicly financed risk pooling is still in the nascent stage, the private insurance programs are mainly confined to urban areas and certain segments of the population. A number of publicly funded health insurance schemes have been launched over the last two decades at different scales and sizes, such as Rashtriya Swasthya Bima Yojana (RSBY) by the government of India, Aarogyasri by the Government of Andhra Pradesh, Chief Minister's Health Insurance Scheme by different states, and many others. Experiences gained through implementation of these schemes and the need to bring-in strategic reforms in health care sector forced the government to move towards Universal Health Coverage (UHC). After series committees, reports and debates over the last few years, the Government of India recognised the fact that UHC would be the way to address the financial hardships faced especially by the poor and vulnerable population due to ill-health and health service utilisation.

A nationwide Universal Health Coverage scheme in the name of Pradhan Mantri Jan Arogya Yojana (PM-JAY) was recently launched by the Government of India with the initial

target coverage of about 10 crore families with a health insurance coverage of Rs.500,000 per family per year. National Health Agency (NHA), an autonomous registered society has been recognised as the nodal agency for implementation of PM-JAY.

Challenges

The recent national health accounts estimates (2014) reveal that of the total health expenditures, i.e. Rs.451,286 crores, nearly 28 percent is spent on pharmacies and 25 percent is spent on services from private hospitals³. Implications of this structure of spending on financing UHC is of critical importance.

A review of the composition of public expenditure reveals that 51 percent is spent on primary services, 22 percent on secondary care services, 14 percent on tertiary care services while 10 percent of spent governance and administration. Budgetary allocation to these services under the ambit of financing UHC and its implications on public health infrastructure and human resources is an area of concern at least in the short run or the immediate future.

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Chapter 3:
Health Technology
Assessment- What is it?

Health policy decisions are becoming increasingly important as the opportunity costs of making wrong decisions continue to grow, especially in countries where health sector is underfunded. A finite health budget means that policy makers are faced with difficult decisions regarding prioritisation of health on a daily basis. For example, should the government pay for a Human Papillomavirus Vaccination program to prevent cervical cancer, or for reimbursement of those being operated for cataract? One woman with breast cancer may be treated with chemotherapy for the same cost as treating 20 lakh children for intestinal worms. Moreover, government also plays the role of strategic purchaser of Healthcare. This poses a complex problem in front of policy-makers as to decide which health condition and population to be prioritised and why? Health Technology Assessment (HTA) offers scientific solutions to such complex problems and assists policy makers in taking transparent and prudent decisions. In order to solve such issues in a judicious manner, HTA is a widely used methodology internationally for optimization of resource allocation in health. Employing a scientific and evidence based methodology, HTA assists in judiciously allocating the financial resources so that maximum people can have access to quality healthcare at minimum cost. HTA tries to identify the most cost- effective strategy among the available alternatives, so that greatest amount of health can be bought for every rupee spent. In 2014, the World Health Assembly adopted a resolution on use of HTA to ensure Universal Health Coverage (UHC).

HTA refers to the systematic evaluation of properties, effects, and/or impacts of health technology.¹ The word 'technology' can include interventions like drugs, devices, diagnostics, treatments, vaccines or health programs. It is a multidisciplinary process that summarises information about the medical, economic, social, organizational, legal and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. These effects are then comparatively evaluated for the available alternatives to decide that which alternative offers best value for money.



Figure 1: Scope of Health Technology Assessment

Approaches used in HTA

Despite its policy goals, HTA must always be firmly rooted in research and the scientific method. HTA employs the principles of economic evaluation to identify the most cost-effective health technology. Economic evaluation refers to comparative analysis of alternative courses of action in terms of both their costs and consequences. The aim of the health economic evaluation is to clarify the relationship between the costs and consequences of a (new) health technology compared with one or more relevant alternatives. Health economic evaluation is primarily of four types: cost minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA).

Cost minimisation analysis is the simplest type of economic evaluation which assumes that the consequences (the health gain) arising from the use of the health technologies compared are the same. Therefore, it is sufficient to assess the costs of both the alternatives. In cost-effectiveness analysis, both the costs and consequences arising from use of the health technologies are identified, measured and valued and compared. The consequences are assessed in natural units, e.g., mm Hg reduction in systolic blood pressure, cases prevented, lives saved, life years gained. Cost-utility analysis differs from cost-effectiveness analysis in that the consequences are measured and valued in the form of quality-adjusted life years (QALYs). The years of life gained are therefore quality-adjusted with health-related quality of life in order to assess QALYs. This kind of analysis makes it possible to compare outcomes of interventions across different activities in the health care sector, where natural units of outcomes are different otherwise. Cost-benefit analysis is the broadest type of economic evaluation where both the costs and consequences are measured and valued in monetary terms, net gain can therefore be calculated directly.

Economic evaluations provide evidence on how to maximize health benefits within a given budget, accounting for the societal value of health. It, however, does not generally

provide information about the distributional value of health benefits in a given setting. Therefore, apart from comparing the health and economic consequences of available policy options, HTA also assesses their feasibility of implementation with regard to social, legal and ethical aspects. Social aspects such as effect on out of pocket expenditure, catastrophic health expenditure, impoverishment rates are assessed with the help of equity analysis, so that the proposed health technology confers to the principles of distributional justice. Equity analysis can be performed by using mathematical programming, measurement of distribution of opportunity costs, multi-criteria decision analysis, distributional cost-effectiveness analysis (DCEA) and extended cost-effectiveness analysis (ECEA).⁴ However, as the term inequity goes beyond measurable differences in health status to include moral and ethical dimensions also⁵, all the organizational, legal and ethical issues are assessed with the help of stakeholders' discussions.

Practice of HTA

HTA provides an internationally-accepted and structured approach to form the basis for evidence-based priority setting and policy decisions. It is widely used to inform healthcare resource allocation in numerous countries in Europe, Scandinavia, Asia, and Australia. Nascent institutions are also being established in South East Asia, the West Pacific, South America and Africa.⁶ These countries utilize HTA for the purpose of informing content of health benefits packages, such as the universal health coverage program of Thailand, or the National Health Service (NHS) in the UK, and the essential medicines lists (NLEM) in low and middle income countries, such as Thailand, Indonesia, the Philippines, and Mozambique.

To facilitate the process of transparent and evidence informed decision making in the field of health, Government of India has also established Health Technology Assessment in India (HTAI).⁷ HTAI will generate and compile evidences related to cost- effectiveness, clinical- effectiveness and safety of medicines, devices, vaccines and health programmes by means of Health Technology Assessment (HTA) studies. It will evaluate appropriateness and cost effectiveness of the available and new health technologies in India. Establishment of HTAI is a remarkable step towards achievement of UHC, one of the targets under Sustainable Development Goals (SDGs), as it aims to encourage the process of development of standardized cost effective interventions that will reduce the cost and variations in patient care, expenditure on medical equipment directly affecting the cost of patient care, decrease

overall cost of medical treatment, reduce out of pocket expenditure of patients and streamline the medical reimbursement procedures.

Challenges and Opportunities

HTA in India brings with it several challenges that need to be recognized and addressed. The first and foremost challenge pertains to the gross deficiency in the human resource capacity to undertake HTA studies in India.⁸ Second challenge is ensuring technical rigour and methodological and process consistency across all the agencies doing HTA studies, making the results authentic and comparable.⁷ The third challenge relates to data availability and quality as the effective conduct of HTA depends on the availability of reliable data.⁹ Transparency of the process and the way of addressing conflict of interest of those performing the HTA studies poses another challenge.⁷

In order to achieve UHC, several difficult resource allocation decisions must be made. Using the evidence-based and transparent HTA processes, these decisions can be made in a manner that ensures efficient and equitable health care provision. This opportunity of explicit priority setting is viewed as the most effective way in which to make decisions as to the best way a health budget is spent, weighing up all options, and coming to a fair and just conclusion, towards the ultimate goal of UHC.

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Chapter 4:
HTA in international
context

At international levels, there has been a great attention to strengthen the health systems from the very beginning of 21st century; particularly as an inherent component of Sustainable Development Goals. Apart from focus to increase the spending in healthcare sector, need is to have rational spending and 'Best-buys' approach in policy making for high performance health system. Health systems performance has the crucial challenge of rationally adopting new health technology, to improve quality and efficiency of the systems. Particularly in countries, which have publicly funded health systems; there must be greater accountability for spending from public revenues and there, process of rational decision making is even more important.

Health technology assessment (HTA) is being used for making evidence-based healthcare decisions from last three decades by many countries in the developed region (e.g. Europe, US, Canada etc.) and is now also being adopted by the developing world (especially in the South Asian region, South Korea, Taiwan and Thailand etc.) which have formally started adopting HTA as part of their decision making process in last few years.

Historical Development of HTA, National and International HTA agencies

The term Technology Assessment first came into origin in 1965 in the U.S. House of Representatives during scientific deliberations and first healthcare program was established under the same in 1975. The first formal HTA committee was structured in 1984, in Catalonia, Spain; which later served as the foundation of Catalan Agency for Health Technology Assessment (CAHTA). In 1987, Sweden constituted the Swedish Council for Technology Assessment in Health Care (SBU) for institutionalizing HTA in the country. Across Canadian region, different provinces started establishing their HTA institutions like Council for Health Technology Assessment of Quebec was created in 1988; Ontario Health Technology Advisory Committee in 2003 etc. In 1991, WHO held a meeting of HTA experts in Geneva raising relevance of HTA and Economic Evaluation at global level. In 1985, International Society for Health Technology Assessment (ISTAHC) was constituted. In 1995, Germany started doing HTA and formally established German Scientific Working Group Technology Assessment for Health Care (GSWG-TAHC) in 1997. United Kingdom established National Coordinating Centre for Health Technology Assessment in 1996. In 1999, National Institute for Health and Clinical Excellence (NICE) was established to support the evidence-based decision making process in the National Health Service in England.

Table 1. National Agencies for HTA internationally and their roles

AGENCY	COUNTRY	ROLE
Institute for Clinical Effectiveness and Health Policy	ARGENTINA	Consultative
Australian Safety and Efficacy Register of New Procedures	AUSTRALIA	Consultative
Institute of Technology Assessment	AUSTRIA	Consultative
Belgian Health Care Knowledge Center	BELGIUM	Consultative
Canadian Agency for Drugs and Technology in Health	ONTARIO, CANADA	Consultative
Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé	QUÉBEC, CANADA	Consultative
Institute of Health Economics	ALBERTA	Consultative
Instituto Nacional de Higiene Epidemiología y Microbiología	CUBA	Consultative
Danish Centre for Evaluation and HTA (DACEHTA),	DENMARK	Consultative
Finnish Office for Health Care Technology Assessment Helsinki	FINLAND	Consultative
Comité d'Evaluation et de Diffusion des Innovations Technologiques	FRANCE	Consultative
German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information	GERMANY	Consultative
Health Economics and Health Technology Assessment Research Centre	HUNGARY	Consultative
Israeli Centre for Technology Assessment in Health Care	ISRAEL	Consultative
Health Statistics and Medical Technologies State Agency	LATVIA	Consultative
Mexican Institute of Social Security	MEXICO	Consultative
New Zealand Health Technology Assessment	NEW ZEALAND	Consultative
Norwegian Knowledge Centre for the Health Services	NORWAY	Consultative
Galician Agency for Health Technology Assessment Santiago de Compostela	SPAIN	Consultative
Center for Medical Technology Assessment	SWEDEN	REGULATORY
Swiss Network for Health Technology Assessment	SWITZERLAND	Consultative
Health Intervention and Technology Assessment Program	THAILAND	Consultative
Agency for Healthcare Research and Quality	USA	Consultative
National Institute for Health and Care Excellence	England	REGULATORY

Then in 2000, European Collaboration for Assessment of Health Interventions was established and in 2001, an HTA unit was established in McGill University Health Centre (MUHC). Later in 2003, the International Society for Health Technology Assessment (ISTAHC) was dissolved and HTA International was created for the coordination among various international HTA agencies in 2003 at Canmore, Alberta. An elected International Board; which, in turn is supported by a secretariat, working group, executive committee and multiple advisory committees in their structure, run HTAi. International Network of Agencies for Health Technology Assessment (INAHTA) was established in 1993 with its secretariat at IHE, Canada and has collaborating groups and member agencies from 32 various countries from Europe, American region, Asia, Africa and New Zealand. In 2005, a group of 35 organizations across the Europe led by Danish Centre for Health Technology Assessment started collaborative activities which led to the EUnetHTA collaboration in 2009; which is at present network with about 80 collaborative organizations. Table 1 summarizes some of the national and provincial HTA agencies and their roles in the respective country.

HTA in developing countries

Many developing countries including India, China, Iran and Philippines etc. have adopted HTA as a tool for policy change and are on the path of transitioning to evidence-based decision making. There are various factors affecting this evolution, which may facilitate or hinder the process of economic evaluation and overall HTA. Some of these factors are listed below:

Barriers in Developing Countries:

1. Lack of trained Human Resource
2. Cost and time restrains for transformation of systems
3. Educational Barriers
4. Organizational barriers
5. Poor dissemination of research results to policy makers
6. Lack of local HTA evidence
7. Limited awareness among policy makers

Conducive factors:

1. Large public funding than private and public purchasing systems
2. Political will and legislation (China, Taipei, Indonesia, Republic of Korea)
3. Good handholding by national agencies (INAHTA, HTAi, NECA, HITAP, IDSI, CDE etc.)

The process of doing HTA and differences in results and recommendation even for similar intervention may vary due to differences of geography, epidemiology, political environment, organization of health systems, income and various local intangible factors. The main focus of world health patron should be the introduction of evidence-based decision making process into all the systems to improve the health status of communities in line with Sustainable Development Goals. Many lessons can be learned by developed world from the journey of HTA in different regions and its impact on performance of healthcare systems. India has the need as well as opportunity to adopt HTA in decision making which becomes evident from international HTA experience especially from countries like Thailand and Cuba.

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Chapter 5:
Health Technology
Assessment in India
(HTAI_n)

The Government of India is committed to extend healthcare services to its 1.25 billion population as part of India's Universal Health Coverage (UHC) agenda. However, the rising cost of healthcare has not been matched by a corresponding increase in the government healthcare budget. Therefore, it is a challenge for the government to devise ways to reduce catastrophic out of pocket health expenditure and ensure affordable access to essential health care for the entire population with the limited resource envelope it has. The magnitude of the problem can be estimated from the fact that in 2014, World Bank reported that the out-of-pocket (OOP) spending on healthcare in India to be as high as 89%. To make the matter even more complex, despite having lowest public health spending in the world, India is the hub for production of new drugs, diagnostics and medical devices which have an inflationary effect on health care costs. Extending adequate healthcare services to the population requires optimal utilization of existing resources to ensure that the greatest amount of health is bought for every rupee spent. This can be ensured with the help of Health Technology Assessment (HTA), which is a widely used methodology internationally for optimization of resource allocation in health. HTA is a method of evidence synthesis that considers aspects pertaining to clinical effectiveness, cost-effectiveness, safety, social, ethical, and legal implications of the use of healthcare interventions.

To facilitate the process of transparent and evidence informed decision making in the field of health, Government of India has set up Health Technology Assessment in India (HTAI) under Department of Health Research (DHR). HTAI is entrusted with the responsibility to generate evidences related to cost- effectiveness, clinical- effectiveness and safety of medicines, devices, vaccines and health programs by means of Health Technology Assessment (HTA) studies. It will evaluate appropriateness and cost effectiveness of the available and new health technologies in India, so that maximum people can have access to quality healthcare at minimum cost in the country. Establishment of HTAI is a remarkable step towards achievement of Universal Health Care, one of the targets under Sustainable Development Goals (SDGs), as it aims to encourage the process of development of standardized cost effective interventions that will reduce the cost and variations in patient care, expenditure on medical equipment directly affecting the cost of patient care, decrease overall cost of medical

treatment, reduce out of pocket expenditure of patients and streamline the medical reimbursement procedures.

International use of HTA for priority setting

HTA is widely used to inform healthcare resource allocation in numerous countries in Europe, Scandinavia, Asia, and Australasia. Nascent institutions are also being established in South East Asia, the West Pacific, South America and Africa. These countries utilize HTA for the purpose of informing content of health benefits packages, such as the universal health coverage program of Thailand, or the National Health Service (NHS) in the UK, and the essential medicines lists (NLEM) in low and middle income countries, such as Thailand, Indonesia, the Philippines, and Mozambique. In 2014, the World Health assembly adopted a resolution on use of HTA to ensure Universal Health Coverage.

Activities of HTAIn

- To support the process of decision-making in health care at the Central and State policy level by providing reliable information based on scientific evidence.
- Develop systems and mechanisms to assess new and existing health technologies by a transparent and inclusive processes.
- To appraise health interventions and technologies based on available data on resource use, cost, clinical effectiveness, and safety
- To collect and analyse evidence in a systematic and reproducible way and ensure its accessibility and usefulness to inform health policy
- Disseminate research findings and resulting policy decisions to educate and empower the public to make better informed decisions for health
- All these activities will be conducted to achieve the following objectives:
 - i. Maximizing Health
 - ii. Minimizing Out of Pocket Expenditure
 - iii. Minimizing inequality

Immediate goals of HTAIn are:

1. To inform Government Health Department Officials about the clinical and cost effectiveness of any intervention to be undertaken in public health programs.
2. To inform Research Agencies about evidence gaps and unmet health needs.

3. To inform Hospitals and other Health Care Organizations and help in decisions regarding technology acquisition and management.
4. To inform Clinicians and Patients about the appropriate use of Health Care Interventions for a particular patient's clinical needs and circumstances.

Other possible roles of HTAIn as it evolves

1. To Inform Regulatory Agencies about the commercial use (e.g., marketing) of a drug, device or other medical technology.
2. To inform Payers (Governments Health Departments. Health Plans/ Drug formularies, Patient Groups etc.) about the technology coverage and reimbursement in any Healthcare Program.
3. To inform Health Care Experts about the role of health technology in Clinical Protocols or Standard Treatment Guidelines.
4. To inform lawmakers and other political leaders about policies concerning technological innovation, health financing and regulation of health care.

Structure

HTAIn consists of a DHR in-house Secretariat, Technical Appraisal Committee (TAC), Technical Partners (TP), Regional Resource Hubs and a Board. The Secretariat co-ordinates between the User Department, TAC and TP/ Resource Hubs and the Board. User Department could be Central and State Health Ministry or any Government Healthcare Provider or Agency that are directly or indirectly involved in the health sector in India. Secretariat takes up the topic(s) for assessment from the user department, prioritizes it, identifies the potential TP and allocates the topic to them to conduct HTA study. It keeps monitoring the progress of the study and also provides necessary assistance to the TP wherever required. Secretariat can also undertake topics for HTA analysis in certain situations. Secretariat conducts all the TAC and Stakeholders consultation meetings in DHR and ensures transparency at all stages of HTA by consultation and regular updates. HTA proposals as well as the outcome of the study is appraised by the TAC and stakeholders. Thereafter, final outcome, after the approval from the Board, is forwarded to the User Department that came up with the topic initially. The Board is mandated to consider and approve the recommendations from the Technical Appraisal Committee on all the HTA studies and submit its recommendations to the user Department for further adoption in the health system of the Country.

Technical Partners are Institutes of the Central/ State Government which have been identified with regards to their capacities, expertise and previous experiences in the HTA. TP will undertake the HTA study allotted to them and ensure consistency and uniformity with Process Manual through regular interactions and by also making a template available for each stage of the 'Assessment'.

Regional Resource Hubs are the extended arms of HTAIn establishes by DHR in collaboration with the State Governments in Institutes administered by the Centre/ States. DHR will provide requisite manpower to these hubs so that these hubs provide technical support for a bunch of States located in the vicinity. The mentor of the hub would liaise with the officials of the State Governments and sensitize them about a need for Health Technology Assessment (HTA) for any health intervention. The hubs would also ensure robust HTA on the topics relevant to the States and also ensure uniformity/ consistency of methodologies/ processes documented by DHR in its Process Manual.



Structure of Health Technology Assessment in India (HTAIn)

Activities So Far:

At present 6 resource hubs have already been established in various States:

- (i) Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh.
- (ii) Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala.
- (iii) National Institute for Research in Reproductive Health (NIRRH), Mumbai.
- (iv) National Institute for Research in Tuberculosis (NIRT), Chennai.
- (v) Regional Medical Research Center (RMRC), Bhubaneswar.
- (vi) Indian Institute of Public Health (IIPH), Shillong.

Besides all these, approval for the resource hub in SAST –Karnataka, Civil Hospital/IIPH, Gujarat and Medical College, Bhopal is underway. DHR is also getting in touch with other states' health officials regarding the establishment of hubs such as Delhi and Uttar Pradesh.

So far, 11 HTAIn Technical Partners have been identified across India - (i) AIIMS, Delhi (ii) NIMS, Delhi (iii) NHSRC, Delhi (iv) PHFI, Delhi (v) Institute of Economic Growth, Delhi (vi) IIT, Mumbai (vii) NIV, Pune (viii) NARI, Pune (ix) IIMR, Jaipur and (x) IIPH, Bhubaneswar and, (xi) IIT, Chennai

Right now eleven topics have been assigned to various technical partners and resource hubs to conduct HTA analysis out of which the Outcome Reports have been through from the TAC and Stakeholders and is to be presented before Board. These topics are:

- i. Health Technology Assessment of Intraocular Lenses for treatment of Age-related Cataracts in India – HTAIn Secretariat, Delhi.
- ii. Cost Effectiveness of Safety Engineered Syringes for Therapeutic Use In India – PGIMER, Chandigarh.
- iii. Health Technology Assessment of Strategies for Cervical Cancer Screening in India– PGIMER, Chandigarh.
- iv. Health Technology Assessment for Screening of Type 2 Diabetes & Hypertension in India – PGIMER, Chandigarh.
- v. Health Technology Assessment for breast Cancer Screening in India– NHSRC, Delhi.
- vi. Health Technology Assessment of Long Acting Reversible Contraceptives in India – NIRRH, Mumbai.
- vii. Health technology assessment of uterine balloon tamponades to manage postpartum haemorrhage in India – NIRRH, Mumbai.
- viii. Health Technology Assessment (HTA) of Diagnostic efficacy of digital hemoglobinometer (TrueHb), HemoCue and non-invasive spectroscopic device for screening patients for anemia in the field settings – AIIMS. Mumbai in collaboration with PHFI, Delhi.
- ix. Health Technology Assessment of various RT-PCR kits/methods for the diagnosis of Influenza A/H1N1pdm09 virus in all age group patients in India – NIV, Pune

- x. Hypothermia Detection Devices (BEMPU and ThermoSpot) for Premature Low Birth Weight Neonates in India - IIPH-Shillong.
- xi. Universal neonatal hearing screening program using 'Sohum' hearing screening device in India - RMRC, Bhubaneswar.

Besides these HTA Studies HTAIn has also proposed a Multi Research Unit (MRU) Costing Studies of Health Care across India. PGIMER, HTAIn Secretariat and MRUs across India will be coordinating together in this ambitious project which will help in creating a "Cost-Database" for India that in turn will be helpful in future HTA as well as other studies that requires costing.

HTAIn looks forward to generate good capacity building in the field of HTA for efficient and evidence based decision making that will in turn help Indian healthcare system in moving towards Universal Health Coverage (UHC).

Chapter 6:
Topic Selection for HTA:
Choosing the Right Topic

HTAs are used to support important policy decisions. A HTA topic should reflect a worthwhile research question on which an economic evaluation can be conducted to assist decision makers to formulate **evidence-based policies** for incorporating or excluding health technologies into the health system. It is important that topics for assessment are policy-relevant so that the assessment findings can properly inform policy-makers in making rational and effective policy decisions that address unmet needs in the health system.

Who can submit topics?

HTA topics are typically formally submitted by those in policy-making positions with administrative control over a health scheme or program to inform investment decisions, e.g. the CEO Ayushman Bharat, State National Health Mission Directors, or Directors of State health insurance schemes such as Aarogysri in Andhra Pradesh or the Chief Ministers scheme in Kerala. However, HTA topics may also be identified through service providers or users, such as a patient representative groups and clinical practice representatives.

How are topics prioritised?

It is imperative that topics selected for HTA are the most important to those who are the beneficiaries of publicly-subsidised care – the patients and carers. There is a growing international concern that the HTA agenda is set by industry, individual scholars, or private investment. By ensuring a transparent, fair, evidence-based, and inclusive topic-selection process, the HTAIN aims to protect the Indian HTA process from conflicts of interest.

To ensure that HTAIN carry out policy-relevant HTAs of maximum benefit to the healthcare system, a prioritisation process is used to select HTA topics, according to the following criteria:

Indicator	Key question to be addressed
<p>Size of population affected by disease</p>	<p>How many people are affected by the disease or health problem that is treated or prevented by the proposed intervention among Indian population at a specified time?</p>

Indicator	Key question to be addressed
Severity of disease/health problems	What is the severity of disease or health problem that is treated or prevented by the proposed intervention by considering the burden of disease/health problems?
Comparative effectiveness of health intervention	How good is the intervention at doing what it is supposed to do (e.g. a drug to treat pain, a BP device to diagnose hypertension, or a vaccine to prevent rotavirus) compared to what is already being done at present?
Inequality, ethics, and equity	What is the situation of inequality in accessibility to and utilization of health services by region and population? Are there important ethical and equity considerations in relation to the intervention in question?
Economic impact on household expenditure	What is the impact on household expenditure as a consequence of providing health intervention to a family member with consideration of catastrophic illness or health catastrophe?
Availability and relevance of evidence	What is the availability and relevance of evidence required for conducting HTA?
Health sector priority and policy objective	Is the clinical area of interest a well-recognised local and/or national priority?
Feasibility of implementation	Can the proposed intervention be implemented in reality within the constraints of the Indian health system?

How does the availability of evidence affect HTA topic selection?

One of the primary aims of HTA is to use available evidence to improve current screening programs, treatments, or prevention schemes. It is very important that evidence for clinical effectiveness (how well something does what it is supposed to do) is already available when conducting a HTA, so that this information can then be weighed alongside other evidence such as cost and quality of life to assess whether an intervention is good value

for money. If such evidence is not available, a HTA cannot be done, and primary research such as a randomised control trial or impact assessment may need to be done first, before a HTA can be conducted.

It can be difficult to identify which topics should be considered for HTA and which are not appropriate. Figure 1 provides an algorithm to help guide whether a topic is appropriate for HTA or not.

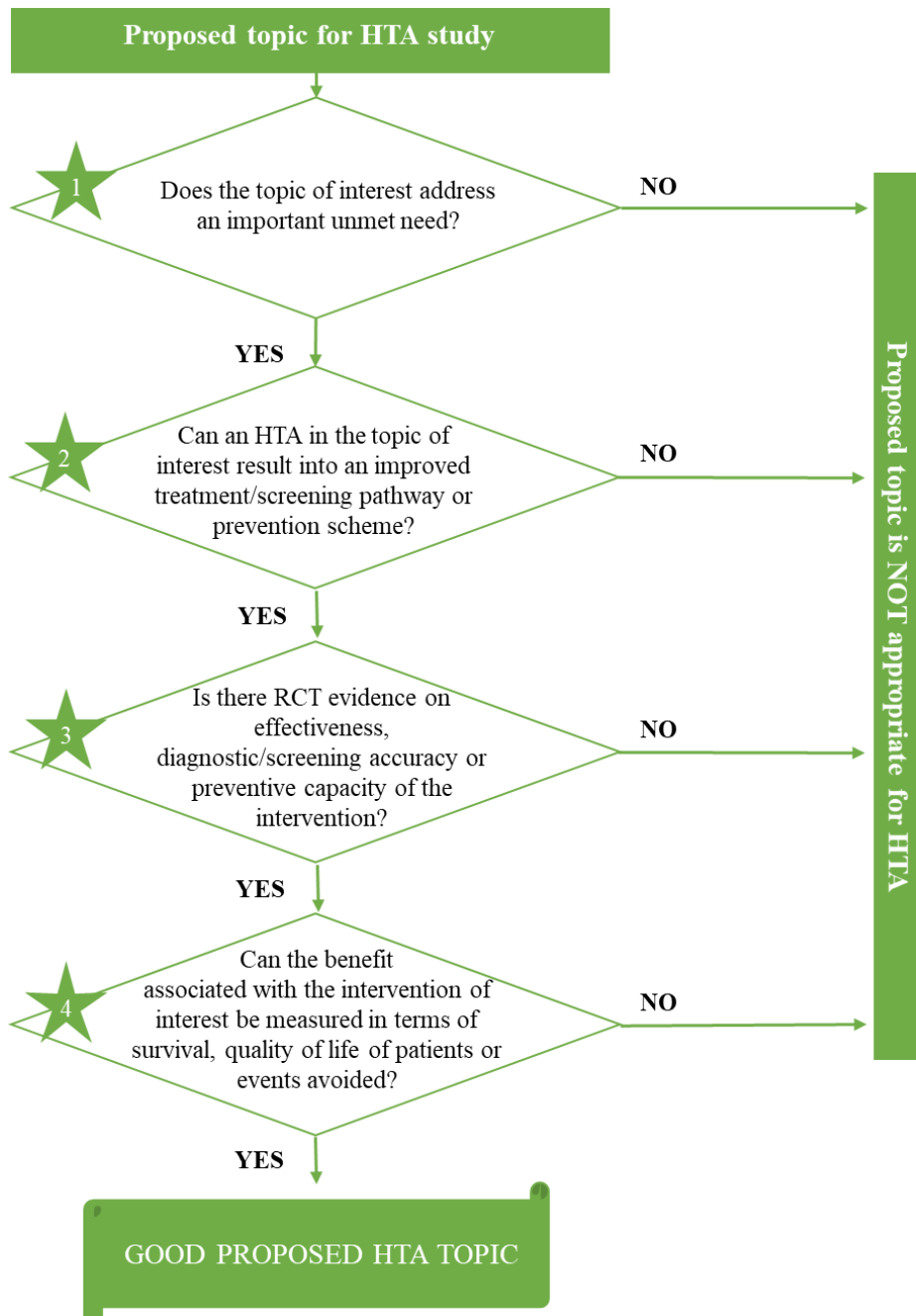


Figure 1: An algorithm to guide choosing the right HTA topic

HTA: health technology assessment; RCT: randomized control trial. Note: “unmet need” generally indicates that a particular disease cannot be adequately treated, or perhaps treated at all, with currently available treatments. In case of screening/diagnostic technology, “unmet need” generally mean that current screening methods are not sufficient for accurate disease diagnosis. In case of prevention activities, “unmet need” indicates that there are not effective prevention schemes in place where there should be.

Further Reading on Topic Selection:

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Chapter 7:
Framing of HTA proposal

When framing a proposal for a health technology assessment, one needs to be aware of the applicability of the study to the decision problem. This awareness will enhance the conceptual model validity and may increase use of the results for decision-making. First, the objective, audience, and perspective of the analysis should be defined. Further, the population, intervention, and comparators need to be specified. In addition, the time horizon and boundaries of the analysis should be defined, as should the type of analysis. Although sometimes it is inherent to evaluate the intervention as it would have been used in daily practice, this is not made explicit. To understand how to go about framing the proposal we need to understand the scope of the HTA study and all that would be involved in it so as to be prepared on what all to include in the proposal. To start things a set of ten principles, listed below, is to guide the HTA process and its formulation.

- i. The goal and scope of the HTA should be explicit and relevant to its use
- ii. HTA should be an unbiased and transparent exercise
- iii. HTA should include all relevant technologies
- iv. A clear system for setting priorities for HTA should exist
- v. HTA should incorporate appropriate methods for assessing costs and benefits
- vi. HTAs should consider a wide range of evidence and outcomes
- vii. A full societal perspective should be considered when undertaking HTA
- viii. HTAs should explicitly characterize uncertainty surrounding estimates
- ix. HTAs should consider and address issues of generalizability and transferability
- x. Those conducting HTAs should actively engage all key stakeholder groups

Following these principles helps visualize what is needed out of the whole HTA exercise so that the formulation of the proposal becomes easy and all key criteria needed for the study are included. Additionally we also need to make sure that certain key topics are all being covered while framing the proposal (figure 1).

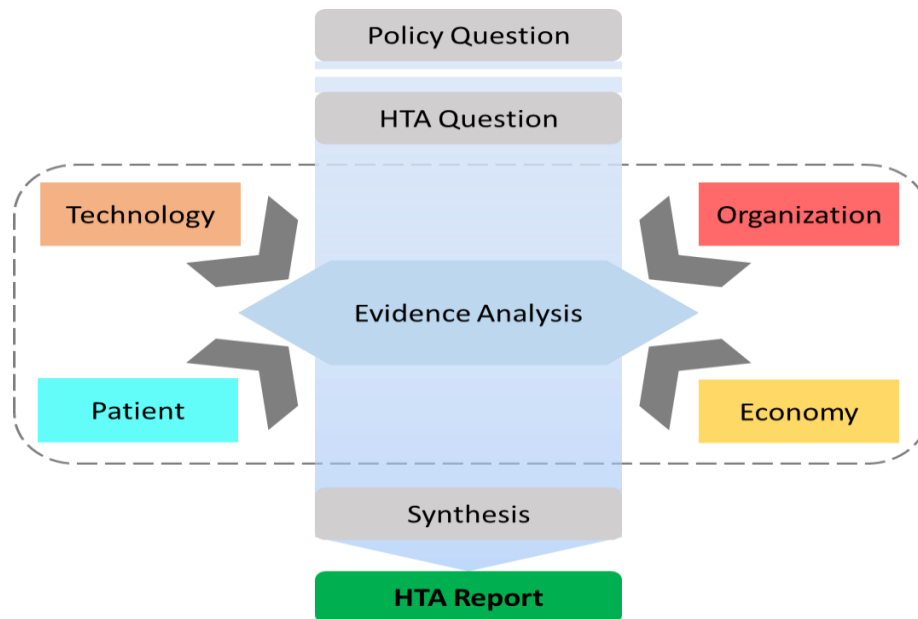


Figure 1: Illustration of the crux of the HTA Process

To summarize the illustration whenever we start framing we have a policy question that has to be addressed on which the HTA question is centred. For this, there are four major topics that need to be addressed; first of which is the technology in question and data relevant to the same in terms of their efficacy, safety, clinical effectiveness, etc. and the same for all alternatives being used as comparators. Second, come the patient related issues like the impact of the health technology, access, affordability and the acceptability in terms of any socio-cultural, ethical or equity issues. Third is the economic evidence in terms of the costs incurred and the overall cost-effectiveness of the health interventions in question. The costs and their analysis will be covered in later chapters in detail. Last is the organization being affected by the whole intervention and its implementation; does it need to be reengineered or does it require any kind of modification. All this data is collected and pooled together to be sifted through and analysed, individually as well as collectively, the evidence is then synthesized to extract a consolidated result in the form of an HTA report.

The whole process can be broken down in to the following steps which would detail the steps in involved in the overall HTA study formulation:

- Defining the policy question
- Framing the methodological protocol

- Systematic review of all available evidence
- Mathematical modelling and evaluation
- Analysis of further impacts (equity, budget, etc.)
- Compiling the final report

Now once the policy question has been identified and the HTA question framed, we need to look at all the parameters that need to be incorporated in the HTA proposal. The proposal should have all the factors listed below explained in a brief and to the point (explicit). The points have been explained with the kind of question they address and what is the expected information needed from the investigator.

Checklist for all factors incorporated in the HTA proposal

S. No.	Factor	Question
1	Objective	What is the purpose of the HTA? (E.g., contribute to evidence, inform adoption decisions)
2	Audience	Who are the principal users for the HTA? (E.g., government, pharmaceutical companies, insurance companies, patient groups, jurisdiction)
3	Perspective	Which viewpoint or perspective is relevant for the HTA? (E.g., societal, healthcare system, insurer, payer)
4	Population	What is the patient population relevant for the decision problem? (E.g., age, health status, gender, other characteristics)
5	Comparators	What are the relevant comparators for the decision problem? (E.g., care as usual, alternative technologies)
6	Clinical Practice	How are the technologies embedded in the clinical practice? (E.g., diagnostics, clinical instead of research protocol)
7	Timeline	What is the time in which the study will be completed in terms of data collection, analysis and final report generation? (E.g., 6 months, 1 year, etc.)
8	Time Horizon	Which time horizon is relevant for the decision problem? (E.g., lifetime, one year, one month)

9	Consequences	Which consequences are relevant for the decision problem? (E.g., final versus intermediate outcomes, indirect and/or rare consequences)
10	Patient Use	What is the patient use that is relevant for the decision problem? (E.g., uptake, compliance, adherence)
11	Professional Use	What is the use of the technology by the healthcare professionals that is relevant for the decision problem? (E.g., skills, experience, beliefs)
12	Price & Resource Use	What price level and resource use are relevant for the decision problem? (E.g., personnel providing the intervention)
13	Equity and Social Issues	How are the equity and social issues being addressed and what data would be collected for the same?
14	Budget Impact	Would a budget impact analysis be done and if it is done, at what level would be undertaken? (E.g., local, state, national)
15	Additional Analysis	Will any other additional analysis of data be done (if needed)?
16	Ethical Justification	Will ethical clearance be taken from the parent institutions with all the ethical issues for the study being stated
17	References	All reference materials, papers, articles, journals, etc. being duly acknowledged in Vancouver style (till any other specific pattern is recommended)
18	Annexures	Is there any data collection tool being used – pre-validated or not? (E.g., Cost data collection tool, Quality of Life questionnaires)

All the above mentioned points then need to be put down in a format so as to clearly reflect what is needed for the HTA and what will come out of it. The general pattern when writing the proposal has been laid down for better understanding how to put in all the aforementioned factors into writing.

Heading-wise sections of the Proposal:

- Title Page – Stating the title of the HTA study (highlighting the PICOT)
- Abbreviations – Any and all abbreviations to be used in the proposal
- Introduction – A brief on the history and current scenario of the intervention in question; at the global, national and local level in sequence
- Review of Literature
 - Clinical effectiveness – literature pertaining to the clinical efficacy and effectiveness of the intervention and comparator in question, preferably local/Indian evidence
 - Cost effectiveness – cost data and cost effectiveness literature on the same, preferably local/Indian evidence
 - Equity and socio-cultural review – literature on equity-related and other social issues around the interventions in question
 - Gaps in literature – existing gaps/lacunae in the literature that your study would fill in; usually the lack of local/Indian evidence
- Aim of the Study
- Objectives of the Study
 - Primary objectives
 - Secondary objectives
- PICOT (Population, Intervention, Comparator, Outcome, Timeline)
 - Additional specifics like costing perspective, time horizon for analysis and cycle length to be used in it

- Methodology
 - Conceptual Framework and Model Overview (Decision tree or Markov; whichever is to used)
 - Estimation of Costs – How and what costs would be considered and analysed
 - Health Outcome Valuations – What health outcomes are being taken in terms of the cost effectiveness analysis
 - Discounting – The discounting rate chosen with its justification
 - Sensitivity Analysis (which one will be done and its method)
- Ethical Justification/Considerations – if required
- References – Any and all papers used for reference in Vancouver style
- Annexures – Any data collection tool that would be used in the study

This completes all the requisites of how a proposal should be framed. A complete proposal is the key to undertaking a full-fledged and meaningful HTA.

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Chapter 8:
Valuing Health Outcomes

There is an increasing interest in including patient-reported outcome measures (PROs) in clinical studies specifically those in tandem with economic evaluations or as part of an HTA. PROs include measures like patient satisfaction and their health-related quality of life (HRQoL) and these capture certain treatment effects that are not captured by the main clinical outcomes. Moreover, since quality-of-life (QoL) measures focus on treatment effects that primarily impact the patient's well-being, their relevance becomes all the more important for HTA studies. QoL measures are thus divided into two categories.

- *Disease-specific, or condition-specific measures:* These concentrate on the main QoL impacts of a particular disease. E.g., the EORTC instrument for cancer, CatQuest for Cataract
- *Generic measures:* These do not focus on the impacts of a particular disease. Rather, they consider a broad range of dimensions of quality of life that, in principle, could be impacted by any disease, including physical function, mental well-being, social function, and pain. The most widely used measure of this type is the EQ5D (-3L or 5L)

What is a good measure for health outcomes?

An important characteristic required for a measure of health is that it should be able to compare changes across diseases and interventions. Now, as a cost-effectiveness analysis looks to compare the costs and effects of alternative interventions for one disease it does beg the question; why is comparison important? Consider that there is one intervention with a higher cost but with better overall health outcomes as compared to other interventions. The dilemma that arises now is whether to invest in such an intervention or not? As an example just for the resource allocation, one would need to know if the additional health benefits are more or less costlier than with any other intervention for the same condition. Thus, even though the evaluation might focus on a single disease, the resource allocation and service utilization needs to be looked at with a comparative lens.

Another characteristic required is that the health measure have a scale with interval properties. The reason for this is that firstly, we need to know by how much the health change has occurred, be it for better or for worse. Secondly, these health changes need to be related to the monetary changes to be scaled either up or down. In this, the scale may be binary, ordinal or cardinal depending on the conditions and requirements of the study.

With a binary scale, people may prefer to be alive or not or have a disease or not but that is the extent to which their preferences may be known. A scale with ordinal properties is one where the preferences or choices are ranked in some set increasing or decreasing order. The catch however is that we know that the preferences are ranked by some difference between themselves, but not by how much. A cardinal scale eliminates that as it can have either interval or ratio properties. Now another issue arises that the interval would mean that equal intervals do exist between the preferences but we cannot make any assumptions about the absolute size of these preferences. An example of this is that on a scale that has numbers 10, 20, 30 and 40; we know there exists a specific interval of 10 points but that does not clear the picture of the absolute change in this interval – is the change of 10 arithmetic or exponential, etc. Therefore, it is recommended to use ratio scales as these have a true zero point and are able to compare the size of numbers rather than just the size of the change.

Thirdly, the health measure should be able to reflect the preferences, either of individual patients or of the public. Another set of characteristics derived from principles of psychometrics are summarized below:

1. *Reliability*: how much can the measure produce repeated results from an unchanged population with minimum random error
2. *Validity*: to what extent does the measure capture what it aims to quantify. It may be in the form of content validity (the appropriateness of items within a tool) or construct validity (extent to which results correlate with other indicators, measures or concepts of interest)
3. *Practicality*: the measure should be acceptable to respondents and ethics committees as well as being easy to administer, score and interpret findings
4. *Responsiveness*: a measure should be able to detect clinically and socially meaningful changes in the health status over time. In most cases an ‘effect size’ is calculated, which is the difference between the mean baseline and mean follow-up scores divided by the standard deviation of the baseline scores

Now coming to the outcomes of concern (apart from PROs) to us while conducting an HTA or an economic evaluation. Quality adjusted life years (QALYs), disability adjusted life years (DALYs) and life years gained (LYG) are all common outcome measures in economic evaluations of health interventions. While LYG is a pure measure of mortality, QALYs and

DALYs combine mortality with morbidity into one single numerical unit, an exercise that involves trade-offs between the quantity and quality of health.

Life Years Gained (LYG)

Traditionally, the impact of health care has been measured in terms of its effect on mortality, for e.g. deaths averted. A potential drawback of using deaths averted to measure health effects is that it does not take into account the age parameter. LYG is a modified mortality measure where the remaining life expectancy of the individual in question is also taken into account. This means that the life remaining will get age adjusted depending on the life expectancy of the individual. Life years are calculated as the remaining life expectancy at the point of each averted death. The life expectancies are taken from life tables specific to the region and which have been age standardized.

Quality Adjusted Life Years (QALYS)

In QALYs, premature mortality is combined with morbidity by assigning a quality weight to each health state such that value 0 represents death, while value 1 represents full health. The number of QALYs for a health profile is found by multiplying the HRQoL of the health state, with the duration of the health state.

Disability Adjusted Life Years (DALYS)

Two important principles are underlying the DALY concept, first of which is that the burden calculated for like health outcomes should be the same, and second is the restriction of characteristics, not directly related to health, to age and gender. Which means that characteristics like income, education, ethnicity, etc. should not be taken into account. These propositions represent intensions of creating a methodology that treat people as equal as possible.

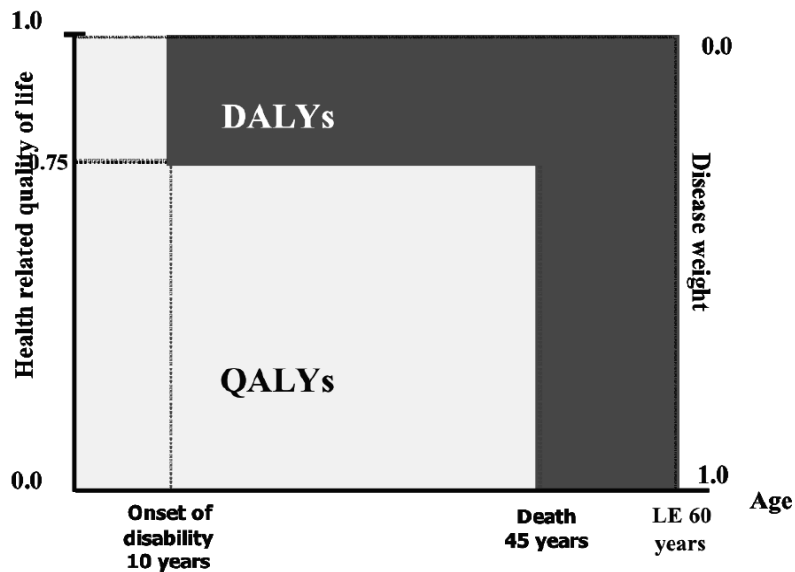


Figure 1: Relationship between QALYs and DALYs when the DALYs are not age-weighted

Valuation of Health Outcomes

The valuation of health outcomes requires the measurement of the health status of an individual. The tools for this may be either for a single attribute or for multiple ones.

- Single (comprehensive) measurement
 - Visual Analogue Scale
 - Standard Gamble
 - Time Trade-Off
- Multi-attribute utility measurement
 - E.g., EuroQoL (EQ-5D), Health Utility Index (HUI), Short Form 6D (SF-6D)

These will be discussed in brief in the next part of this chapter so as to impart a basic idea on how to use these as tools to collect health status related data from an individual. The use itself depends on what type of study is being conducted and in what form does one want the data while computing the health outcomes.

Visual Analogue Scale (VAS)

This is the simplest approach to measuring preferences by asking individuals to first rank health outcomes according to preference in an ascending or descending order, and second, to place these outcomes on a scale. This is in such a way that the intervals in-between the outcomes corresponds to the differences in preference as perceived by the individual.

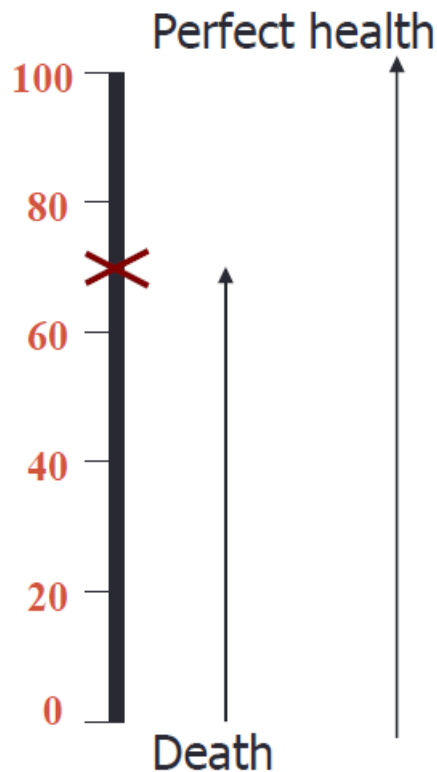


Figure 2: An illustrative visual analogue scale (VAS) of 0 to 100
(death to perfect health)

Standard Gamble

In this, the individual has two alternatives to choose from and based on this we get an idea of how one perceives their health status.

- Choice A: Is the certain outcome that they will stay in the chronic health state for some time of life (t years).
- Choice B: If a hypothetical treatment which has two possible outcomes: either the patient returns to full health for the rest of his life with a probability ' p ' or they die immediately with a probability ' $1-p$ '.

The probability ' p ' mentioned here is varied until the individual is indifferent between the two alternatives. This indifference probability, p , is the utility value for health state A in the utility value between death (0) and full health (1).

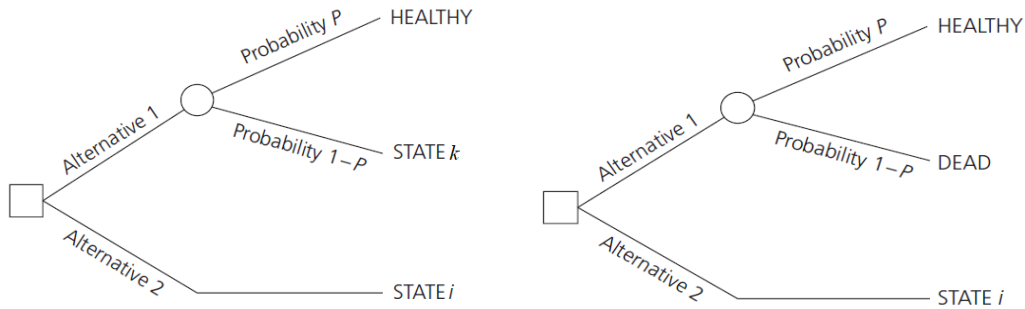


Figure 3: Standard Gamble for a chronic health state preferred to a temporary health state and death respectively (from left to right)

Time Trade-Off (TTO)

In this method also, the individual is asked to decide between two alternatives:

- Choice 1: Being in health state 'A' for 't' years
- Choice 2: Being in full health for a period of 'X' years (where $X < t$) followed by death

Time 'X' is varied until the individual is indifferent to the choice between the two alternatives, at which point the preference value for health state A is given by X/t in the value between death and full health, i.e., 0 and 1 respectively.

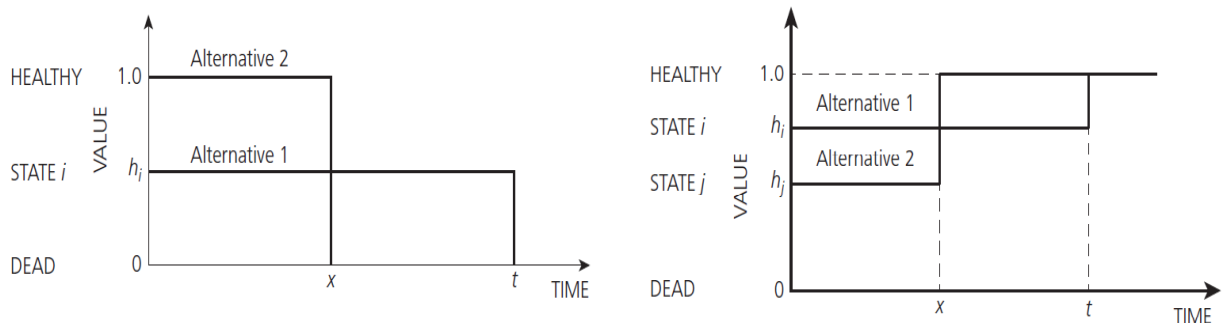


Figure 4: Time trade-off for a chronic health state preferred to death and for a temporary health state (from left to right)

EQ5D

The EuroQoL Group, a consortium of investigators in Western Europe, developed a system with five attributes (previously six): mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each attribute has three levels: no problem, some problems, and major problems, thus defining 243 possible health states, to which have been added

‘unconscious’ and ‘dead’ for a total of 245 in all – EQ5D3L as it has three levels of choices in each dimension. Correspondingly, another system has five levels per dimension called the EQ5D5L. Both are supplemented with a VAS scale; a vertical 20 cm thermometer scoring from zero (worst imaginable health state) to hundred (best imaginable health state). The respondent rates their current health state on this EQ-VAS by drawing a line from the box marked “your own health state today” (the bottom) up to the appropriate point or mark the appropriate point with a cross/check mark.

This brings us to the conclusion of how to value various health outcomes and what all to consider in the whole process of choosing, measuring and collecting data on the requisite health outcome and parameter.

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Chapter 9:
Cost and Cost Analysis

Cost refers to *'the sacrifice (of benefits) made when a given resource is consumed in a programme or treatment'*. It is **often confused with price** (amount which beneficiary pays, e.g. fee paid to get ECG done), but is rather the actual expenditure made by service provider to deliver the service, which implies the sum of monetary value of all resources utilized during service delivery. Accurate measurement of costs is very important to decide health insurance package rates, Economic Evaluation and in the overall process of Health Technology Assessment. Calculation of unit cost of a service (surgery/consultation/diagnostic test etc.) or cost of rolling out a program in lower middle income countries like India is often very difficult due to various conceptual and practical

C

Some cost-related terminologies

Direct cost: Resources utilized in the implementation and continuation of a health care service or program. (e.g. costs on surgical equipment, drugs etc.)

Indirect cost: Resources utilized or forgone by patients or attendants to enable them to receive service. (e.g. productivity loss due absence from work during treatment)

Overhead costs: Resources, which are not utilized directly in providing services but are necessary to support the organization or program (e.g. electricity etc.).

Capital cost: The value of resources which have long useful lives, usually greater than one year (e. g. building of a hospital or OT table etc.).

Recurrent cost: The value of resources which are consumables and need to be replenished regularly as they have small useful lives (e. g. gloves, syringes etc.).

Fixed cost: The value of resource that does not vary with variation in the levels of output (e.g. rent of healthcare facility etc.).

Variable cost: The value of resource that varies directly with variation in the levels of output (e.g. gloves, syringes etc.).

Marginal cost: The change in the total cost if one additional unit of output is produced.

Opportunity Cost: Value of the next best alternative choice forgone, by making decision to deliver a service. (e.g. opportunity cost of providing free treatment to cervical cancer patients can be loss of opportunity to immunize 20 young girls for HPV)

Annualization: A process to spread the cost of a capital resource over the life-time period of the same on the basis of average life expectancy of the capital resource.

Discounting: A process intended to adjust costs borne in future or past to today's equivalent costs or present value of resource. It also helps to adjust the value of costs and outcomes which occur in different time periods.

Approaches for costing

There are different known approaches for costing of healthcare services.

1. *Normative costing* is an exercise to estimate unit cost of service delivery by taking assumptions and expert opinions about various resources required. Here, analysts take expert opinion from various clinical and administrative experts; who make consensus about resources like staff, equipment, essential drugs and other consumables etc.
2. *Clinical trial data* can be used to find the unit cost of the intervention either prospectively, by planning costing exercise along with clinical trial or by using trial data retrospectively. By this approach, it is comparatively easier to avail the required data but results from clinical trials cannot be generalized to real world settings.
3. *Pragmatic costing* approach is most appropriate to estimate costs for doing HTA as well as for deciding package rates; but, is relatively most difficult among all three approaches, especially in lower and lower middle income countries due to lack of maintenance of records.

Different types of costing methodologies

Top down costing is done using annual expenditure during given financial period. Total expenditure during given financial period is divided by total number of services delivered during that periods. This is comparatively easier to do but does not give accurate results pertaining unit cost of specific disease or procedure.

Bottom-up micro-costing is widely considered most appropriate as it takes into account, all relevant cost components utilized for patient groups or subgroups. This costing methodology has feasibility issues due to being very elaborative and time consuming besides other challenges like un-availability of records in hospitals. In countries like India, researchers usually have a trade-off between accuracy and feasibility.

Many a times, mix of top-down and bottom-up methodology is used to ascertain the unit cost of healthcare services. Top down approach is adopted for share resources and those resources, which make small proportion of overall unit cost (e. g. Overheads); whereas,

bottom-up approach is used for resources which are exclusive for given service or make large proportion of the overall cost (e. g. Human Resource).

Steps for costing exercise

For costing exercise to be streamlined and to address the needs of stakeholders, a clear plan needs to be followed. Inadequately planned costing exercise can lead to repeated visits to healthcare facilities or collection of irrelevant data. Broadly, following steps wise approach can be followed:

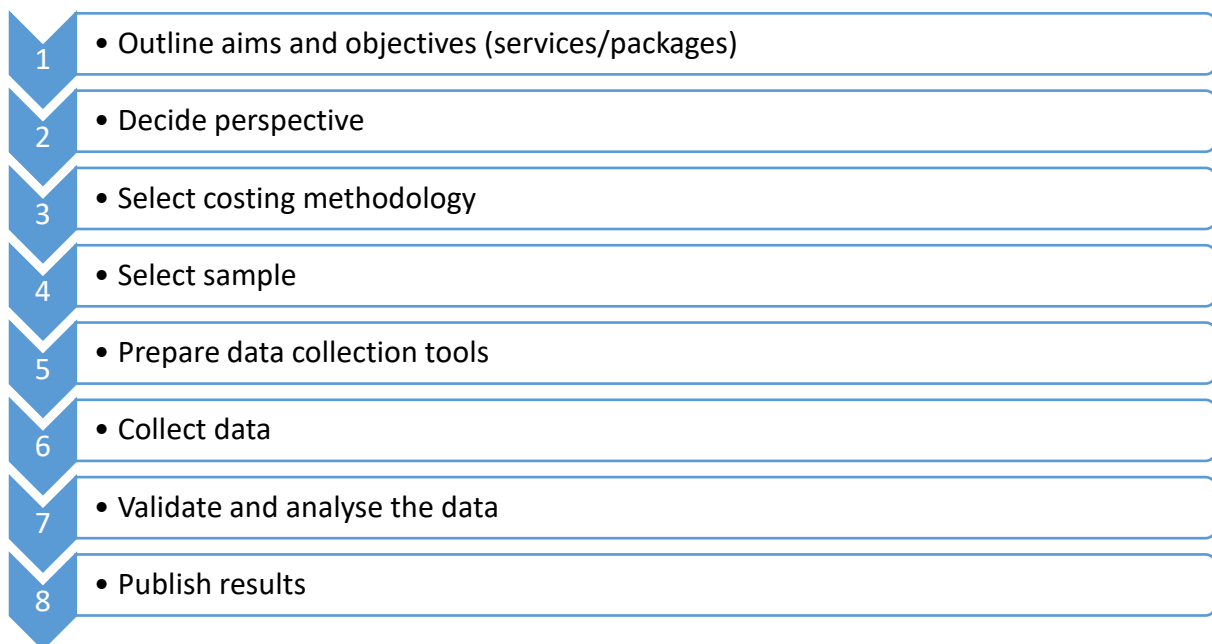


Figure 2. Steps to undertake costing.

1. Outline the aims and objectives of the costing exercise explicitly and make a list of services or packages, whose costing is planned to be done. Researchers should also acknowledge existing data sources, facilitators and barriers in obtaining data, budgeting and timeline etc. Plan of study can be discussed with all the stakeholders to streamline the data collection process and to ensure the acceptance of results.
2. Decide the perspective of costing study according to requirements of policy question. Perspective is a criteria to decide, which all costs are to be included in the analysis of to calculate unit cost of a service. This depends upon context and nature of service being delivered. See box below to know about all three types of perspectives. Also clearly define all the inclusion and exclusion criteria for resources being utilized for

provision of the service (e. g. whether time and budget of study allows researchers to estimate productivity losses of the patient or not). Researchers should try to include as many resources as possible, keeping feasibility of the study into consideration.

Perspectives

- 1. Perspective, Healthcare Provider's:** When only costs borne by healthcare provider are accounted for while estimating cost of service delivery. This is relevant in cases where most of cost to deliver services is being borne within hospital or by the public healthcare provider, e. g. In India, ART services are provided free of cost to HIV patients in public healthcare facilities. If HTA needs to be done or if government wants to know about total expenditure per patient, costing can be done from healthcare provider's perspective.
- 2. Perspective, Patient's:** When only costs borne by patient are accounted for while estimating cost of treatment. In many cases, a big proportion of cost is born by patient in the form of out of pocket expenditure.
- 3. Perspective, Societal:** When all direct and indirect costs borne by healthcare provider as well as patient are accounted for, while estimating cost of a healthcare service.

3. Take guidance from reference case or existing evidence and choose appropriate methodology for costing. Costing methodology (top-down/bottom-up/mixed methodology) should be selected based on priorities of all the stakeholders and resources available. Time horizon, approach for data collection (prospective/retrospective) and data period (year/month) should be well-defined.
4. Select appropriate sample of service providers based on type of ownership, city of location (rural/urban), level of healthcare facility (primary/secondary/tertiary), occupancy rates and quality of service (NABH or other accreditation). If costing is being done for economic evaluation or HTA, characteristics (severity of disease or age) of patients should be same during estimation of cost as well as effectiveness.
5. Identify all the cost centres in given sample of hospitals (OPD/ward/OT/laundry etc.) and prepare appropriate data collection template or tool. Data collection tool must be comprehensive enough to include all sources utilized under different heads, all capital

as well recurrent resources. There should be provision to collect data required for apportioning of shared resources.

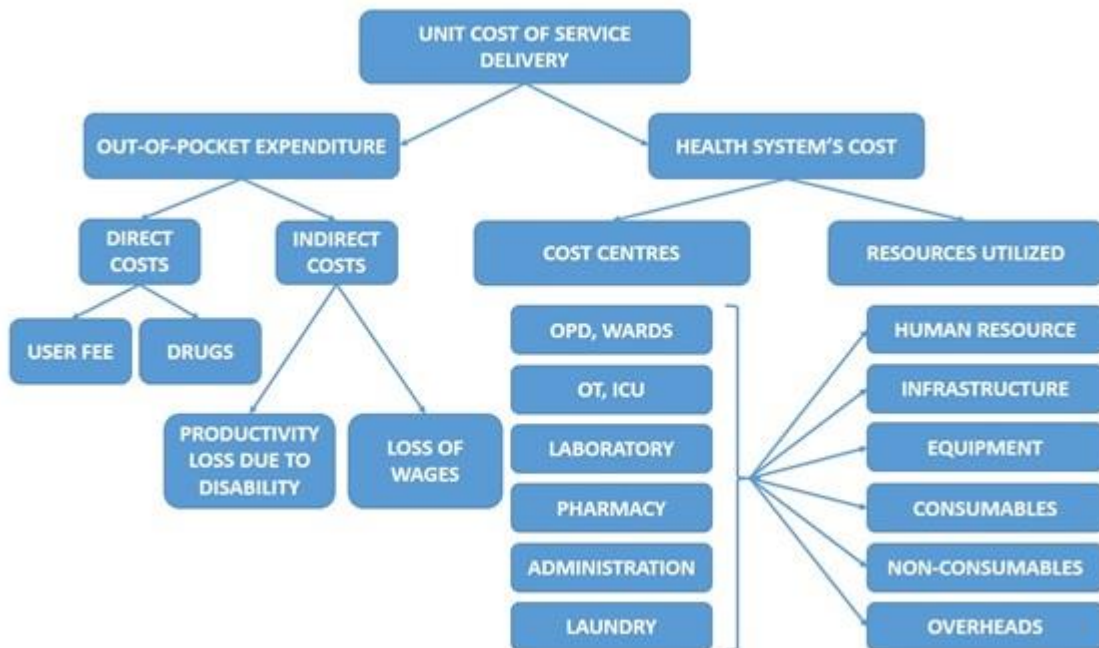


Figure 3. Illustrative components of unit cost of services delivery in a hospital.

6. With help of data collection tool, identify all resources being used in respective cost centres. Measurement of volume/number of resources being used should be done and finally, collect the unit cost of each resource used, so that total expenditure can be calculated. Data collection should be started from those resources, which make major proportion of total cost. Data can be collected from various cost centres by assessing health records (hospital census or IPD records etc.), accessing administrative databases (e. g. indent forms from various departments, stock registers of equipment and furniture, bills paid during given financial year etc.), patient interviews, staff interviews, questionnaires, checklists etc. Any missing data can be substituted by consultation of expert panel (e. g. average life of equipment can be obtained from store in charge and OT technician, based on their experience). In Indian context, estimation of infrastructure costs is challenging because data pertaining cost of construction and renovation is not available. This is usually done by making some realistic assumptions or proxies as illustrated below:

Estimation of land and building costs

1. Determine cost of a recently built building or new part of same building and extrapolate the cost of whole healthcare facility. Adjustments structure, size and inflation should be made for old building.
2. Estimate the cost of constructing same healthcare facility at present by taking inputs from civil department of hospital.
3. Use local data from quotations of public sector constructions and adjust for area.
4. Take annual lease rate of similar facility in the area as proxy and consider infrastructure as recurrent cost.

7. Import or enter data in Excel and clean to make it appropriate for analysis. Check the data for format (e.g. units) and completeness, remove irrelevant data or irreconcilable data. All recurrent and capital costs should be apportioned rationally across the services provided in given healthcare facility using time allocation studies (for salaries) or number of patients (e.g. for overheads). During analysis of capital assets, depreciate the cost and also annualize the same over period of its expected life. If original price of asset and year of purchase is available, adjustment for inflation can be done using GDP deflator or Consumer Price Index; otherwise, it is better to use replacement cost of the asset. If costs are being estimated from clinical trial data, modelling may be used to extrapolate costs beyond end-point of the trial. All assumptions, extrapolations and steps of analysis should be documented to improve transparency of analysis and any iterations, if required.
8. Present results in the form relevant for stakeholders, e.g. details about share of different resources in total cost, segregation according to type of facility, occupancy rates and location etc. Detailed methodology, assumptions and limitations of the study can also be incorporated into outcome report for peer-review. Sensitivity analysis will add to quality of study by adjusting results to variation due to salaries across the states, rates of procurement of drugs.

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*Chapter 10:
Economic Evaluation and
Decision Modelling*

Economic Evaluation (EE) is one of the important aspects of a health technology assessment. Classically, an EE is defined as a comparative assessment of two or more interventions, in terms of their costs and consequences¹. As the definition suggests, any EE would comprise of two measurements – costs and consequences, which has to be done for both the intervention and the comparator/s. The key question is that how should we measure the costs and consequences, such that our methodology is comprehensive, and it measures all the important costs and consequences which accrue as a result of a given intervention. Consequently, such an assessment can be done alongside any epidemiological study which is being used to measure the effectiveness or efficacy, if we also piggy-back measurement of costs alongside. However, an epidemiological study may not be able to measure all costs and consequences comprehensively, in a manner which may be considered appropriate for an EE. This leads to the need for decision modelling.

Section 1 of this chapter describes the limitations of undertaking EE alongside a clinical trial which necessitates use of a decision model. Subsequently, in section 2 we describe how a decision model is able to bridge the limitations of an epidemiological study in undertaking EE. We also introduce the 2 type of decision models which are used for EE, i.e. decision tree and Markov model. Section 3 uses an illustration of each of the two types of decision models for explanation. A hypothetical example of implementation of special newborn care units at district hospitals to treat sick newborns is used to explain a decision tree. Similarly, a published cost-effectiveness analysis of use of sorafenib – drug used for treatment of hepatocellular carcinoma to treat hepatocellular carcinoma is used to explain use of Markov model. Finally, we conclude on what caution should be exercised by the researchers undertaking economic evaluation for health technology assessment (HTA).

Can RCT alone be used to do an Economic Evaluation?

As introduced above, the measurement of costs and consequences in an EE can be undertaken alongside an epidemiological study. Classically, a randomized controlled trial (RCT) is considered the epidemiological study with highest degree of rigour for internal validity, hence the word RCT will be used as a proxy for an epidemiological study.

Table 1: Differences in the approach of Randomized Controlled Trial and Economic Evaluation

Characteristic	Approaches for Undertaking Economic Evaluation	
	RCT	Decision Model
Focus of Assessment	Internal Validity	External Validity
Time Horizon	Usually short – enough to estimate proximal clinical endpoints	Usually long – to comprehensively estimate downstream costs and consequences
Measure of outcome	Usually proximal clinical endpoint, eg. Reduction in blood pressure	Utility based measure such as Quality Adjusted Life Year (QALY)
Number of Comparators	Limited	No limitation

An RCT is generally done to evaluate the clinical efficacy of a drug, device, treatment or health care intervention. If alongside the measurement of the health consequences, which is used to measure efficacy, data on cost of delivering the intervention and comparator is also collected, this information can then be synthesized to produce the results for EE. This appears to be a very good approach for undertaking EE, as there are numerous RCTs carried out to assess clinical efficacy, and all it needs is an additional data collection for cost of care. However, there are several limitations to using a RCT for doing EE.

Firstly, the focus of RCT is to determine the clinical efficacy. In view of this objective, careful selection criteria are applied to recruit subjects and the interventions are delivered in the most optimal manner. While this may be perfectly justified to produce results which have high internal validity, there may be some limitation to generalizability. For example, a trial done to evaluate the vaccine efficacy ensured that all the kids who were immunized were previously healthy, vaccine was potent and injected in the recommended manner in correct dose and route of administration. However, in reality, when immunization is introduced in a public health program setting, not all children may be vaccinated. Similarly, there may be breakdowns of cold chain leading to lowered potency of vaccine, and some babies may be

given vaccine using sub-optimal dose or incorrect route. Hence, the effectiveness may be lower than the efficacy reported in RCT. For an EE which is dealing with a policy question of whether to introduce the vaccine in national immunization schedule, the data on pragmatic real-world effectiveness is more useful than efficacy.

Secondly, several trials may be done for determining clinical effectiveness in terms of outcomes which may be perfectly rational to a particular health condition, but may not solve the needs for an EE. For example, a RCT for determining clinical effectiveness of new anti-hypertensive drug compared to the existing treatment measured its effectiveness in terms of reduction in blood pressure. However, the appropriate outcome measure which is recommended for an EE is a generic utility based measure such as quality adjusted life year (QALY). This is so because it allows comparison of efficiency across a range of different types of interventions applicable for different diseases in different types of patient population. Hence again, RCT falls short of providing solution for EE.

Thirdly, on grounds of feasibility, most of the trials are run for short period of time which is appropriate enough to document clinical effectiveness. However, an EE aims at measuring all the costs and consequences which are a result of the intervention. For example, a clinical trial which may be carried out for a hemophilus influenza type 'b' (Hib) vaccine (given to children at 6,10 and 14 weeks of age) which offers protection against pneumonia and meningitis due to the said organism, measured the episodes of Hib disease among vaccinated and unvaccinated cohorts during a 1 year period following vaccine administration. While this may be sufficient for measuring the vaccine efficacy, however, the protection against Hib disease continues as long as child is susceptible, which is generally about 5 years, and to a lesser degree as long as 15 years². Hence there is a reduction of disease episodes much longer than the trial period. So, while a trial in this case may measure all costs accurately – as all costs related to vaccination are incurred in year 1, it underestimates the health benefits as well as cost savings (due to decrease in treatment costs). In order to overcome this problem of measuring benefits, RCTs will need to be extended till the time intervention continues to be beneficial, so that all costs and consequences are valued credibly. However, this can sometime become unfeasible. For example, in case of a preventive intervention such as vaccine for human papillomavirus (HPV) to protect against cervical cancer among women, while the vaccination is recommended to be done around the age of 10-12 years, reduction

in the cancer cases continues to happen as late as 60 or 70 years or even later³. And it may not be feasible to have resources to follow-up a trial cohort for a lifetime. Hence, RCTs may not offer the medium to generate data for EE.

Fourthly, a trial is generally conducted to evaluate a few alternative options for treatment or addressing a particular health problem. However, decision making in the field of policy is full of possible scenarios which need to be evaluated. For example, a single question of which is the most appropriate method to screen women for cervical cancer can be further stratified into several scenarios based on which method should be used (pap smear, visual inspection with acetic acid or HPV DNA), which population should be screened (30-65 years, 40-65 years, 50-65 years), how frequently (annual, 3 yearly, 5 yearly, 10 yearly, once in a lifetime). Together these can constitute 16 possible scenarios. However, it may be difficult to have a single RCT with 16 arms to evaluate all possible scenarios. In view of this limitation again, RCT alone cannot be used to generate evidence for EE.

Bridging the limitations of RCT: Role for Decision Modelling

A solution to bridge the limitations of RCT is to either undertake decision modelling alone, or use decision model alongside the evidence generated in RCT. A decision model used for EE is a biologically plausible sequence of occurrence of health consequences as a result of the decision of undertaking an intervention. The model so prepared, does not only shows relationships, but also mathematically quantifies the probability of occurrence of such a health consequence or outcome as a result of an intervention. In the mathematical parameterization of a decision model, the researcher can use pragmatic data on effectiveness from a real-world study rather than a RCT. Alternatively, an assumption which justifies the constraints of program implementation or treatment administration in real-world could be incorporated to generate an output which is more acceptable. For example, one may consider findings of a national evaluation which shows that the coverage of routine immunization is not likely to be more than 90% in the best possible scenario, and hence the efficacy of treatment derived from RCT could be modelled on only 90% of the intervention cohort to generate the health consequences.

Secondly, the evidence from a 1-year trial of anti-hypertensive drug on reduction in blood pressure could then be used along with evidence from other studies for effect of

lowering blood pressure on long-term consequences such as coronary artery disease (CAD) or mortality or quality of life, to model long-term consequences of the anti-hypertensive drug on survival, life years and QALY.

The third limitation of a RCT was its inability to have a longer time horizon to capture all costs consequences satisfactorily. A decision model can use a lifetime study horizon to capture all costs and consequences which can accrue as a result of the intervention. Having said that, however, it does not mean that this can be generated without a previous evidence. So, a model, uses synthesizes evidence from various inputs to predict long-term costs and consequences. Finally, a model construction is not limited in terms of the number of scenarios which it can potentially evaluate. So, it overcomes the last limitation of a RCT by enabling comparison of several possible treatment or program interventions to deal with a given health problem.

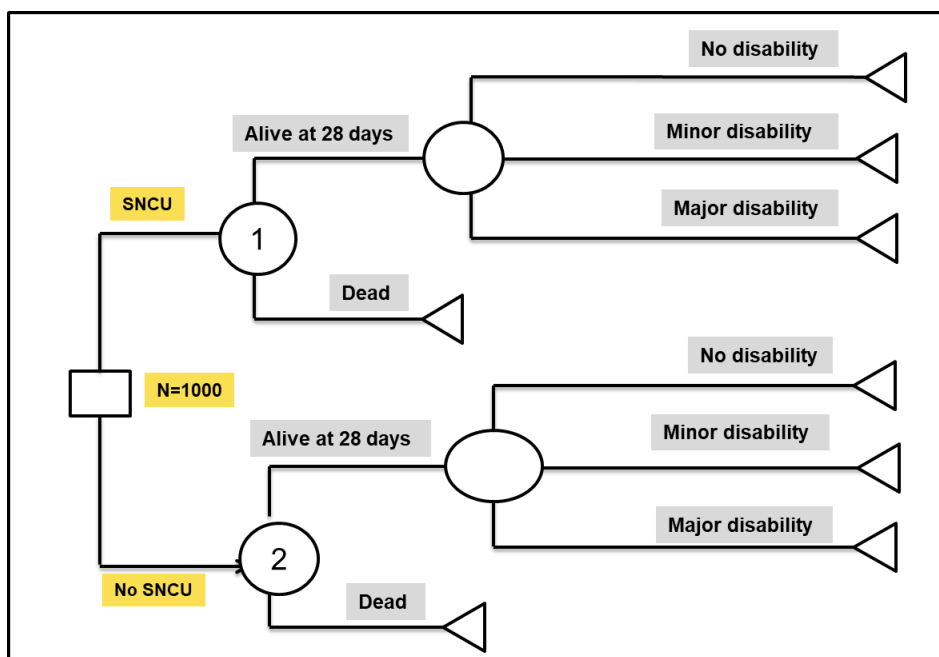
Two most commonly used decision models in EE are decision tree and Markov model. Classically, a decision tree is a unidirectional flow of events which begins with the decision of giving an intervention or not. This is followed by occurrence of different sequence of outcomes which may continue to happen with a given probability or chance at each step in a unidirectional way. The tree ultimately ends with a terminal event in which individual may return to full health or may die. The major limitation of a decision tree is its unidirectional flow. This may be suitable for acute disease conditions which follow a particular course since their onset and the patient may either recover completely and live, or may live with some long-term sequelae or may die. However, this may not be the case with chronic non-communicable diseases. For example, a patient diagnosed with hypertension may not necessarily remain hypertensive all his life. He may recover back to be normotensive with treatment, or may progress to a worse off health state. Modelling such chronic diseases requires application of a Markov model which differs from a decision tree in allowing transition from any one health state to any other health state, which is biologically plausible as per the scientific understanding of disease course.

The subsequent sections illustrate the use of a decision tree and a Markov model for better understanding.

Decision Model 1: Decision Tree

The following hypothetical example illustrates estimation of incremental cost per QALY gained with implementation of a strategy to create sick newborn care units (SNCU) – a level II intensive care unit, at the level of district hospitals, against a comparator of routine management of sick newborns in these hospitals. A decision tree was constructed for comparing these 2 treatment options as shown in Fig 1. It was assumed that the sick newborns could die or remain alive within 28 days of birth following treatment at SNCU or from routine management based on current practice. If the newborn dies within 28 days, it signifies the end of outcome or event and is represented by a terminal node (triangle). However, if sick newborn remains alive till 28 days of birth, it may become fully cure with no disability or may develop minor or major disability. Similarly, the cost of treating the sick child at SCNU or routine care is also summarized in table 2. Further, the table 2 shows each of these probabilities, quality of life for each state, average life expectancy and cost of being in each state.

It was assumed 1000 sick newborn were treated with either of the competing treatment practice. Assigning all the probabilities and costs to each of the arms in the decision tree total cost of treating 1000 newborns with each of the treatment strategy is shown in Fig 2. Multiplying the number of newborns treated with probability of a given outcome, life expectancy of that outcome, and quality of life of that outcome provides an estimate of total number of quality adjusted life years for that outcome stream. Similarly, QALYs via all outcome possibilities (alive, minor disability and major disability) were estimated. The cost of each outcome stream was estimated using number of newborns in that stream and the unit cost. Finally, it was seen that SNCU resulted in a gain of 14,652 more QALYs per 1000 newborns at an additional cost of INR 222,152 as compared to routine management (absence of SNCU), yielding an incremental cost effectiveness ratio of INR 15.16 per QALY gained.



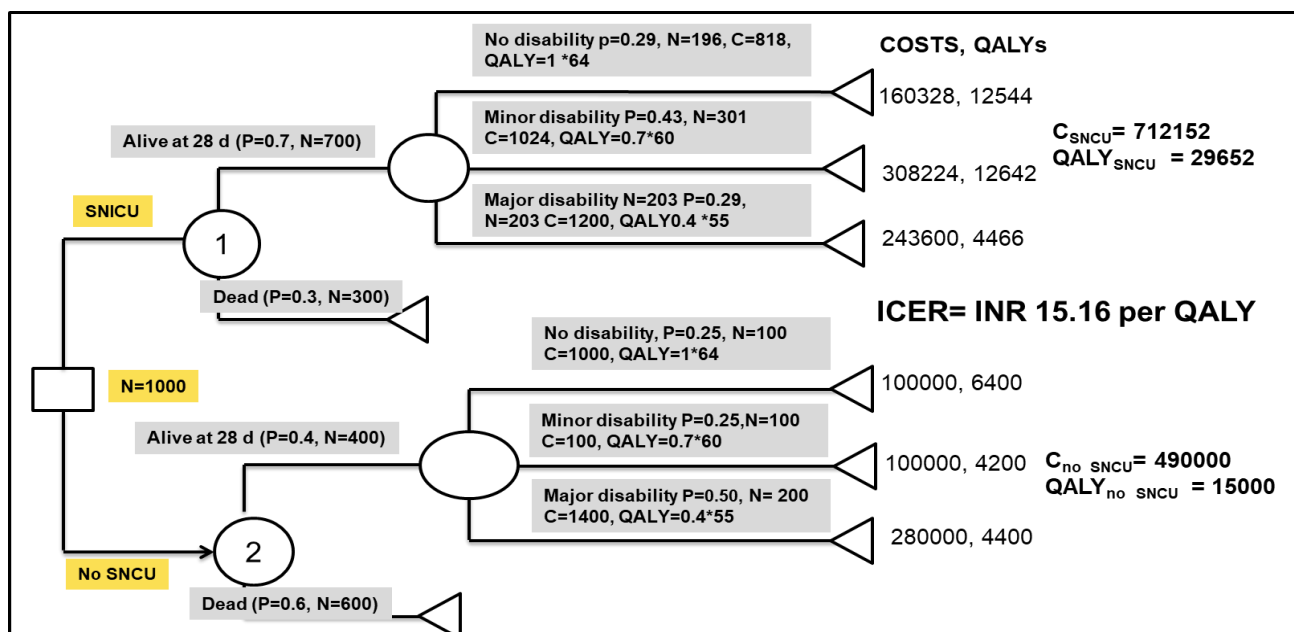
*SNCU: Sick newborn care unit

Figure 1: Decision tree structure

Table 2: Parameter values

Parameter	Parameter definition	Hypothetical Values
Transition Probabilities	Probability of dying following treatment in sick new born care unit	0.3
	Probability of dying following treatment based on current practice	0.6
	Probability of developing minor disability following treatment in sick new born care unit	0.43
	Probability of developing major disability following treatment in sick new born care unit	0.29
	Probability of developing minor disability following treatment based on current practice	0.25
	Probability of developing major disability following treatment based on current practice	0.5
Cost parameters	Cost of treating a newborn in sick new born care unit who develops no disability	818

(in Indian Rupees)	Cost of treating a newborn in sick new born care unit who develops minor disability	1024
	Cost of treating a newborn in sick new born care unit who develops major disability	1200
	Cost of treating a newborn (who develops no disability) based on current practice	1000
	Cost of treating a newborn (who develops minor disability) based on current practice	1100
	Cost of treating a newborn (who develops major disability) based on current practice	1400
Quality of life	With no disability	1
	With minor disability	0.7
	With major disability	0.4
Life expectancy (in years)	With no disability	64
	With minor disability	60
	With major disability	55



*SNICU: Sick newborn care unit; QALY: Quality adjusted life years; ICER: Incremental cost effectiveness ratio; P: Probability; C= Cost; N=Number of sick newborn.

Figure 2: Solved Decision tree analysis

Decision Model 2: Markov Model

In this, we use an example of a cost-effectiveness analysis which was used to evaluate sorafenib – a drug used to treat hepatocellular carcinoma (HCC) ⁴. HCC is the primary malignant neoplasm of the liver. Majority (70%) cases of HCC in India present at advanced stage (Barcelona Clinic Liver Cancer (BCLC) stage C and D) in which curative resection is not possible. For these unresectable, advanced HCC cases with extra-hepatic spread or vascular invasion, treatment options are limited. Targeted molecular therapy – sorafenib, is indicated for such advanced BCLC stage C patients of HCC. Sorafenib has been reported to have an increased median overall survival and time to progression in advanced HCC as compared to Best Supportive Care (BSC). The alternative to giving sorafenib is BSC which comprises of standard routine care and complications management. Sorafenib and BSC arms are considered as intervention and control respectively. In order to model life-term costs and consequences, patients are segregated into two alive health transition states termed as Progression Free State (PFS) and Progressive Disease (PD) in intervention and control arm respectively. As shown in the Figure 3, HCC patients diagnosed in PFS health state can advance to PD or Death from all-cause mortality health states. Death from HCC happens from PD health state only.

Figure 3: Markov Model structure

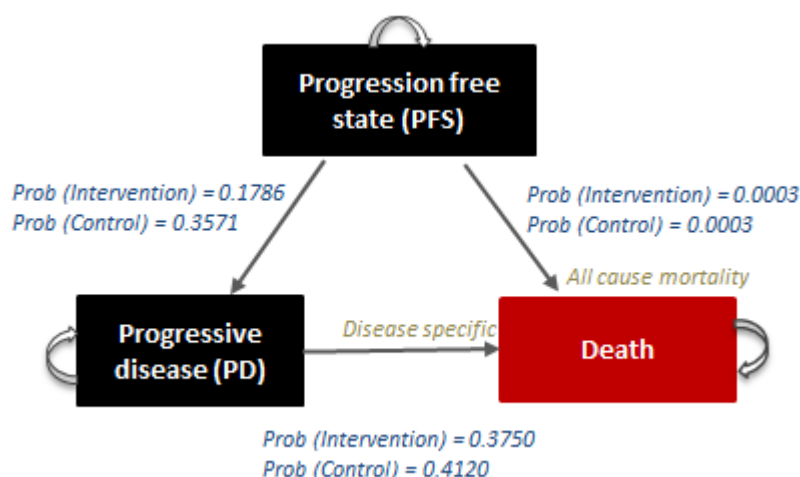


Figure 3 is next converted to Table 3 and 4 which show a transition matrices which represents the probability of moving from each health state to the next state in sorafenib and BSC arm respectively.

Table 3 Intervention (sorafenib) arm transition probability matrix

	PFS	PD	Death from disease	All-cause mortality
PFS	0.8211	0.1786	0	0.0003
PD	0	0.6250	0.3750	0
Death from disease	0	0	1	0
All-cause mortality	0	0	0	1

Table 4 Control (BSC) arm transition probability matrix

	PFS	PD	Death from disease	All-cause mortality
PFS	0.6426	0.3571	0	0.0003
PD	0	0.5880	0.4120	0
Death from disease	0	0	1	0
All-cause mortality	0	0	0	1

Let us decipher intervention transition matrix. Before we begin it is important to understand that sum of the probabilities mentioned in each of the vertical health states should be equal to one. Example:

- Horizontal row for PFS in Table 2 = $0.8211 + 0.1786 + 0 + 0.0003 =$ should be equal to 1

To understand how other probabilities are going in the matrix. It is important to keep in mind the markov schematic and the flow of one state to another. For PFS to PFS probability is mentioned as 0.8211 which is derived in terms of $1 - (0.1786 + 0 + 0.0003)$. Similarly, for remaining in the PD state the probability of 0.6250 is deduced from $1 - (0 + 0.3750 + 0)$. The values 0 describes no relation between the health states. As for Death from disease and All-cause mortality since patients cannot move to any health state once they are in Death so the probability to remain in the same health state is always 1.

In the next stage, using the information above, year-wise number of HCC patients in each of the health states is predicted. This is done using the information of transition probability which is multiplied by the number of person in that health state. Similarly, applying the cost per person in each health state along with total HCC patients of that health state, the

overall cost is computed. This is continued till all the patients have reached the terminal stage or died – i.e. lifetime study horizon. Each HCC patient in respective health state for a given cycle length

This exercise is performed for both the scenarios, i.e. sorafenib and BCC. Finally, incremental cost-effectiveness ratio is computed as the ratio of difference in costs and difference in benefits.

Conclusion

Overall, an economic evaluation needs measurement on costs and effects for 2 or more possible alternative which are being compared. In order to do so, an epidemiological study which is being conducted to estimate efficacy in one option. However, as we discussed, a RCT may have limitations in certain context to generate robust evidence for an EE. As a result, decision models become imperative. However, it needs to be recognized that decision models are not free of inaccuracy. These decision models can lead to erroneous findings due to several reasons – firstly, if the model structure is incorrect and is not biologically plausible, then it leads to incorrect output. Secondly, a model is as good as the values of parameters which are fed to generate output. Hence, any uncertainty in the values of these parameters can lead to uncertainty in estimate of the incremental cost-effectiveness ratio (ICER). This is not an unthinkable option, as each epidemiological study also has some uncertainty around the sample estimate which it generates, due to sampling variation. As a result, just as the 95% confidence interval is computed around the estimate found in a RCT, similarly it calls for a sensitivity analysis in a decision-model based EE to compute 95% confidence intervals. Subsequently, it needs to be assessed whether the null value for the ICER lies within the 95% bounds. Thirdly, the population group which is considered in a decision model may not be representative of the certain population groups. Sub-group analysis is the way forward in such situations.

To conclude, one can say that each of the methodology has certain limitations. However, the decision modelling does overcome several limitations of a RCT based EE. As a result, gradually, there is a trend towards EE which are done using a decision model alone, or using a decision model alongside a RCT ⁵. Such as decision model would need evidence for parameters, which could be limited. However, the key would be to use as much robust data

to parameterize the model and then take a decision. After all, a policy maker or program manager or a clinician can have 2 options to make a decision about the appropriate intervention – either wait for the best possible data to be generated, or make the best possible decision (using a model) with the available data! There can always be options to revisit the decision when better data is generated.

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*Chapter 11:
Results of Economic
Evaluation (ICER) and
Sensitivity Analysis*

The first part of this chapter focuses on interpreting the evidence arising of an economic evaluation in the form of incremental cost effectiveness ratio (ICER) and how it can be used to undertake evidence based informed decision making while comparing different health care interventions or programs. Subsequently, the second section gives a basic understanding of the concept of sensitivity analysis undertaken to deal with uncertainties arising as to the accuracy of the parameter values and assumptions made within a cost effectiveness analysis.

Interpreting evidence

Incremental cost effectiveness ratio (ICER) is the summary measure used to report cost-effectiveness of competing interventions. It is defined as the ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives. This ratio provides an intuitive metric, which is the incremental cost per unit of health outcome with a intervention in question (usually newer or latest health care innovations) relative to its comparator and assists decision-makers in allocating resources efficiently on those interventions that have proven to yield best value for money.

The results of an economic evaluation are usually plotted on a graph known as cost effectiveness plane (Fig 1). Cost effectiveness plane typically comprises of 4 quadrants, with x-axis by convention representing difference in effects across the comparator interventions and the vertical y-axis measuring difference in costs. Suppose we are comparing a new chemotherapy regimen with an old one for a particular type of cancer. There can be four possibilities, which can also be identified in the cost effectiveness plane. If the value of ICER falls in the north-east quadrant, the newer treatment is more effective and also costs more. In the south-east quadrant, the intervention of interest is both more effective as well as less costly and thus, it dominates the old treatment. If ICER comes in north-west quadrant, the opposite holds true, i.e., the newer intervention is more costly and less effective and is dominated by the older treatment. Finally, the value of ICER in the south-west quadrant represents that the new intervention is both less effective less costly. Most of the attention is focused in NE quadrant, where it needs to be checked if the higher costs are justified by the higher effects of the new intervention.

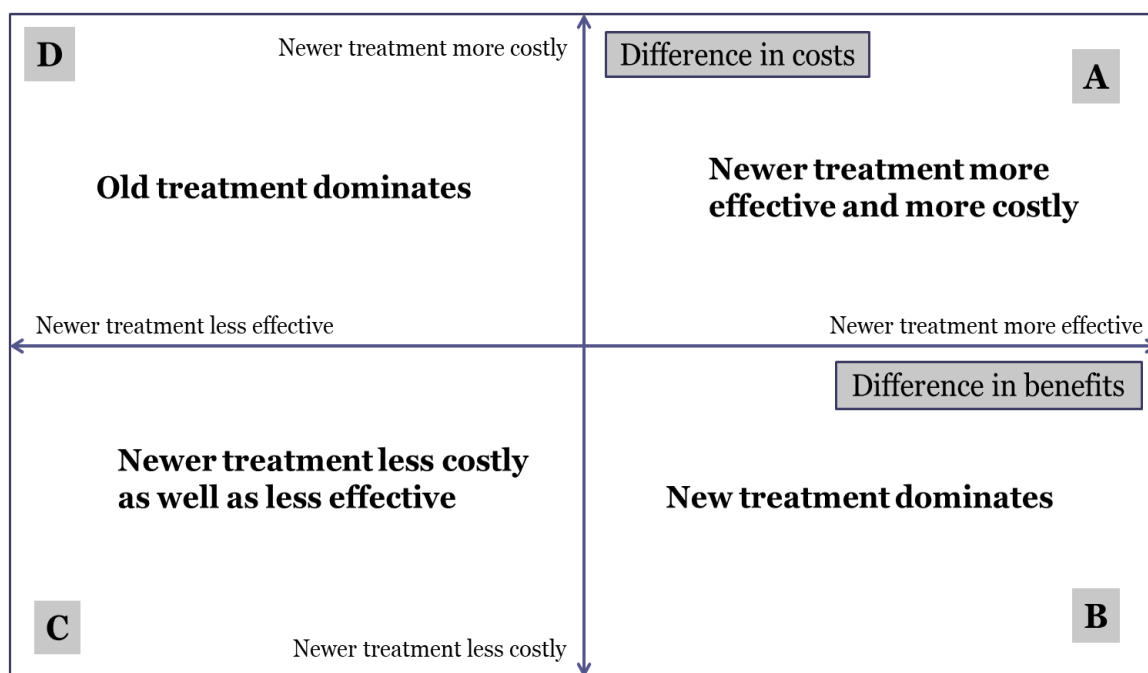


Fig 1: Cost effectiveness plane

Cost-effectiveness thresholds

The concept of cost effectiveness thresholds was introduced to help determine that a particular value of ICER represents the best use of resources. In economics, a health care intervention can be only categorized as 'cost-effective' if its health effects are greater than the opportunity costs of health benefits forgone. These opportunity costs of forgone health benefits are reflected with cost-effectiveness threshold.

The threshold value should ideally reflect the budget size (funding arrangements within a country) as well as other opportunities available for using these scarce resources. The most commonly used cost-effectiveness threshold is based on country's per-capita gross domestic product (GDP). In 2005, (WHO-CHOICE) suggested that "interventions that avert one DALY (disability-adjusted life-year) for less than average per capita income for a given country or region are considered very cost-effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost-effective; and those that exceed this level are considered not cost-effective". (1) These thresholds just try to indicate that whether the newer intervention provides very good, good or poor value for money and should not be used alone, as a justification for funding or a measure of affordability.

Sensitivity analysis

Sensitivity analysis is a way to address the extent of uncertainty in the results and outcomes of an economic evaluation arising due to underlying assumptions (both in model structure and methods), precision of the parameter estimates and generalizability. Methodological uncertainty pertains to disparities in the choice of methods used in an economic evaluation related to assessment of costs, health consequences, quality of life, perspective, etc. Similarly, uncertainties arising due to underlying assumptions and scientific arguments made while designing and interpreting the structure of a decision analytic model are defined under model structure uncertainty. Parameter uncertainty occurs due to ambiguity related to the true value of model parameters such as relative risk, survival rates, transition probabilities, etc. Generalization relates to extent to which the results of a cost effectiveness analysis can be applied to different settings in terms of different geographical regions, population groups, etc.

There are two basic types of sensitivity analysis approaches i.e., Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). Deterministic sensitivity analysis is carried out to assess that how the results of an economic evaluation are sensitive to variation or change in values of certain parameter. For example, a parameter value is changed from upper to lower bounds to see how sensitive the ICER value is w.r.t the change in specific parameter. Generally there are three main types of DSA used in health economic evaluations i.e., one way or univariate, two-way or bivariate and multi-way or multivariate sensitivity analysis. The traditional univariate sensitivity analysis tries to examine the change in an ICER by varying the value of one variable at a time and holding all other parameter constant. Similarly, in two-way and multi-way analysis the value of 2 and more parameters are changed simultaneously and its impact on ICER is seen. A sub-type of one-way sensitivity analysis is threshold analysis. Under this, the value of a certain parameter is varied over a range and a level is determined, below or above which the conclusion of the study changes. For example, a threshold analysis can be undertaken to assess the minimum coverage of an immunization or a screening program necessary to maintain the cost-effectiveness of the program. A type of multi-way analysis is scenario analysis. Under this, a range of scenarios is constructed based on the set of certain circumstances across parameters and is compared

with the 'base' case analysis. For example, the worst and best case scenarios comprise of those extreme circumstances consisting of parameter values leading to the highest and lowest cost effectiveness ratios respectively.

In probabilistic sensitivity analysis, all the uncertain parameters are varied as per predefined distributions by means of e.g. Monte Carlo Simulations. (2) Appropriate distributions are needed to be used for each of the uncertain modeling parameters depending upon the type and nature of the variable. In comparison to deterministic analysis, PSA allows us to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs. In PSA, the first step is to convert point estimates of each of the parameter values into distributions. Once the distributions has been assigned, a number of simulations are run (say 10,000), which allow sampling from the various distributions. For each simulation, different values are picked from the distributions, and many different ICER values are calculated. Finally, a mean or median ICER value is reported along with 95% confidence interval or 2.5th and 97.5th percentile respectively.

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Chapter 12:
Equity Considerations for
Health Technology
Assessment

This chapter will address the importance of equity considerations in the HTA process, elements that address equity considerations and frameworks for integrating these concerns.

Equity as a concept is represented by ideas of social justice or fairness. As Braveman and Gruskin point out equity is an ethical concept, grounded in principles of distributive justice. Equity in health can therefore be defined as the absence of socially unjust or unfair health disparities (Braveman and Gruskin: 2003). They identify four key points relating to health equity is given in box 1. It is clear from this definition that the concept of equity has both a social and ethical aspect to it that has relevance for HTA.

Box 1. Key points in defining Health Equity

- A definition of equity in health is needed that can guide measurement and hence accountability for the effects of actions.
- Health equity is the absence of systematic disparities in health (or its social determinants) between more and less advantaged social groups.
- Social advantage means wealth, power, and/or prestige—the attributes defining how people are grouped in social hierarchies.
- Health inequities put disadvantaged groups at further disadvantage with respect to health, diminishing opportunities to be healthy.
- Health equity, an ethical concept based on the principle of distributive justice, is also linked to human rights.

According to Culyer and Bombard, there are two domains of equity that are particularly relevant for HTA. “One is fairness of the procedures used in the conduct of HTAs. The other is equity as a decision criterion, like efficiency, for ranking health care interventions” (Culyer and Bombard:2012; 148)

Going by the four key points mentioned in Box 1, there is a need to address multiple determinants of equity for HTA like the choice and implementation of technology, the role of the health service system to make it available, accessible, affordable and acceptable (4 As)

across social groups and the costs of the technology and its use. The health service system is an important determinant of equity and therefore the four As stated above need to be factored as an important consideration. It is vital that the assumptions and trade offs be clearly stated through the deliberations regarding the choice of technology by the HTA process. Draborg et al have further elaborated the importance of resources and the health system performance for equity in HTA. They state that HTA is a multidisciplinary process that systematically evaluates the effects of a technology on health on the availability and distribution of resources and on other aspects of health system performance such as equity and responsiveness (Draborg et al: 2005). In our view this definition is broader than merely a costing exercise.

The following figure explicates the social and ethical domains associated with the HTA process. It highlights the multiple actors, domains and pathways that are determinants of social and ethical dimensions of HTA.

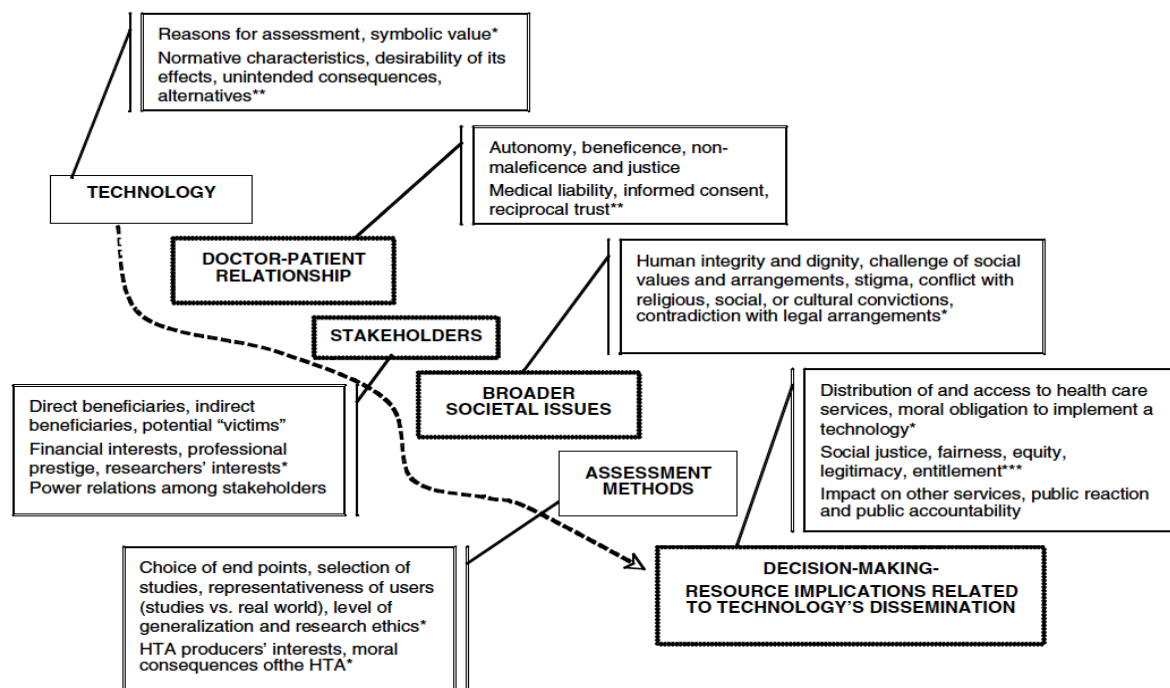


Figure 2. Social and ethical issues associated to key components of an health technology assessment (HTA). *Adapted from Iofmann (16); **adapted from Heitman (18); ***adapted from Hasman (15).

The HTA process has to engage with several determinants of equity that are not mutually exclusive of one another. These include the following:

- Socio-economic inequities in health outcomes and access to health services
- The political support for health services
- Availability, accessibility, affordability and acceptability of health services
- Capacity of health services
- Cost of technology, cost to the health services and to the users of the services
- Safety aspects of the technology
- Clinical effectiveness
- Legal aspects

Given that India is a low middle income country with marked socio-economic inequalities there is concern about how this gets reflected in health outcomes and access to services. As the Commission on Social Determinants pointed out the financing and organization of health services play an important role in either exacerbating or mitigating inequities. It is also the case that there is a social gradient in inequities in health outcomes and access to health services. This essentially means that it is not a mere poor and rich divide but there is a large, highly differentiated middle income group that has difficulty accessing health services because of rising costs. This is largely due to a weak public sector and a private sector that is large and unregulated.

While there is a broad agreement among the HTA community that equity concerns are important it is often overtaken by cost considerations (Lehoux and Blume:2000). Therefore costing exercises tend to relegate equity concerns to social economic inequities alone. The user perceptions are elicited through QALYs at an individual level and then aggregated to social groups. There is a methodological problem with this approach. Once again this is a challenge for the HTA process.

Equity as a concept is premised on the principle of fairness, which has roots in ethics and morality. It embodies ideas of social justice and rights. The concept of equity underlines the fairness in the production, choice, delivery and responsiveness of technology across

different sections of the population. Thus technology is not value neutral and implicitly has moral and ethical dimensions. The evaluation of technology needs to address questions around who produces and markets the technology, full disclosure on the safety, clinical effectiveness and the research; the cost of the technology; health system preparedness to deliver the technology at a population level.

In the last section of this chapter we present a framework for including in the HTA process developed by Culyer and Bombard that is useful for identifying the key domains of equity for HTA. Deliberating and incorporating some of the features of this framework on a case to case basis could provide a more robust approach to integrating equity concerns in the HTA process.

Table 1 A Framework of Equity Considerations for Health Technology Assessment

Domain	Elaboration	Questions
1 Equity and equality	<p>There can be fair inequalities and unfair equalities. Equity ought not to be equated with equality (of something) but, if it is, the ethical weight to be attached to the "something" needs consideration. Equality and inequality imply a degree of quantification (minimally an order of states of more or less). Check on empirical research for quantified measures of inequity. In the absence of good-quality research, identify other sources such as expert opinion but be alert to the possibility of expert prejudice.</p> <p>The focus of the analysis of equity. This could be on health care inputs, processes, direct outcomes, indirect outcomes, disease patterns, patient types, or subgroups. The desired focus is likely to be context-dependent and may depend on the rulings of a higher tier authority.</p>	<p>Equality (or inequality) of what? Common candidates include need, deservingness or responsibility, capacity to benefit (or be harmed), degree of incapacity or current health state, history of health or ill health, prognosis with and without the intervention; health outcome—quality of life; and dependents (caregiving responsibilities). Seek empirical and quantitative information about how equal or unequal the relevant factors are.</p>
2 Adequacy of the domains of equity	<p>Common offenses include discrimination by age, gender, disability, ethnicity, race, nationality, language, and sexual orientation and discrimination in the workplace and in education; there are also institutionalized discrimination and implicit and in direct discrimination.</p> <p>Minimal requirements for equity, axiomatic statements, applicability of such principles in current context.</p>	<p>Should the domain of equity relate to health care inputs, processes, or outcomes? Might there be unintended consequences that raise equity issues? Should the domain of analysis be disease focused, or should some other basis for differentiating individuals and subgroups be used? What are the equity-related consequences of this categorization?</p> <p>Have the relevant local legal obligations concerning age, gender, disability, ethnicity, race, nationality, language, and sexual orientation been considered? Are there any legislative requirements concerning institutionalized, implicit, or indirect discrimination in the respective jurisdiction?</p>
3 Legal obligations	<p>Common offenses include discrimination by age, gender, disability, ethnicity, race, nationality, language, and sexual orientation and discrimination in the workplace and in education; there are also institutionalized discrimination and implicit and in direct discrimination.</p> <p>Minimal requirements for equity, axiomatic statements, applicability of such principles in current context.</p>	<p>Have a set of guiding principles or axioms been established concerning what constitutes equality (or fair inequalities) in the current context? Is it possible to infer specific equitable guidance in the current context from the general guidance? Are there precedents that could guide in the present context?</p> <p>Are there inequities in the measurement or methodological processes informing the HTA? For example, does the outcome measure omit significant dimensions and thereby differentially exclude key outcomes for some groups? Are the standard weights attached to gains and losses affecting different people (usually but not necessarily, unity) deemed suitable in the current context? Do the measures of inequity weight distance from the average in an acceptable way? Are there any aspects of the intervention, in addition to the direct effects, that may raise equity concerns?</p>
4 General principles	<p>Minimal requirements for equity, axiomatic statements, applicability of such principles in current context.</p>	<p>Have a set of guiding principles or axioms been established concerning what constitutes equality (or fair inequalities) in the current context? Is it possible to infer specific equitable guidance in the current context from the general guidance? Are there precedents that could guide in the present context?</p> <p>Are there inequities in the measurement or methodological processes informing the HTA? For example, does the outcome measure omit significant dimensions and thereby differentially exclude key outcomes for some groups? Are the standard weights attached to gains and losses affecting different people (usually but not necessarily, unity) deemed suitable in the current context? Do the measures of inequity weight distance from the average in an acceptable way? Are there any aspects of the intervention, in addition to the direct effects, that may raise equity concerns?</p>
5 Embedded inequity	<p>Possible unfairness built in to concepts (e.g., omitted dimensions of outcome or cost), framing effects in experimental approaches, possible unfairness inherent in the intervention (e.g., threat to autonomy).</p>	<p>Are there inequities in the measurement or methodological processes informing the HTA? For example, does the outcome measure omit significant dimensions and thereby differentially exclude key outcomes for some groups? Are the standard weights attached to gains and losses affecting different people (usually but not necessarily, unity) deemed suitable in the current context? Do the measures of inequity weight distance from the average in an acceptable way? Are there any aspects of the intervention, in addition to the direct effects, that may raise equity concerns?</p>

(continued)

Domain	Elaboration	Questions
6 Institutional bias	Inequity resulting from jurisdictional scope in clinical practices, provider institutions, workplaces or in the distribution of consequences.	Do any of the following cause particular costs or benefits to be omitted or distorted: the agency's parent organization, the culture of the HTA agency itself, provider institutions, workplaces?
7 Implicit stereotyping	Definitions and concepts that exclude or prejudice individuals. Aspects of the effects of the intervention that have differential impact on individuals, that make in untested assumptions about what does and does not matter, or that are stigmatizing.	Is the measure or conceptualization of the health benefit or cost or state biased? Have assumptions about what matters been tested by consulting those affected? Is the current context one in which there are likely to be marked differences in culture between analysts and client groups that could give rise to implicit stereotyping? Are there people who might be affected but whose interests have not been taken into account?
8 Contexts and circumstances	Aspects of the context that could disadvantage some relative to others (e.g., geography, culture), tests for whether any of the following could affect the balance of advantage: usual demographics (age, sex, ethnicity, SES), location of delivery (e.g., home or institution), language, education of clients, religious beliefs, sexual orientation, stigma, multiple deprivation. Aspects of the context that render the proposed methods of HTA inappropriate (e.g., methods used in a high-income country being applied in a low-income country, Western values being applied in an aboriginal or first-nations context).	Do any of the following circumstances affect the balance of negative and positive consequences: geography, demographics (age, sex, ethnicity, SES), location of delivery of care (e.g., home or institution), education, language, religion, sexual orientation, or multiple deprivation? Are methods developed in one culture being appropriately applied in another?
9 Processes in HTA	Processes that deny suitable representation to people with a legitimate interest, processes that deny consideration of the interests of absentee stakeholders.	Has the scoping of the HTA caused a bias in the processes through which information germane to equity is gathered or considered? Is the current guidance devoid of any implicitly biasing elements, such as the exclusion of relevant consultation groups, in the current context? If not, can the matter be addressed and rectified? Are the appropriate health outcomes measures and stakeholders included in the HTA process (including patients and members of the public)?

(continued)

TABLE 1 (continued)

Domain	Elaboration	Questions
10 Hidden opportunity costs	<p>Costs inflicted on those affected indirectly by the intervention and those anonymous people who are affected through consequential changes in the distribution of resources if the recommendations of the HTA were implemented. The identity of the individuals who lose may not be known. It may also be that the weight to be attached to any such opportunity cost might vary according to what is known about those most likely to be losers relative to those directly affected by the intervention.</p>	<p>Has due regard been paid to the interests of the anonymous clients of the health care system from whom resources will be removed as a consequence of the implementation of the recommendation of the HTA? Do those most likely to be affected in this way have distinctive characteristics suggesting that differential weights ought to be attached to the impacts on them? Are there any empirical estimates of any such relevant effects?</p>
11 Processes in delivery of care	<p>Processes in the delivery of care that are prejudicial to, demeaning of, or embarrassing for some who are affected. Some processes favor those adept at managing their way through complex or unfamiliar processes. Thus, other inequities for those lacking such social skills or that impose differential costs/burdens on some clients and stakeholders relative to others might not be known or even revealed.</p>	<p>Are there processes in the delivery of care, apart from those that are embedded in institutions, that discriminate unfairly? Are any of the likely delivery processes prejudicial to, demeaning of, or embarrassing for some clients relative to others? Is there a middle-class bias that favors those with skills at dealing with receptionists, bureaucrats, professionals, and other unfamiliar groups of people?</p>
12 Special claims	<p>Claims such as claims of need (e.g., low initial health status?), claims of responsibility (e.g., life styles hazardous to health), claims of history (e.g., past endurance of ill health, past receipt of the intervention), claims of desperation (e.g., last chance), claims of unfair innings (lived life span), claims of nonhealth consequences (other welfare effects), claims of willingness to pay (e.g., top-ups).</p>	<p>What, if any, special claims ought to be considered? Are there claims or interests not being heard but deserving of a voice? Are their claims that are not ethically significant? Can the claims that might carry weight bear empirical testing for their veracity and size? Are there precedents for dealing with claims of the sort in the current context? How do special claims compare to the putative claims of those not represented in the HTA process?</p>
13 Cumulative effects	<p>Consideration of cumulative past disadvantages or advantages that might be relevant in assessing benefit or cost or their distribution across affected parties.</p>	<p>Has a holistic perspective been taken or merely the sum of the individual parts? Have historical disadvantages been considered? Are there any other respects in which the cumulative experience or the combination of experiences of those affected may be of equitable concern?</p>

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Chapter 13:
What Evidence Do You
Need To Do HTA?

The main purpose of Health Technology Assessment (HTA) is to provide policy-makers with **evidence-based information** on a health technology, so they can formulate health policies that are safe, effective, cost-effective, patient-focused, sustainable and equitable. Very importantly, HTA can therefore provide a robust tool to inform evidence-based allocation of resources, with the final aim to maximize the health of the population. All this would not be possible if assessment of a health technology was not supported by relevant, unbiased, valid and transparent evidence. The question is: What type of evidence is needed to conduct an HTA?

Two main types of evidence are required to perform a health technology assessment: 1) clinical effectiveness, which provides information on the clinical benefit and safety of health technologies and 2) cost-effectiveness, which helps to answer the question: “Is this health technology worth investing in compared to other things the health system could do with the same resources?”. In addition, the appraisal of health technologies should consider evidence on equity issues and financial sustainability. The former provides information on the potential differential benefit of a health technology across the population, whereas the latter inform policy makers on the financial sustainability of a health technology by estimating the impact on the healthcare budget.

Evidence on clinical effectiveness

The definition of clinical effectiveness depends on the type of health technology being appraised, but generally can be defined as the measure of effect on the course of the relevant disease/topic of interest. Evidence on treatment effect and safety of health technologies is commonly derived using experimental or observational study design. In experimental studies the investigator applies a treatment to a pre-defined group of patients and measures the effect, whereas in observational studies the investigator observes individuals without manipulation or intervention. The most common form of experimental study is the randomized controlled trial (RCT), which is considered the ‘gold standard’ for producing the most reliable evidence of relative treatment effect, for the controlled and randomized design allows to minimize potential external influences and prevents selection bias in the allocation of intervention.

A shortcoming of treatment effect measures coming from a single study design is the limited generalizability of results in populations others than the one studied. To address such limitation, systematic literature review (SLR) should be used to identify all relevant studies available, with the aim to maximize the sample population on which the estimate of clinical effectiveness is based, as well as to minimize study selection bias. The SLR should be conducted following a well defined protocol to enhance the quality and transparency of results. Evidence on RCTs must be identified by searches in recognized databases such as PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, SCOPUS etc., using well defined inclusion and exclusion criteria. The methods identified evidence should then be quality assessed and, when appropriate and feasible, pooled using a meta-analysis to generate more precise and reliable conclusions on treatment effect measures. Meta-analysis should be undertaken following explicit criteria and transparent/reproducible.

Evidence from non-RCT experimental and observational studies may be required when RCTs are not available or to supplement RCT data, for example to obtain estimates of treatment effect over longer time horizons or measures of particular outcomes that have not been included in available RCTs. In such cases when a SLR includes non-RCT studies, any potential bias associated with the non-RCT design of studies included should be reported and discussed.

When evidence on the treatment effect is missing, an RCT should be conducted following complying with standard RCT guidelines.

Evidence on cost-effectiveness

Health economic evaluations are a critical part of health technology appraisals. Decision-analytic models follow a systematic approach in bringing together evidence on clinical effectiveness, health-related quality of life (QoL) and costs associated with a health technology relative to another (or more) alternative(s), with the aim to provide information on whether estimated health improvements justify the costs, that is whether the technology is cost-effective. The reliability of the cost-effectiveness results, therefore, strongly depends on the quality of data used to populate the decision-analytic model. Further, expert judgment of clinicians may support in assessing the face validity and plausibility of the evidence and assumptions used in the cost-effectiveness model.

Major types of inputs used to populate model parameters are:

- Treatment effects and adverse events
- Utilities
- Resource use and costs
- Baseline risk of clinical events

Relative treatment effects and incidence of adverse events should be obtained from head-to-head RCTs, single or pooled as appropriate (see section on clinical effectiveness above). When head-to-head RCTs against the comparators of interest do not exist, evidence from an indirect treatment comparison (ITC) analyses may be used to derive relative treatment effect. A feasibility assessment should be performed prior to undertake an ITC analysis and any potential bias should be reported. Finally, in considering cost-effectiveness, measures on treatment effect over longer time horizon than RCTs are often required. Thus long-run observational studies and/or extrapolation methods may be used to simulate treatment effect over the desired time-horizon of the cost-effectiveness analysis.

Utilities data allow to incorporate the relative impact of a health technology on the QoL of patients. Both utility data, QoL in a given health situation, and disutility data, temporary decrements in QoL due to acute transitory events, should be considered in the economic evaluations, as appropriate. Utility data should be obtained from studies using European Quality of Life 5 Dimensions (EQ5D5L) tool and Thai value set should be used to generate mean utility scores until a QoL tariff for India becomes available (in development at the time of this writing). Potential sources of QoL evidence are RCTs, observational studies, databases/registries on health-related QoL, cost-effectiveness studies. A SLR may be undertaken to ensure all relevant QoL evidence is identified. If utility data are obtained from RCTs and are available per treatment arm, no further QoL decrements should be applied to treatment related adverse events via disutility data, as these have been captured in treatment specific utility values. If no studies reporting QoL for the topic of interest exists, primary HRQoL data collection may be considered as an option.

Cost data are important drivers of cost-effectiveness, as they quantify in monetary terms the effects of health technologies on the use of medical and non-medical resources.

Decision-analytic models should be populated with cost data from the societal perspective: direct medical and non-medical cost borne by patients and direct medical cost borne by the health care system. Productivity loss may be considered where appropriate, however it is not recommended for base-case analysis in India. A national costing database to estimate health care system's costs in India is currently being developed. Until database disclosure, direct costs borne by the health care system should be estimated using primary data collection based on a micro-costing approach. Before undertaking primary data collection on cost, the literature should be searched to identify any existing studies reporting Indian costs for the topic of interest. Data on patients out-of-pocket (OOP) expenses should be obtained from the NSSO 71th round, where available. As for health care system costs, if OOP data are not available from Official sources, data may be obtained from relevant studies in India identified through a review of existing literature or by primary data collection, when no other alternative is available.

Baseline risk of clinical event define disease progression which is not impacted by the appraised health technologies. Observational studies are usually best-suited to provide this type of evidence. A SLR should be conducted on the disease/topic of interest to identify all available relevant studies and avoid study selection bias. Included studies should be quality assessed and any potential bias reported and the expected impact on model results should be discussed.

Equity

To ensure equitable distribution of health, it is of key importance to estimate how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may be included in an HTA using a quantitative or qualitative approach. The Reference Case for India recommends to undertake Distributional Cost-Effectiveness Analysis (DECA) for analyzing equity considerations in economic evaluations. In addition, the Extended Cost-Effectiveness Analysis (ECEA) should be performed to measure the impact on financial protection or the avoidance of catastrophic health expenditure due to OOP, which is very relevant in the Indian context.²

Evidence on financial sustainability

A cost-effectiveness analysis provides information on whether a health technology is value for money given anything else that could be done instead. A cost-effectiveness threshold is used to objectively inform whether a technology should be considered cost-effective, by taking into account both affordability and societal preferences (willingness to pay). However, this is not telling us whether the use of such technology will be financially sustainable given current real budget of the health care system (at local, regional or national level) and/or patients. Such a question may be answered by undertaking a budget impact analysis, which estimate the financial consequences of increasing uptake of a health technology in a target disease population over the near future (3 to 5 years). In addition to cost data, as for cost-effectiveness analysis, populating budget-impact models requires epidemiological inputs, to define the target patient population, market shares, which define the current distribution of treatment alternatives, and expected uptake of the health technology being assessed.

Conclusion

A health technology assessment is just as good as the evidence that goes into it. As emphasized in the sections above, for HTA to assist decision makers in priority setting, evidence on clinical effectiveness, cost-effectiveness, equity and financial sustainability should be of highest standard, reproducible, comprehensive, but fit to purpose and based on transparent and validated sources.

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Recommended key readings

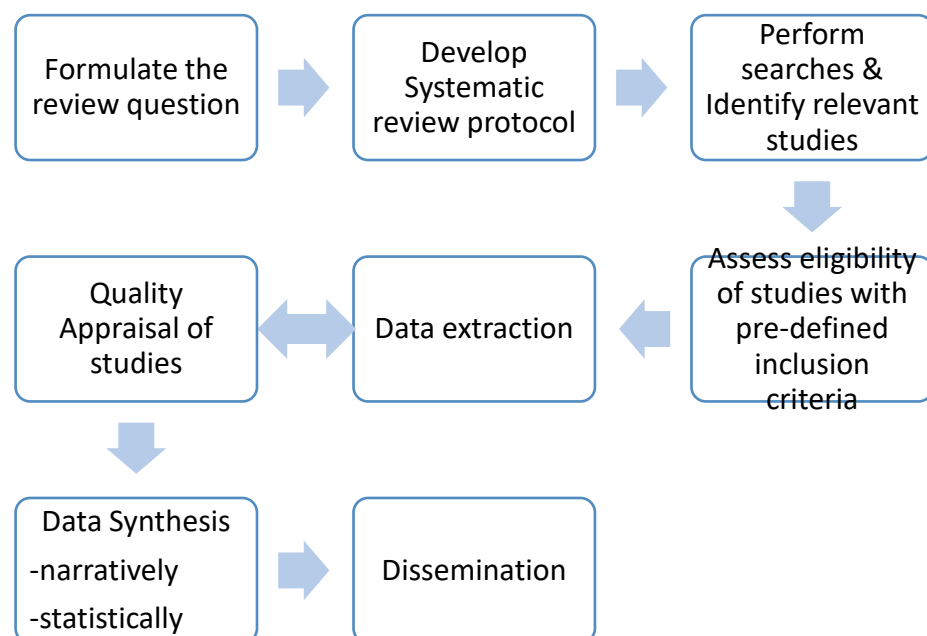
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Chapter 14:
Evidence Synthesis

Multiple sources exist for generating evidence for use while undertaking health technology assessments (HTAs). Unstructured reviews, expert opinion, systematic literature reviews and meta-analysis are examples of few of the sources, generally secondary methods, of generating this evidence. It is well-recognized that unstructured reviews and expert opinions may have inherent biases in them and henceforth should be used with caution while consolidating evidence for cost-effectiveness analysis or HTAs. Systematic reviews and meta-analysis are the preferred medium of evidence generation for efficacy or effectiveness of health technology as they diminish different types of bias and provide robust information to address the decision problem at hand. They have been considered to offer the highest quality of evidence for consolidating information on clinical effectiveness.

A systematic review is “a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review.”

A systematic review broadly involves a series of steps shown below:



Check a priori if any other systematic review on the same topic has been done and its timeframe. A systematic review can be done to generate new insights if not previously addressed or if required, it can update on the previous systematic review.

Main steps of the systematic review briefly are:

1. Define the purpose of systematic review.
2. Developing a review protocol and deciding in advance on the review question, inclusion (peer-reviewed articles, grey literature inclusion) and exclusion criteria, search strategy, methods and designs under study selection, data extraction and relevant software, tools for quality assessment and how to synthesize data; this helps in minimizing the risk of introducing bias into the review. A PICOS or PICO format can be used to guide on the review question and the literature searches.
 - Population: can be any condition, stage of disease, risk factors, emographics
 - Intervention: health technology or its type, health intervention, drugs (dose/frequency/regimen), diagnostic tests (mode/frequency), health policy
 - Comparator: depending upon research question, standard care or routine
 - Outcomes: morbidity, mortality, quality of life

Some studies also specify timing (in terms of duration of follow up) and setting (in terms of home care, primary care, inpatient, outpatient, community) in their evidence questions and then it becomes PICOTS.

3. Perform searches comprehensively and document all searches- Electronic searches, bibliographic and website searches are examples of the types of searches usually carried out. Use of Boolean operators (OR, AND, NOT) is recommended while doing electronic searches. The choice of databases for electronic searches depends on its accessibility, topic coverage and type of data covered.
4. Based on pre-defined inclusion and exclusion criteria, eligibility of studies should be assessed. The PRISMA flow diagram is generally preferred to account for included and

excluded studies. Duplicate publications are removed as appropriate. Listing of included studies is done and reasons of exclusion are also mentioned.

5. Data extraction on specific characteristics of the included studies in accordance with review question and protocol should be done. The information on PICO elements should be included.
6. Quality appraisal of evidence retrieved should be done with appropriate tool and documented. Some researchers do quality appraisal of included studies first and then extract data. However, any of the sequence can be followed appropriately.
7. Data synthesis involves the collation, combination and summary of findings of individual studies included as part of the systematic review. Pooling of findings can be done-statistically or narratively. A meta-analysis is a statistical analytical method that combines results from separate but similar studies to arrive at a single conclusion. In cases where undertaking meta-analysis is not appropriate (either clinically or methodologically diverse studies); a narrative summary of the findings of the systematic review can be given.

For undertaking meta-analysis of interventional studies, data on a standard outcome measure across the included studies is necessary. Results from individual studies with binary outcomes, for example, treated or not treated will report on effect measures in terms of odds ratio, risk ratio while those with continuous outcomes (blood glucose) will have means, difference in means and primary studies with survival data will report hazard ratios. On the contrary, in meta-analysis of diagnostic accuracy studies, sensitivity, specificity, likelihood ratios will be the primary outcome. Review manager (RevMan) is the commonly used software for undertaking meta-analysis of interventional studies. While for diagnostic accuracy meta-analysis, STATA, SAS, R are the suggested softwares by Cochrane Collaboration.

Common types of meta-analysis are:

- Meta-analysis of dichotomous outcomes-Four widely used methods including three fixed effects (Mantel-Haenszel, Peto and inverse variance) and one random effects (DerSimonian and Laird) are there and available in Review Manager. While only odds

ratios are pooled under Peto method, the rest of three methods mentioned previously can pool odds ratios, risk ratios and risk differences.

- Meta-analysis of continuous outcomes- Two commonly used methods in RevMan are the inverse-variance fixed effect and the inverse-variance random-effects method.
 - Meta-analysis of diagnostic accuracy studies- The Cochrane Collaboration recommends the use of two random-effects methods: the bivariate model, and the hierarchical summary ROC (HSROC) model. The former meta-analyses a summary estimate for sensitivity and specificity together. The latter models the parameters for the summary ROC curve.
8. Subsequently, the findings of systematic review and meta-analysis should be presented to suitable audience or stakeholders for dissemination and use in decision-making.

For undertaking model based economic evaluations, often published literature (for example randomized controlled trials, observational studies) is referred for finding relevant parameters to populate the decision model. Information from other sources, for example, registries in case of cancer or local jurisdiction data for prevalence rates may be sought. The key principle is to seek all the relevant evidence possible within resource constraints and reasonable limits. Most of economic evaluation models rely on probabilities and rates estimates to characterize the likelihood of a particular event/s within a pre-specified time period. Consider a simple example of a Markov model comparing treatment with no treatment for a disease and with three health states-well, diseased and death. The possible probabilities required in this case can be:

- Risk of progression of disease from well to diseased health state
- Probability of moving from well to diseased state
- Probability of being in well health state
- Probability of being in diseased health state
- Probability of moving from well/diseased health state to death

A probability by definition is the likelihood of a particular event over a given period of time and expressed on a scale from 0 to 1. On the contrary, a rate is “the instantaneous potential for an event at any point in time”. Rate can be from 0 to infinity.

$$\text{Probability/Risk} = \frac{\text{Number of events occurred in a time period}}{\text{Number of people followed for that time period}}$$

$$\text{Rate} = \frac{\text{Number of events occurred in a time period}}{\text{Total time period experienced by all subjects}}$$

It is important to note that rate and probability are related in a way that the magnitude of a probability and its variation over time is in turn governed by an underlying rate, given as:

$$R = - [\ln(1-p)]/t$$

Here, r is the rate (assumed constant over time), p is probability over the time period t with \ln as the natural log. As rate is an instantaneous potential, therefore expressed as events per patient per unit of time. Further re-arrangement of above equation, leads to expression of probability as a function of a rate (where the latter is again assumed constant over time):

$$P = 1 - \exp(-rt)$$

where \exp is the exponent

Often it is seen that the probabilities as required in the decision model are different from those available in the literature in terms of time period specified by the model. For example, probability of a side effect over the first month of a treatment or transition probabilities in a monthly cycle in a Markov model. Further, probabilities cannot be simply divided or multiplied if they exist in different timeframe in the literature. Henceforth, it is imperative to calculate the underlying rate (assumed constant over time) to adjust for the required time period and then to recalculate the probability for that time period.

Continuing with the previous example of a simpler Markov model (well-diseased-death health states), assume that probability of moving from well to diseased state over 1-year period is required for this model. Through published literature, we found only a 5-year probability for

this event estimated as 0.2. In this case, we need to first recover the underlying rate per patient year (assuming it is constant over time) as per expression for rate mentioned above

$$\text{Rate per patient-year} = -[\ln(1-0.2)]/5 = 0.04463$$

Further we need to translate this annual rate into annual probability as per expression for probability to arrive at:

$$1 \text{ year probability} = 1 - \exp(-0.04463) = 0.043648$$

A simple recalculation based on dividing 0.2 by 5 would have yielded 0.04 as the annual probability which would be inappropriate as it ignored the relation between rate and probability. Such errors may lead to incorrect estimates in the decision model.

Thus, to summarize it is important to identify relevant evidence, suitable to the decision context, to populate the decision model in an economic evaluation. A decision model may necessitate evidence on clinical parameters, underlying baseline risks of clinical events, prevalence or incidence data, resource use, costs, quality of life or accuracy of diagnostic tests. Further, this evidence should be recognized in an unbiased and transparent way, with central measures of clinical effectiveness estimated through systematic reviews and meta-analysis if appropriate.

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*Chapter 15:
Presenting and
Interpreting Results &
Recommendations for HTA*

Health technology assessment (HTA) provides the basis for evidence-based priority setting and policy decisions. The aim of HTA in India is to inform allocation of resources to health technologies which give the most value for money, with the aim to maximizing health, reducing Out of Pocket Expenditure (OOP), and minimizing inequality in healthcare services.

At the core of HTA stands the question: “Is this health technology worth investing in compared to other things the health system could do with the same resources?”. Health economic evaluations attempt to address this question by bringing together diverse sources of evidence within a single analytical framework, often referred to as decision analytic models. HTA In Reference Case recommends that the results of such models are assessed against a cost-effectiveness threshold (CET) equal to 1% of gross domestic product (GDP) in India³, which serves as an objective criteria to support decision-makers in deciding which health technologies are worth investing in.

In presenting and interpreting results of health economic evaluations, it should be recognized that all models are subject to variability and uncertainty in parameters’ estimates and this may have implication of on policy decisions. Such issues are important and should be carefully considered when conducting HTA of health technologies. Moreover, equity implications and financial sustainability should be explored alongside evidence on clinical effectiveness and cost-effectiveness to ensure health technologies are comprehensively appraised.

Presenting and Interpreting Results

A simple definition of health economic evaluations is the comparative analysis of alternative health interventions/technologies in terms of both their costs and health outcomes. Health outcomes may be represented as clinically defined states/events, such as diabetes/myocardial infraction, or health indices, i.e. life years (LYs) and quality-adjusted life years (QALYs). The former are defined as intermediate outcomes which can be used to estimate the incremental cost per disease/event avoided of a health technology vs alternatives. The latter are defined as final outcomes, which are projected via intermediate outcomes and are used to estimate the incremental cost per LYs or QALYs gained. These

results are also known as incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR), respectively.

The HTA In Reference Case stipulates that models present results using final health outcomes in terms of QALYs.³ As a first step in running the model, results should be estimated with the most likely (or best available) set of assumptions and input values, referred as base-case analysis, and should be presented as:

$$ICUR = \frac{Cost\ A - Cost\ B}{QALYs\ A - QALYs\ B}$$

Results of such joint comparisons can be visualized in a 2-dimensional plot, generally referred to as the “cost-effectiveness plane” (Figure 1).

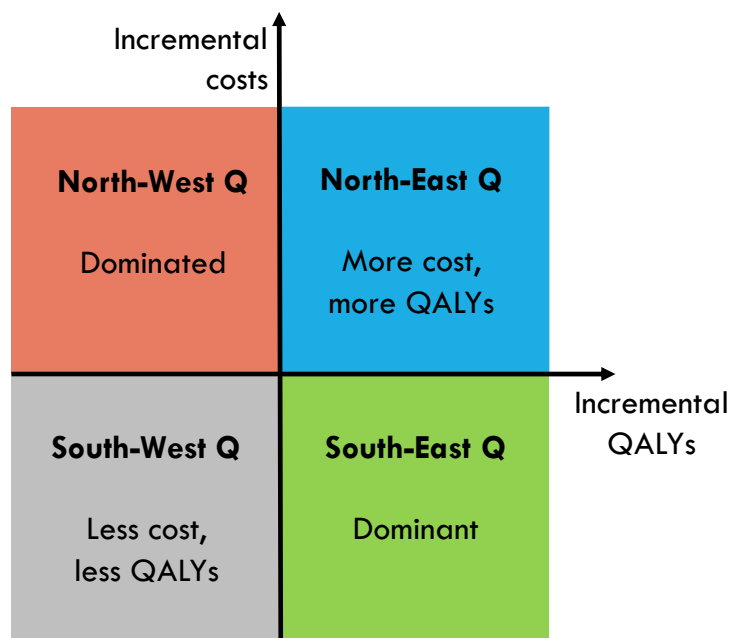


Figure 4 – Cost-effectiveness plane

In two instances, the interpretation of results is straightforward:

- Health technologies that are both cost-saving and elicit QALY gains over alternatives should always be considered acceptable (ICUR falls in the South-East quadrant of the cost-effectiveness plane). This situation is also referred to as the dominant position.

- Health technologies that come at higher costs and do worse in terms of health outcomes should never be considered acceptable (ICUR falls in the North-West quadrant), i.e. the dominated position.

Two instances requires judgements when interpreting results:

- Most health technologies assessed in a HTA topic of interest, will come at higher costs and will elicit QALY gains over alternatives (ICUR falls in the North-East quadrant). In such cases, ICURs are typically judged against the predefined CET, and the question to be answered is: do the additional benefits offset the additional costs?
- Even though it happens rarely in HTA context, a given health technology may be cost-saving and projects a certain loss in QALYs with respect to the alternative (ICUR falls in the South-West quadrant). In such cases, the interpretation of results is less straightforward and the question to be answered is: how much QALYs are we willing to sacrifice for a given saving in cost? A possibility to help interpretation of these results is to revert the comparison to assess against WTP threshold whether the alternative is cost-effective vs the health technology of interest.

In addition to base-case analysis, variability and uncertainty around parameters' estimates should be assessed and comprehensively described. One-way sensitivity analyses (OWSA) may be used to assess how variations in key model parameters impact base-case results. Model parameters should be varied within a predefined range and results can be illustrated in a Tornado diagram, which enables simultaneous visualization of multiple OWSA and ordering of the outputs in terms of the impact of parameters' variation on base-case results.

Uncertainty around model parameters is assessed in probabilistic sensitivity analysis (PSA). PSA tests the impact of second order uncertainty by random, simultaneous variation of parameters. PSA is performed by assigning probability distributions to model parameters and repeatedly sampling values from these distributions to estimate ICURs. Generally, 1,000 simulations are run, i.e. 1,000 sets of model inputs parameters, and for each simulation expected costs and QALYs are projected. The results of the PSA are visualized on a cost-effectiveness plane and represented with in terms of cost-effectiveness acceptability curve (CEAC). The former shows the distribution of joint incremental cost and QALYs under

uncertainty, thus indicating the proportion of simulations that are located in each quadrant of the cost-effectiveness plane. In the presence of large uncertainty, joint incremental cost and QALYs from each simulation will be scattered across the cost-effectiveness plane, whereas when PSA results are concentrated around base-case ICUR, it may be concluded that the model is robust. The CEAC provides information on the likelihood of being cost-effective at given acceptability thresholds.

Recommendations for HTA

The Technical Appraisal Committee (TAC) is an independent advisory body convened by DHR. Members are drawn from the Indian health and policy system, from both Central and State-level institutions. Membership is multi-representative from the academic, government, clinical, and non-government organization community. The TAC is engaged at the scoping stage to ensure that the HTA proposal is sound, at key stages of development to ensure that the analyses are being done to a high standard, and finally to appraise the final HTA and make recommendations from the outputs.

When making recommendations, the TAC bases its decisions on the clinical and cost-effectiveness evidence presented, any clinical implications that may require change of practice, equipment and skill availability across the country, and any ethical and equity considerations. Where cost-effectiveness results require some judgements, they should be assessed against the predefined WTP threshold to ensure objective appraisal of health technologies. In addition, probabilistic analysis should be used to assess the uncertainty around estimates of model parameters. Uncertainty should be comprehensively reported and should always be considered when interpreting model results and when such evidence is used to inform healthcare policy design.

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Chapter 16:
The HTAIn Reference Case-
A Recipe for India

Considering the increasing costs of healthcare interventions, diagnostics and devices, their formal assessment is imperative to inform cost-effective health policy decisions in India and prevent waste. Budget constraints, competing agendas between and among diseases and interventions, and lack of scientific evidence in decision making, justify a dire need for conducting economic evaluation in India. However, it is important that a standardized approach and consistent methodology is adopted while undertaking economic evaluations. Heterogeneity and lack of methodological appropriateness can lead to improper interpretation of the results and cast doubt on the credibility of the evaluations. It has been reported that the economic evaluations in India lack both consistency in methodology and quality. This is unsurprising given that there are no clear guidelines or reference case which can be adopted by the Indian researchers while undertaking economic evaluations. There is an urgent need to define and promulgate guidance for researchers on what methods to use while conducting an economic evaluation in the Indian setting. This standard set of methods, more specifically referred to as the *Reference Case*, will help in standardization of economic evaluations undertaken in India thus maximizing the health gains from limited resources

The HTAIn Reference Case provides a guide to how HTA analysis should be conducted and reported as part of the HTAIn program of work. This ensures that the way in which all analyses carried out are done in the same way, according to the same fundamental methods and principles. Reference case will enable HTAIn or other institutions and individuals wanting to use economic evaluation to inform their decisions to do so in full knowledge of its limitations and relevance to the decision problem at hand. Further, adherence to reference case would increase the quality, interpretability and transferability of future economic evaluations.

Principles of HTAIn Reference Case

There are a number of principles or key components that come together to form a reference case for economic evaluations for undertaking HTA. Each component is important and the decisions taken as to how to best address these will have important ramifications for the conduct and outcome of the HTA analyses in India.

1. Transparency

Transparency refers to the process of being open about all aspects of the HTA process. The most methodologically robust economic evaluation, constructed from the strongest evidence

available may not be trusted by the public, academic community, industry, and/or policymakers if the conduct and results are not reported clearly and transparently. Clear and transparent economic evaluations can also improve the transparency of the decision-making process. Further, transparency in reporting also allows enhanced usage or transferability of a part or whole of the economic evaluation results.

Recommendations for India: The HTA undertaken should be made available through a full HTA report, made available online. For this a comprehensive reporting template should be used to report the analysis in a clear and transparent way.

2. Comparator

Comparator is the most relevant alternative which is to be assessed against the new intervention. Identification of correct comparator is crucial as it ultimately drives the cost effectiveness ratio. Comparators may be chosen from current practice, best practice or no intervention at all.

Recommendations for India: It is recommended to use current practice in use as the comparator. This is a more accurate and realistic comparator in terms that the money would have ideally been invested here in absence of the intervention being evaluated. Comparators should be verified as reasonable by stakeholders and clinical expert advisers.

3. Perspective

Perspective refers to the viewpoint from which the analysis is conducted. The perspective used in an economic evaluation is extremely important as it defines what costs and effects are to be considered. Different perspectives can generate different conclusions, even in the same settings, thus resulting in inefficient resource allocation.

Recommendations for India: In the HTAIn reference case, a disaggregated societal perspective is recommended. This means that the analyst should present results based on both societal perspective as well as healthcare provider perspective. A disaggregated approach is justified on basis that in the Indian context we have a multi-payer system which makes economic evaluation process more diverse and complicated.

4. Source of evidence for effectiveness

The evidence on effectiveness is available from a variety of study designs. However all research designs are not equal as they vary in terms of risk of bias and confounding factors which influence the overall results.

Recommendations for India: The evidence on effectiveness should be taken from systematic review and meta-analysis of randomized controlled trials (RCTs) as it ranks highest in credibility of evidence. In case of non-availability of RCTs evidence from the next highest study design i.e. quasi-experimental studies, cohort studies, case control studies, case reports should be considered providing optimum justification.

5. Measuring costs

Costs reflect the resource use and unit costs/prices that are incurred (or anticipated in case of new interventions) when interventions are delivered in the health system. Cost is a highly important aspect to the cost effectiveness analyses and is most often the key driver as to whether an intervention is considered cost effective (or not).

Recommendations for India: All relevant costs should be identified and taken into consideration. The HTA In Reference case recommends including direct medical and non-medical costs borne by the patients (Out-of-pocket expenditure), direct medical costs borne by the health system in the analysis. Indirect costs/productivity losses should be omitted in base-case analysis. However, results including the indirect costs may be presented additionally as a separate section in scenarios where they are considered to be of enough relevance.

6. Measuring outcomes

The measure of health outcome refers to the impact on health, and should capture positive and negative effects on length of life and quality of life. It is important to use a measure of health outcome that is broad enough to capture all socially valued aspects of health and is applicable across investment types.

Recommendations for India: It is recommended to use Quality adjusted life years (QALY) as the measure of health outcome for India. Usage of QALY as a measure of health outcome is recommended because it is a generic measure accounting for both quality and quantity of life of the following reasons. Further, it will aid comparison with International HTA studies as majority of the countries use QALYs as measure of health outcome.

7. Time horizon

Time horizon is the specified duration of time over which the costs and outcomes of the decision problem i.e. the intervention and the comparator are considered.

Recommendation for India: The time horizon to be used while undertaking an economic evaluation should be long enough to capture all relevant costs and effects. A lifetime horizon is recommended to assess the impact on survival or other health outcomes as well as the costs incurred in the long run. Shorter time horizon may be used for analysis in cases where the decision problem may not have long term sequels example acute diseases. In general, the time horizon should be based on the natural course of the condition and the likely impact that the treatment will have on it. Time horizons should be verified as reasonable by stakeholders and clinical expert advisers.

8. Discounting

Discounting should be done to adjust future costs and health outcomes to its present value. Discounting reflects society's rate of time preference i.e. people value future costs as less significant than today's costs and today's benefits more significant than future benefits. Accordingly, costs or outcomes anticipated beyond one year's time should be discounted.

Recommendation for India: A standard discount rate of 3% for both costs and outcomes is recommended by the HTAI reference case. 3% is the most commonly used value in published economic evaluations undertaken in India and other jurisdictions. A common discount rate will ensure comparability and standardization across evaluations. In addition, undiscounted results should also be presented to show the impact of discounting. Sensitivity analysis by varying the discount rates from 0-5% should be undertaken to verify the robustness of the results of the analysis.

9. Heterogeneity

Cost effectiveness ratios are highly influenced by heterogeneity. Heterogeneity is different from uncertainty in terms that it is known and identifiable. Heterogeneity is a result of variable population characteristics. As interventions can have different impacts depending on population characteristics, there may be reason to suspect that an intervention is only cost effective within a certain sub-population and not the whole population. It is therefore important that the researcher identifies these heterogeneities and classifies the population into subgroups, followed by performing subgroup analysis.

Recommendation for India: The existence of any population heterogeneity should be examined through subgroup analysis as common practice by those conducting HTA. The subgroups identified should be verified as reasonable by stakeholders and clinical expert advisers

10. Uncertainty

Uncertainties in economic evaluation are pervasive as precise estimates for are often not available. However, in order to be accountable for the decisions, the decision makers must be aware of the magnitude of the uncertainty in the results. Uncertainties may be an outcome of different reasons like limitations of previous studies or different study settings.

Recommendation for India: In order to account for the uncertainties in the overall results of the economic evaluations it is important for the analyst to perform sensitivity analysis. All areas where there is a potential for uncertainty should be adequately captured. Probabilistic sensitivity analysis should be undertaken for all analysis to identify any areas where estimates are likely to impact the final outcomes.

11. Equity

The way in which resources available are allocated against competing priorities is crucial as it determines how much health is generated overall and who receives healthcare interventions and who all are left out. Economic evaluation and ICERs inform us about the costs and effects of a technology. However, for the sake of decision making it is important to know the ethical implications of the new technology. The role of economic evaluations should not be limited to maximize health but also to ensure equitable distribution of health. *Recommendations for India:* Equity should be included in the analysis either using a quantitative or qualitative approach or as an additional evaluative criterion or quantify trade-offs between equity and efficiency. It is recommended to use distributional cost effectiveness analysis (DCEA) for analysing the equity considerations in an economic evaluation.

Further Extended Cost Effectiveness Analysis (ECEA) should also be done which assesses the impact on financial protection or the avoidance of catastrophic health expenditure due to out-of-pocket payments, alongside costs and health effects of an intervention. This is particularly relevant in India, where the costs of healthcare can require the sale of assets and property among the poor populations, threatening livelihoods.

Conclusion

The HTAI reference case attempts to define a standard set of methods that should be followed while undertaking economic evaluations in India. It is important for the analysts to abide by the recommendations of the reference case so as to increase the quality, consistency and comparability of economic evaluations undertaken in future. However, in addition to these principles laid in the reference case the analysts should rationalize and report the choices made in every step during the conduct of the economic evaluation.

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Chapter 17:
Putting HTA into practice
in India: Example of Safety
Engineered Syringes

Globally, 16 billion injections are administered each year of which 95% are for curative care. India contributes to 25-30% global injection load. Around 63% of these injections are reportedly unsafe or deemed unnecessary. In 2008, Government of India (GoI) introduced auto-disable (AD) syringes for immunization, but till 2016 there was no prescription for use of safety engineered syringes (SES) in the therapeutic sector which account for bulk of injection use. Till 2017, use of disposable syringes for therapeutic care was being practiced with a potential of unsafe use both in terms of reuse by healthcare providers and causing needle stick injuries (NSI) to healthcare providers. Reuse and NSI both leads to poor health status of population. It is estimated that each year approximately 33% of new Hepatitis B viral (HBV) infections and 42% of Hepatitis C viral (HCV) infections (2 million new infections) are attributable to the unsafe medical injections in developing nations. Similarly, the unsafe injection practices accounts for 9% of new HIV cases in South Asia. Secondly, there is a risk of transmission of BBIs to healthcare professionals (HCPs) in case of adverse event of needle stick injuries (NSI).

Need for Evidence

Recently, some state governments – for instance Punjab state, have shown an interest in considering introduction of SES in therapeutic sector. An important mandate for the technical expert group (TEG), which has been set up to consider introduction of SES in Punjab state, is to provide evidence on its cost-effectiveness. Moreover, the National Pharmaceutical Pricing Authority (NPPA), has shown interest to India’s Health Technology Assessment Board to provide economic evidence on different forms of SES. As a result, a HTA was commissioned and assigned to ‘HTA Resource Hub’ at Postgraduate Institute of Medical Education and Research, Chandigarh, India. Globally, World Health Organization (WHO) is supporting the injection safety campaign and hence, its India country office funded this HTA study. This HTA was done to assess the cost-effectiveness of Safety Engineered Syringes (SES) for therapeutic use in India against a counterfactual scenario of use of exiting use of disposable syringes. Three SES were evaluated – reuse prevention syringe (RUP), sharp injury prevention (SIP) syringe, and those with features of both RUP and SIP.

Study Findings

The introduction of RUP, SIP and RUP+SIP syringes in India will incur an incremental cost of INR 43,064, INR 7,219,687 and INR 209,398 per QALY gained, respectively. A total of 96,296 HBV, 44,082 HCV and 5632 HIV cases will be averted due to RUP in 20 years. Similarly, use of SIP and RUP+SIP will avert 2869 HBV, 3111 HCV and 16 HIV; and 99,166 HBV, 47,193 HCV and 5648 HIV cases, respectively. There is a 93% probability for RUP to be cost effective at a willing to pay threshold of gross domestic product (GDP) of India. While SIP is not cost-effective, there is only 23% probability for RUP+SIP to be cost-effective at a willing to pay threshold of 1-time GDP per capita. RUP syringe will become cost saving at a unit price of INR 1.9. The SIP and RUP+SIP syringes are cost-effective only at a unit price less than INR 1.8 and INR 5.9, respectively.

Study findings suggest only RUP is cost-effective in Indian context. SIP and RUP+SIP are not cost-effectiveness at current unit prices. Efforts should be made to bring down the prices of SES to improve its cost-effectiveness.

Putting HTA into Practice

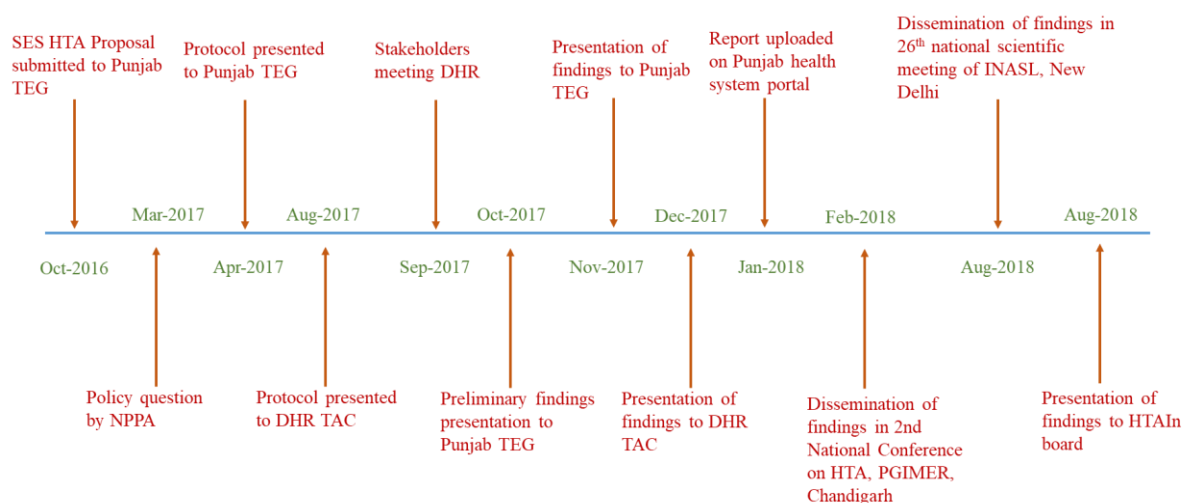


Figure 1: Project timelines of safety engineered syringes HTA study.

(*SES= Safety engineered syringes HTA= Health technology assessment, TEG= Technical expert group, NPPA= National Pharmaceutical Pricing Authority of India, TAC= Technical

appraisal committee, INASL= Indian National Association for Study of Liver, HTAI= Health Technology Assessment of India)

Figure 1 depicts the timelines of different activities done under HTA study conducted for SES. As a mandate, the systematic process set by the HTAI board for any HTA study done in India was followed for this HTA study too. As a first step, in October 2016, the HTA study proposal was submitted to the Punjab TEG. The study protocol was presented for approval in Punjab TEG and HTAI, technical appraisal committee (TAC) on April, 2017 and August, 2017, respectively. TAC constituted at the central level under HTAI has a key role of prioritizing the topics and ensure the quality of HTA studies conducted in India and therefore, approval was sought from the same for wider use of policy evidence. In September 2017, a stakeholders meeting was also organised by HTAI secretariat to seek their inputs. Findings of the study were presented to Punjab TEG and HTAI TAC during November, 2017 and December, 2017, respectively. Suggestions from both the groups were incorporated in the final study report. Dissemination of findings was done at couple of forums i.e. “2nd National Conference on Health Technology Assessment” held on 24th-25th February, 2018 at School of Public Health, PGIMER, Chandigarh and “26th National Scientific Meeting of Indian National Association for the Study of Liver (INASL), New Delhi.” held on August, 2018. Lastly, the study findings were presented to HTAI board members which is comprised of experts from public, private, academic and civil society groups for final approval and recommendation through Ministry of Health and Family Welfare.

As of result of economic evidence generated through this HTA study, several policy initiatives were taken pertaining to use of SES in therapeutic sector in India. In 2017, Punjab state piloted use of RUP syringes in therapeutic sector in 2 districts. On 28th July, 2018 (i.e. World Hepatitis day), State government of Andhra Pradesh passed an order to use auto-disable (AD) syringes in therapeutic sector. Lastly, on 28th July, 2018 (World Hepatitis day), country target of India was set i.e. to achieve 100% SES use for healthcare by 2020.

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Chapter 18:
Health Technology
Assessment in India:
Reflection and Future
Roadmap

India has taken a big leap towards evidence-based policy making by establishing the Health Technology Assessment Board (HTAB) – an institutional structure created in the Department of Health Research (DHR) to support credible evidence for supporting policy decisions. The strategic position of DHR in terms of functional linkage to the Ministry of Health and Family Welfare (MOHFW) as well as National Institute for Transforming India (NITI) – the strategic policy making arm of Central Government, implies that all factors leading research to policy making are favourably aligned. The Secretariat of the HTAB is suitably guided in its functions by the Technical Appraisal Committee (TAC) in key decisions relating to selection of topics for HTA, appraising the protocol as well as findings of the HTA studies and providing overall stewardship to the Secretariat.

Having taken this initial positive direction it is important to outline the future roadmap for HTAB so that India can reap rich dividends of these initial steps as well as ensure that the outcomes are aligned to policy needs and support research environment outside the HTA domain as well. This chapter outlines some of these recommendations. These are broadly classified into the following 3 domains – building capacity, supporting HTA research, ensuring the transfer of research to policy.

The first and the foremost challenge for the HTA is to build a community of credible HTA researchers. The Secretariat at the DHR is taking steps in this direction. A series of capacity building workshops have been initiated to train the participants from technical partners in various aspects of undertaking an HTA. These include developing the research question, synthesizing evidence through systematic reviews and meta-analysis, costing, developing decision models and interpreting evidence. While 3 workshops have already been held at Thiruvananthapuram, Chandigarh and New Delhi, 3 more are likely to be held in the next few months. The Secretariat has also created regional resource hubs to develop local capacity and expertise to support State-specific needs in these regions. It will be important to retain the trained manpower in each of these Technical Partner institutions and Regional Resource Hubs.

The second step which would be important to consider is to develop the data and systems such that it facilitates undertaking HTA studies robustly. An economic evaluation is a comparative assessment of two interventions in terms of its costs and consequences. A review of current evidence highlights two areas where gaps exist – assessment of cost of

health care services, and determining Indian quality of life (QOL) tariff values for health states. These are essential requirements for HTA studies. Majority of the countries which have established HTA systems alongside created databases of cost for various health care services as well as country specific tariff values for QOL of different health states. Once again, the Secretariat of HTA India has invested in both these areas. A nationally representative study to estimate cost of various services and procedures, in both public and private sector, is underway in 13 Indian states. In addition, the Regional Resource Centre at PGI Chandigarh in collaboration with the International Decision Support Initiative (iDSI) has collated the unit level data of earlier costing studies undertaken in 6 Indian states to develop a health system cost database which could be made publicly accessible for researchers and program managers. The ongoing DHR supported study on cost of health care services will further augment and improve the estimates of the cost database.

In addition to the costing study, another large nationally representative study to develop Indian quality of life tariff values for different health states as per the EuroQol's EQ5D5L too is being planned to be undertaken in 6 states of India. These states have been chosen in order to represent the heterogeneity within India in terms of socio-economic, cultural, health status, geographical location. This study holds promise of not only generating a value set, but also trying to answer several questions around some of the key methodological debates around valuation of health consequences in HTA studies.

Besides developing robust data systems for HTA studies, conduct of the analysis also needs to be standardized to ensure that the quality of the studies can be relied upon for taking important policy decisions. A previous systematic review reported heterogeneity in methods for economic evaluations undertaken in India. In this regard, besides the building capacity of researchers, there is a need to standardize the methods used by different HTA researchers so that evidence across studies can be compared at face value. A reference case for undertaking HTA in India has been developed along with a HTA manual which details all the steps and processes to be followed for an HTA study.

In order to make HTA study comprehensive, it will be useful to incorporate aspects of evaluation, beyond efficiency. These include assessment of the impact of interventions and programs on extent to which it affects equity in health outcomes and care utilization, as well

as financial risk protection. These aspects would be quite relevant in order to make HTA contribute to the broad objectives of universal health coverage policies.

An important indicator for success of any research initiative is the impact which it has on policy and program development. Accordingly, the third aspect for future involves enhancing uptake of HTA research for policy. The HTA Secretariat has established liaison with the MOHFW, NITI Aayog, National Health Systems Resource Centre (NHSRC), insurance agencies of various Central and State funded insurance schemes etc. An important aspect which would be quite critical will be the extent to which HTAB contributes to the determination of benefit package as well as other allocation decisions of India's recently announced health insurance scheme – *Pradhan Mantri Jan Aarogya Yojana* (PM-JAY). Secondly, while several of the topics which are being evaluated by the HTAB relate to medical devices, public health programs as well as platforms of care, it will be very important to evaluate the pharmaco-economics of drugs. This is also important in view of the well-recognized fact, that medicines constitute the single largest contributor to out-patient care and significant proportion of inpatient care in India. Hence, the Secretariat should reach out to and develop linkage with the Central Drug Standards Control Organization (CDSCO), as well as National Pharmaceutical Pricing Authority (NPPA). Similarly, since a lot of the drug procurement in India happens at the state level through drug procurement corporations, which involves price negotiations at that level, it is important to for Regional Resource Centres as well as the HTA Secretariat to foster a partnership with these agencies and contribute to their decision-making through generation of credible evidence. Another critical long-pending area which is being currently spearheaded by the Secretariat includes development of standard treatment guidelines (STGs). While previous attempts at developing STGs have clearly limited itself to evidence around clinical effectiveness, it will be pertinent to generate evidence on cost-effectiveness and use it for developing these STGs.

The final aspect to address for future will be how decisions on priority setting are taken. While the HTA Secretariat has taken steps for ensuring greater stakeholder participation as well as dissemination of evidence, besides managing conflicts of interest, it will be critical to continue the same and further strengthen it. An important aspect of decision making using economic evidence is to define whether an intervention, given the economic evidence, is cost-effective or not. This implies setting some threshold for judging the cost-

effectiveness of interventions. So far, while some discussions have taken place, the HTAB has not been explicit about this issue. However, the future of HTA in India calls for developing objective methods and explicit value systems to enable the policy makers on defining a threshold for making decisions. In the absence of a threshold, the arbitrariness of decision making, despite generation of evidence can continue to limit the extent to which HTA can benefit policy making.

The journey of HTA in India has so far enjoyed the support of the political leadership, policy makers as well as researcher community. However, ensuring that it is maintained and rather enhanced, would require an impact assessment of the decisions which were shaped through HTA evidence. Such an evidence in terms of impact of HTA on cost savings for health system, gain in health outcomes, improvement in distributional effects across population sub-groups, and higher financial risk protection will be paramount for future advocacy for HTA in India.

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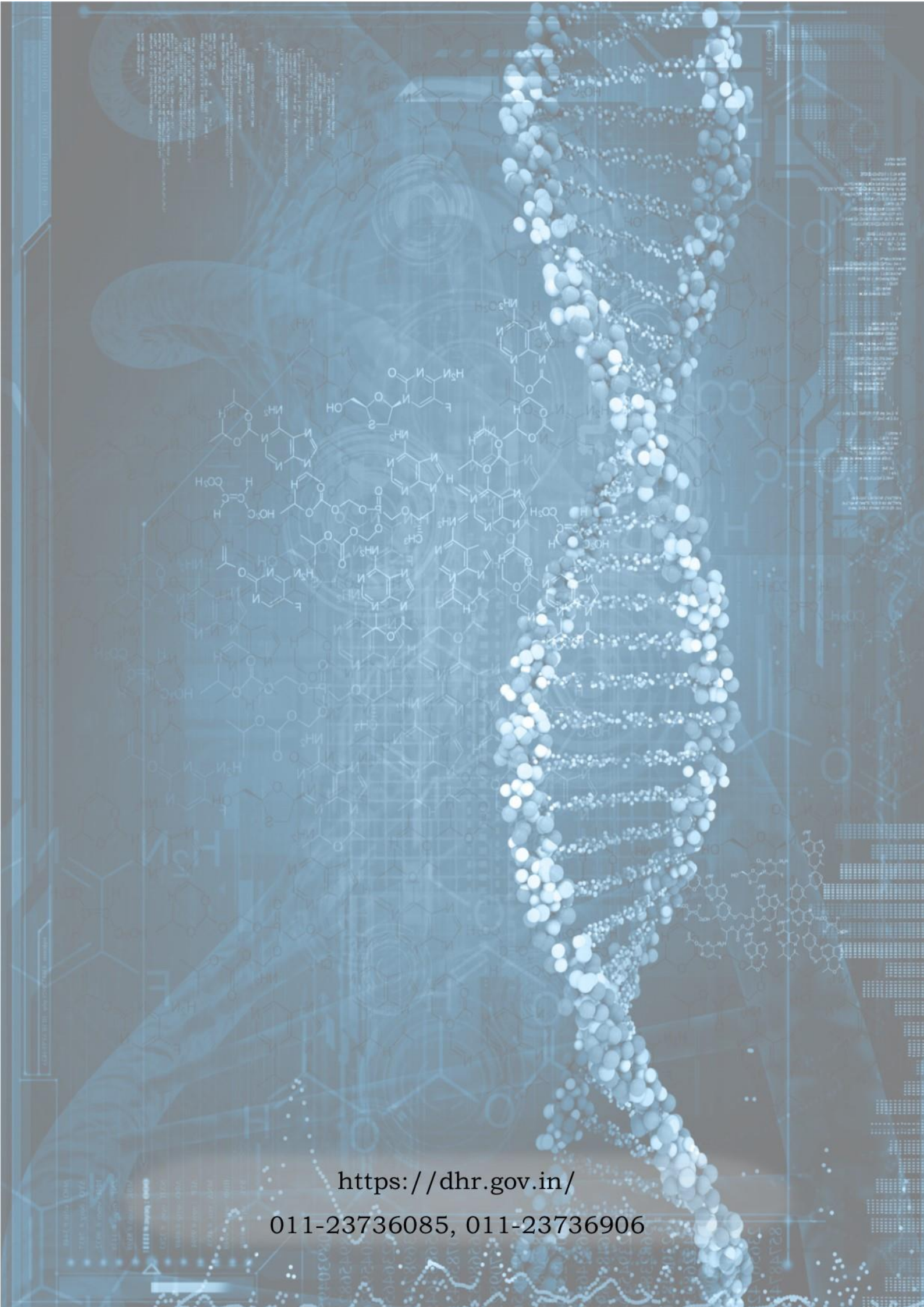
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