Development of the Indian Reference Case for undertaking economic evaluation for health technology assessment

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Summary

Background Health technology assessment (HTA) is globally recognised as an important tool to guide evidence-based decision-making. However, heterogeneity in methods limits the use of any such evidence. The current research was undertaken to develop a set of standards for conduct of economic evaluations for HTA in India, referred to as the Indian Reference Case.

Methods Development of the reference case comprised of a four-step process: (i) review of existing international HTA guidelines; (ii) systematic review of economic evaluations for three countries to assess adherence with pre-existing country-specific HTA guidelines; (iii) empirical analysis to assess the impact of alternate assumptions for key principles of economic evaluation on the results of cost-effectiveness analysis; (iv) stakeholder consultations to assess appropriateness of the recommendations. Based on the inferences drawn from the first three processes, a preliminary draft of the reference case was developed, which was finalised based on stakeholder consultations.

Findings The Indian Reference Case provides twelve recommendations on eleven key principles of economic evaluation: decision problem, comparator, perspective, source of effectiveness evidence, measure of costs, health outcomes, time-horizon, discounting, heterogeneity, uncertainty analysis and equity analysis, and for presentation of results. The recommendations are user-friendly and have scope to allow for context-specific flexibility.

Interpretation The Indian Reference Case is expected to provide guidance in planning, conducting, and reporting of economic evaluations. It is anticipated that adherence to the Reference Case would increase the quality and policy utilisation of future evaluations. However, with advancement in the field of health economics efforts aimed at refining the Indian Reference Case would be needed.

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Keywords: Health technology assessment; Economic evaluation; Guidelines; Reference case

Introduction

Application of health technology assessment (HTA) is a critical step in enhancing the efficiency of limited healthcare resources.[1] It is increasingly being used to support decisions for financing new healthcare interventions and programs, streamlining reimbursement procedures, efficient pricing and procurement, and rationalizing health benefit packages.[2] Quality and standardisation across methods have been recognised as important predictors of the utilisation of HTA evidence for policy.[3–5] Consequently, a need to develop country-specific guidelines/reference case to standardize the conduct of HTA has been felt globally.[6] While most developed countries have established their own guidelines for conduct of HTA, the developing countries either do not have specific HTA guidelines or are yet to introduce HTA altogether.[7,8] It is apprehended that lack of standardisation in methodological approach can result in misinterpretation of the findings of HTA studies and cast doubts on its credibility.

In India, the Health Technology Assessment body, referred to as the Health Technology Assessment in India (HTAIn), was institutionalised in 2017 under the Department of Health Research of the Ministry of Health and Family Welfare.[9] Since its inception, the HTAIn has invested in building capacity of researchers

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Research in context

Evidence before this study

We searched two web repositories namely International Society for Pharmacoeconomic and Outcomes Research (ISPOR) and Guide to Economic Analysis and Research (GEAR). The repositories provide the most comprehensive and up to date information on economic evaluation guidelines, from primary online searches in Medline and Google Scholar. A total of 47 guidelines were identified until August 2020. Only two guidelines were available for Southeast Asian Region countries - Indonesia and Thailand. No guideline was found for India in the review. In addition, we also searched the websites of Ministry of Health and Family Welfare (MoHFW), India, and Health Technology Assessment in India (HTAIn), but no guidelines were available to guide the conduct of economic evaluations in the Indian context. Furthermore, we participated in the consultation meetings of Technical Appraisal Committee and Health Economics Working Group held at the HTAIn in India, where the need for standardising methods for economic evaluation in India was highlighted.

Added value of this study

We developed a standardised set of guidelines for conducting economic evaluation in India referred to as the Indian Reference Case. It provides twelve recommendations, for eleven key principles of economic evaluation, and for presentation of results. The recommendations made were based on review of international guidelines, empirical assessment of adherence and impact of alternate methodological assumptions on results of economic evaluation, in addition to expert consultations. For each principle, the key recommendations are supplemented with justification considering other available options, as well as elaborate guidance for conduct in form of data collection tools and recommendations for types of data to be used and its sources. This is the first guideline of its kind, developed in view of Indian health system financing and functioning dynamics.

Implications of all the available evidence

It is anticipated that adherence to the Indian Reference Case would produce high quality economic evidence, with greater comparability across diseases and interventions. This in turn is expected to increase the utility of economic evidence in resource allocation decision-making. Further, the Reference Case will also allow policymakers to compare all competing evidence using a common approach.

in the HTA domain. An online course, which provides further training, has also been developed.[10] Furthermore, data and information systems are being strengthened to support conduct of HTA studies, such as the National Health System Cost Database, National Cancer Database for cost and quality of life and the EuroQol-5-Dimensions (EQ-5D) value set.[11–13] In addition, guidance documents such as the HTAIn process manual, the handbook for health system costing, and budget impact analysis (BIA) guidelines have also been developed.[14–16] However, as the country progresses in its HTA journey, development of an Indian Reference Case remains a crucial milestone to be achieved.

Prior to the establishment of HTAIn, the analysts relied on international documents such as the WHO guide to cost-effectiveness analysis.[17] However, the WHO guide follows a generalised cost-effectiveness approach against traditional CEA which uses an incremental analysis approach. Furthermore, the WHO guide provides generic guidance with flexible open-ended recommendations that are not context specific. A systematic review by Prinja and colleagues highlighted variations in key methodological components and heterogeneity in reporting across economic evaluations undertaken in India.[18] Analysts used different study perspectives when undertaking an economic evaluation: societal (38%), payer (48%); different time horizons (short [38%], medium [27%] and lifetime [17%]); and different outcome measures (quality-adjusted life years (QALY) [29%], disability-adjusted life years (DALY) [9%] and clinical outcomes [20%]). These differences in the methodological approach limits comparison of economic evaluations and may result in arbitrary differences in incremental cost-effectiveness ratios (ICERs) arising because of variation in methodology. Incorrect ICERs can result in incorrect resource allocation decisions where a cost-ineffective technology may be reimbursed or vice-versa. In addition, lack of methodological standardisation can also result in poor generalisability and limit the transferability of the results of economic evaluations.[19]

The Bill & Melinda Gates foundation (BMGF) supported the development of a reference case through experts from international decision support initiative (iDSI), to guide the conduct of economic evaluations in low-income and middle-income countries (LMICs). The first version of the reference case was published in 2014 as Gates reference case,[20] which was renamed as the iDSI reference case in 2016.[6] International guidelines such as the iDSI reference case may be relevant in the Indian context. However, the recommendations made by the iDSI reference case are flexible in nature and lack detailed technical specifications making it difficult to use for those having little experience. Furthermore, the iDSI reference case recommends contextualisation of the recommendations and itself acts a generic framework to guide country-specific reference case generation. It is based on the premise that while the core principles of economic evaluation remain same in all contexts, the recommendations on methodological

aspects such as economic perspective, health outcome measure, and methods to measure utilities, should be contextually tailored for each country.

The recommendations made by the international reference cases or country-specific guidelines on specific domains of economic evaluation such as study perspective and type of costs, health outcome measure, may not be appropriate in the Indian context owing to contextual differences. The healthcare financing framework in India is very different from the developed countries. Many high-income countries such as USA and UK have a single payer system with the government being the largest purchaser of healthcare services.[21,22] On the other hand, India has a multi-payer system, with high out-of-pocket (OOP) expenditure, and limited insurance coverage.[23,24] These distinct health financing features have important ramifications that necessitate using a broader study perspective such as societal, which may not be recommended in the existing reference cases such as the National Institute for Health and Care Excellence (NICE) reference case and a majority of country-specific guidelines.[25,26]

Similar is the case for the recommendation on health outcome measure. While the iDSI reference case recommends the use of either DALY or QALY as the primary measure of health outcome,[6] an increasing number of international economic evaluations report results in terms of cost per QALY gained.[27] With the development of the Indian EQ-5D value set, the use of QALYs may be a more appropriate choice as the measure of health outcome.[13] Moreover, with rising burden of non-communicable diseases (NCDs)[28] and the need to evaluate interventions to address NCDs, it may be appropriate to use QALYs to detect small differences in utility between different health states. The Indian Reference Case is thus needed to address such peculiarities which are specific to India.

Most of the existing country-specific guidelines are targeted at pharmacoeconomic evaluations.[29] However, in the Indian context, several of the recently commissioned HTA studies have evaluated either programmatic strategies or medical technologies.[30] As a result, it is important that the guidelines for India provide recommendations beyond evaluation of pharmaceuticals. Also, the capacity for undertaking HTA in the country is still in early stages of development. Hence, it is important for the guidelines to extend beyond mere recommendations and provide elaborate guidance for conduct in the form of data collection tools and recommendations for types of data to be used and its sources. Without such considerations it is likely that the recommendations may not be feasible to adhere–a problem noted by a recent systematic review evaluating adherence to country-specific guidelines.[31]

With an aim to create a set of standards for conduct of economic evaluations for HTA in India, which are robust as well as user-friendly, and are applicable for a diverse disease and intervention profile, we undertook this effort to develop the Indian Reference Case. The aim was to provide clear-cut recommendations with a scope to allow for problem-specific flexibility. The current article aims to describe the development process and the recommendations made in the Indian Reference Case.

Methods

To develop the Indian Reference Case a four-step process was followed: (i) review of existing international health economic evaluation guidelines[32]; (ii) systematic review of economic evaluations undertaken in three countries to assess adherence with pre-existing country-specific HTA guidelines[31]; (iii) empirical analysis to assess the impact of alternate structural assumptions for key principles of economic evaluation on the results of cost-effectiveness analysis and its interpretation; (iv) stakeholder consultations to assess appropriateness of the recommendations. The initial two steps were used to inform the content and the structure of the Indian Reference Case, while the latter two steps provided guidance on the recommendations for individual principles of economic evaluation. Fig. 1 provides a summary of development process of the Indian Reference Case.

Review of international guidelines

The key objective of the literature review was to identify existing guidelines/reference cases developed for conduct of economic evaluations as part of HTA or otherwise. It was identified that broadly three reference cases exist–the U.S. Panel Reference Case (first and second version),[33,34] NICE reference case[26] and the iDSI reference case.[6] Furthermore, we identified that individual countries have developed guidelines for pharmacoeconomic or economic evaluation serving similar objectives. A comparative analysis of 31 guidelines was undertaken to summarize the key recommendations made in these guidelines which is published elsewhere.[32] This review assisted in defining the scope of the Indian Reference Case and creating a preliminary structure with identification of major components that should be included. The review concluded that the iDSI reference case and majority of the international guidelines provided recommendations on ten principles of economic evaluation—decision problem, comparator, perspective, source of effectiveness evidence, measure of costs, measure of health outcomes, time-horizon, discounting, heterogeneity, and uncertainty analysis and on presentation of results.[6,29] Additionally, recent guidelines of countries with advanced HTA systems such as Canada, Australia, Ireland, Spain, Thailand, as well as the iDSI reference case also provide recommendations for equity analysis. Hence, the preliminary structure of the reference case comprised of twelve recommendations, for 11

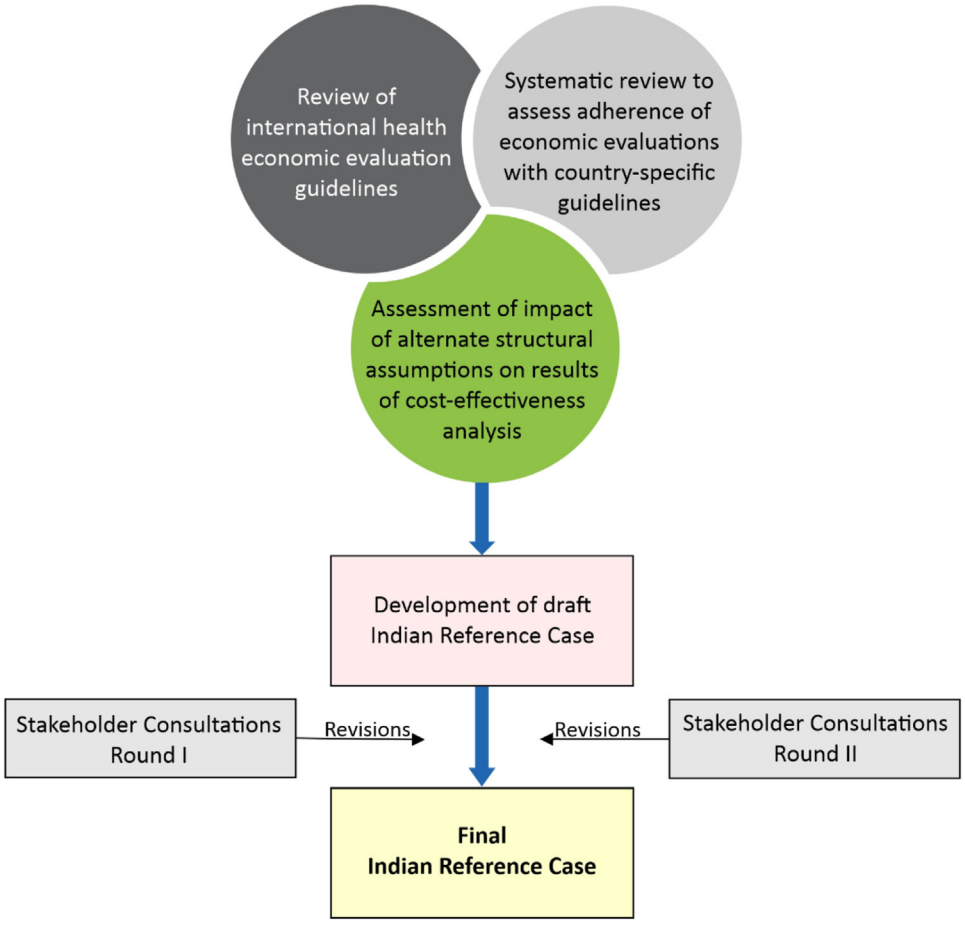

Fig. 1: **Development process of the Indian Reference Case for undertaking economic evaluations as part of health technology assessment.**

principles of economic evaluation and for presentation of results (Supplementary Table S1).

Systematic review to assess adherence of published economic evaluations to country-specific HTA guidelines

While, the review of international guidelines, reflected upon the methodological approaches being recommended globally, the implementation practices with respect to these recommendations were not clear. In this regard, a systematic review to assess adherence of published economic evaluations to the country-specific guidelines in context of Canada, South Africa and Egypt was undertaken.[31] The findings from the systematic review highlighted that multiple contextual factors affected adherence to country-specific guidelines. In addition, individual principles showing poor adherence were also identified (Supplementary material). These caveats were noted and were made use of while suggesting recommendations for the Indian Reference Case.

Impact of alternate structural assumptions on results and interpretation of cost-effectiveness analysis (CEA)

A series of empirical analyses were conducted to assess the impact of alternate structural assumptions for four key principles of economic evaluations (study perspective, time horizon, discount rate, measure of health outcome) on results of CEA and its interpretation. Three previously published Indian economic evaluations were selected as case studies for the empirical analysis.[35–37] It was observed that altering the structural assumptions especially the study perspective and time horizon resulted in a significant change in the ICERs which can have a potential impact on resource allocation decision-making (Supplementary material). The conclusions provided strong argument in favour of providing clear

recommendations for key principles of the Indian Reference Case.

Stakeholder consultations

Based on the inferences drawn from the above processes, the first draft of the Indian Reference Case was developed. The draft version constituted of three parts: (1) a description of individual principles of economic evaluation; (2) a summary of recommendations for these principles globally, and (3) the suggested recommendations for India and the justifications for the same.

The draft reference case was presented to a multidisciplinary group of nine experts comprising of a health economist (n = 1), a policy-maker (n = 1), basic scientists (n = 3), public health professionals (n = 2), and clinicians (n = 2). One of the stakeholders consulted was also a specialist about ethics. In addition, six of them were also directly involved in undertaking HTA studies for India's HTA agency. The experts were either members of the HTAIn technical appraisal committee (TAC), or HTAIn technical partners, or HTAIn regional resource centres, or HTAIn secretariat. All selected expert members had direct experience in undertaking economic evaluations and thus were able to provide constructive feedback on the components of the reference case.

The draft version of the reference case was shared with the experts over email for review, which was followed by virtual in-depth interviews. The overall objective of the interviews was to discuss recommendations on each of the guiding principles of the reference case, as well as to identify aspects needing greater detailing. The expert group largely agreed on the overall structure of the reference case. For nine out of twelve recommendations there was a positive consensus (>80%) among the experts and hence, these were directly included in the final reference case. For the remaining three principles (study comparator, evidence on effectiveness and measure of health outcome), the recommendations were amended building on the stakeholders' feedback. In addition, areas of economic evaluation design and conduct—which needed additional guidance and refinement for decision problems—were also identified and revised (Supplementary Table S1). Furthermore, the experts were asked if any principle needs to be excluded or added. It was concluded based on the consultations that separate documents should be prepared on three important aspects including modelling, budget impact analysis (BIA) and cost-effectiveness thresholds (CET), in near future (Supplementary Table S1). In this context, the BIA guidelines for India have already been published.[16] Similarly, the important aspect of modelling was included in the HTA Quality Appraisal Checklist (HTA-QAC).[38] Finally, the estimation of CET is ongoing and population level data is being collected.[39] The revised draft was again presented to the expert group following which the Indian Reference Case was finalised, Fig. 2.

Ethics approval

The study was approved by the Institutional Ethics Committee, Postgraduate Institute of Medical Education and Research, Chandigarh with the reference number INT/IEC/2020/SP2-1598. The study did not involve any patient level data collection.

Results

Recommendations of the Indian Reference Case

(1) Decision problem

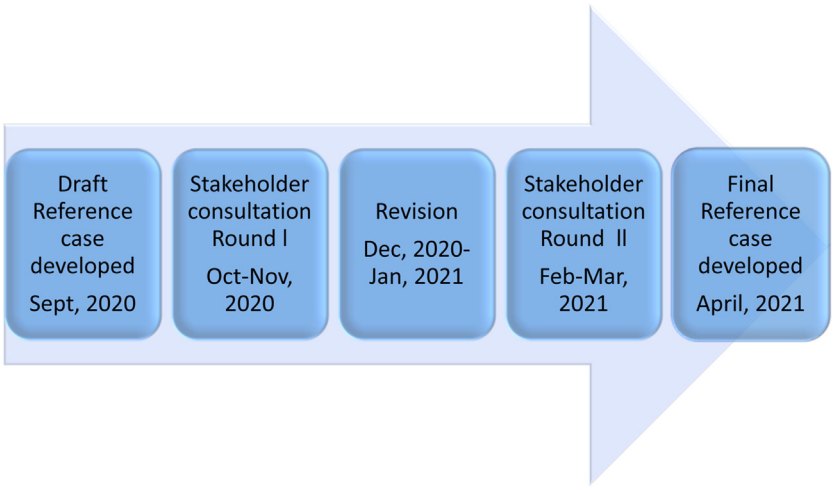

Fig. 2: **Stakeholder consultation process and timelines.**

The decision problem is a brief description of the research question intended to be answered by the economic evaluation being undertaken by the analyst. The decision problem sets up a rationale for undertaking the economic evaluation and provides details with respect to the epidemiological and clinical aspects of the disease, standard treatment options available and the related health outcomes. Many times, the PICO (Population, Intervention, Comparator and Outcome) format is used to describe the decision problem.

Recommendation: The decision problem should be stated clearly in terms of six questions who, does what, to whom, where, when, and how often. The rationale behind the study, the policy questions to be answered should be mentioned. Comprehensive details regarding the nature of the disease/condition under study, intervention and the comparator(s), the study setting, and details of the target population (age, gender, socioeconomic characteristics and other disease specific details) should be provided. Further, the researcher should identify any population subgroups for which the health effects or the costs are likely to be different from the general population under consideration. The details of relevant subgroups should also be provided.

(2) Comparator

The most relevant alternative (drug/therapy/technology) that will be assessed against the new intervention under consideration is referred to as the comparator. It is essential to identify an appropriate comparator as it ultimately drives the cost-effectiveness ratio. In simpler terms, it can be stated that any alternative will look good if it is compared to something that is sufficiently bad. A wide range of comparators have been recommended by existing guidelines. These range from most used alternative to most likely to be replaced alternative or the most effective alternative (best practice) or the cheapest alternative, etc.[32]

Recommendation: The Indian Reference case recommends current practice in use to be considered as the comparator. The current practice may be recognised as the one mentioned in the standard treatment guidelines or the most widely used therapy. In certain scenarios it is possible that there is more than one alternative which is routinely used. Furthermore, each organisation providing care may have a different health benefit package (HBP), which may comprise of different services and hence the inclusion of a new intervention may be compared against an intervention which is already a part of the HBP, or it may be a completely standalone new intervention. For instance, in the case of Pradhan Mantri Jan Arogya Yojana (PM-JAY), payer organisation is the National Health Authority (NHA) which also makes decisions for the HBP. Any intervention that is being included as part of the HBP will either replace an existing intervention already included in the HBP or will be a new intervention in situations where there is currently nothing being included for the particular disease condition. Hence, the choice of organisation and its benefit package influences the study comparator. It is therefore important to identify all relevant comparators including current and future therapies and subsequently appropriate comparator(s) should be chosen for analysis. The selection of appropriate comparators should not be limited by the type of interventions, it is possible to compare pharmaceutical interventions with surgical interventions if they are intended to serve the same purpose of disease cure. Details of the comparator including dose, frequency, duration of treatment, route of administration should be reported in case of pharmaceuticals. Inputs from consultations with stakeholders and clinical experts are important for this. Key stakeholders including clinicians should verify the selected comparator. Multiple comparators may be used after appropriate justifications. In several situations the current therapy may be different from the most effective therapy (best practice), if considered relevant comparison should also be made against this as well.

(3) Perspective

Perspective refers to the viewpoint from which the economic evaluation is to be undertaken. The perspective of analysis is of utmost importance as it outlines which costs and outcomes are to be considered. Even in the same study settings, different perspectives can produce dissimilar conclusions, thus resulting in inefficient resource allocation. The choice of perspective is largely dependent on who is the end user of the results of an economic evaluation.

Recommendation: The Indian Reference Case, recommends using an abridged societal perspective for both costs and outcomes. This means that the analyst should include direct medical and non-medical costs borne by the healthcare payer as well as the patient. Furthermore, it is recommended that the results should be presented separately for abridged societal perspective as well as healthcare payer perspective. A disaggregated approach is justified since India has a multi-payer system for healthcare services which increases the complexity of the economic evaluation process.

First, analysis should be presented from abridged societal perspective which is broader and incorporates all costs and outcomes irrespective of who experiences or bears it. This is especially important in the Indian scenario where there is no central paying agency like National Health Service (NHS) and majority of the healthcare costs are borne by the patients through OOP payments, which should not be overlooked. Further, these OOP expenditures are higher in the private sector which provides out-patient and inpatient care to more than half of the Indian population. Thus, the abridged societal perspective should include direct medical and

direct non-medical costs borne by the provider and the patient including OOP expenditures. Additionally, the indirect costs due to productivity losses should be included as part of sensitivity analysis. The Indian Reference Case does not recommend the inclusion of indirect costs in the base case analysis owing to the reason that methods to quantify indirect costs still suffer major limitations and there is no consensus among the researchers on the standardized methodology.[40] The overall results of any cost-effectiveness analysis are highly sensitive to the method of valuation, human capital approach versus friction cost approach.[41] Also, in India, there is paucity of data for correctly estimating indirect costs. For instance, estimates on friction period, average wages especially for those in the informal sector and homemakers are not available. Moreover, inclusion of indirect costs is subject to equity issues. Furthermore, indirect costs are likely to be higher for diseases which affect the rich and the working population in comparison to poor, young and the elderly. Hence, it is recommended that the indirect costs should be included as part of sensitivity analysis.

Second, the analysis should be presented from the healthcare payer perspective that can be used by the health system in scenarios where they are the direct payers of the healthcare services. The healthcare provider perspective aligns more closely with the viewpoint of the decision-makers and would aid in the financial planning for healthcare services. The findings for the healthcare payer perspective should be presented both from a real-world scenario as well as a futuristic scenario with universal access to proposed intervention being evaluated. In such a scenario analysis, the actual cost which is likely to be incurred by the public payer will be considered. For India, it is recommended to consider the PM-JAY as the payer for curative services and the public healthcare delivery system for preventive care services.

(4) Source of evidence for effectiveness

Evidence on clinical effectiveness may be used from single study designs or a systematic review and meta-analysis of studies. Single study designs such as randomised controlled trials (RCTs), non-RCTs, observational studies, or case reports, provide effectiveness estimates based on only a selected group of patients, that too in a particular research setting. Further, these may vary in terms of confounding factors and risk of bias that influences the overall conclusions. On the other hand, systematic review and meta-analyses generates more reliable evidence and is therefore considered as the gold standard for deriving effectiveness metrics.

Recommendation: To have comprehensive and generalisable results on clinical effectiveness it is recommended that a systematic review and meta-analysis should be undertaken as it is considered to provide highest level of evidence (level 1).[42] While, a systematic review may involve a variety of study designs, however, a systematic review of RCTs will be preferred as it provides evidence based on most scientifically sound and rigorous methodology. Additionally, meta-analysis should be done to quantitatively combine results from several single studies to create more precise and reliable conclusions.

Given the time and resource constraints it is not always possible (advisable) to undertake a de novo systematic review. It is recommended that the researchers should consider using evidence from existing systematic reviews addressing the same research question. The relevance and quality of existing systematic reviews should be adequately evaluated. If deemed appropriate evidence should be used from existing systematic review, else a primary systematic review should be undertaken.

In situations where RCTs directly comparing the intervention and the comparator are unavailable, indirect comparisons using network meta-analysis may be undertaken. Adequate justifications of the methodology of the indirect comparison should be provided. In events when systematic review of RCTs is not possible, it is suggested to use or undertake systematic review of non-randomised trials. Appropriate justifications should be provided for failure to obtain evidence from a systematic review, and the next available source (RCTs) should be used as per hierarchy of evidence.[42] In case there is no published RCT, effectiveness evidence may be obtained from observational studies—cohort, case–control, cross-sectional, large-scale surveys. Expert opinion ranks lowest in the hierarchy of evidence; hence, its use should be avoided.[42] It is recommended that the level of evidence which has been used for estimating the clinical effectiveness of the intervention during the HTA assessment should be specified clearly using standard levels.

(5) Measuring costs

Costing is a critical component of any economic evaluation. Costs reflect the actual or anticipated (for new interventions) resource use for delivering the healthcare intervention. In the Indian context, it is important to capture the costs correctly, as healthcare costs have been shown to be a strong contributory factor to impoverishment in the Indian setting.

Recommendation: All relevant costs in accordance with the abridged societal perspective should be identified and taken into consideration. These should include direct medical and direct non-medical costs borne by the healthcare payer and the patients including OOP expenditure. Additionally, indirect costs due to productivity loss should be included as part of sensitivity analysis.

The cost data for healthcare system costs should be obtained from the National Health System Cost

Database (NHSCD) for India for better generalizability.[11] The database currently provides cost estimates for services delivered at the primary, secondary, and tertiary levels of public healthcare facilities. In addition, it also provides an overall estimate for a health benefit package, which may be useful for undertaking scenario analysis with PM-JAY as the provider. However, the database is still being updated in a phased manner, using cost estimates generated from a national costing study—Cost of Health Services in India (CHSI).[43] In circumstances where cost data specific to the decision problem is currently not available in the database, primary data collection using standard costing methods outlined in the HTAIn costing handbook is recommended.[15]

Estimates for OOP expenditure are available as part of the National Sample Survey (NSS) 75th round report, or more recent versions (in future) which can be used by the researchers.[24] The NSS report provides OOP expenditure estimates both for public as well as private sector. However, this data is available only for broad health conditions, and disease-specific data is not available. For data not available in the NSS report, it is recommended that the analysts may either use data from published Indian research studies providing disease-specific OOP estimates or undertake primary data collection using standardised data collection tools.

For estimation of indirect costs, the human capital approach (HCA) should be used for estimating productivity losses due to morbidity and premature mortality. The results should be presented separately with and without inclusion of indirect costs.

Finally, intangible costs incurred because of pain and suffering should not be included. It has been argued that such costs are adequately quantified in the denominator when measuring the quality of life.[42] Thus, to avoid double counting, intangible costs should be omitted while measuring costs.

(6) Measuring health outcomes

The measure of health outcome refers to the impact of the interventions being compared on the health of the individual/population. It is important that the health outcome measure chosen should adequately capture both negative as well as positive effects on quantity and quality of life (QoL). Depending upon the economic evaluation type there are a variety of methods in which the health outcomes can be measured and valued. The first include single dimension outcome measures such as survival rates, mortality rates, however, these measure only length of life.[44] The second are the multi-dimension outcome measures such as QALYs and DALYs which measure both the quality and length of life.[44] These may be measured using generic or disease specific tools. A generic measure is usually recommended as it aids in identifying additional health benefits that may not be directly related to the decision problem but may occur as a side effect or adverse event. In addition, a generic measure is more comparable than a disease specific measure.

Recommendation: The Indian Reference Case recommends undertaking cost-utility analysis and use QALYs as the preferred measure of health outcome. The use of QALYs is recommended because it is a generic measure and considers both quantity as well as quality of life.[44] The use of QALYs will also aid comparison with international economic evaluations and help in international benchmarking. Furthermore, quality of life weights are available for a larger number of diseases and conditions. Moreover, it is possible to elicit quality of life for multiple health states which an individual with a NCD passes through, and is therefore, a more sensitive measure to determine effectiveness. In addition, an Indian value-set for EQ-5D-5L tariff values has also been recently determined which would help in estimation of QALYs.[13]

However, there may be situations where the use of QALYs may not be possible, especially in decision problems involving infants and young children due to the current non-availability of the EQ-5D paediatric value set for India. In such situations, the researchers may opt for using the QoL tariffs from the adult EQ-5D value set for India or paediatric EQ-5D value set from other countries, however, the use of either of these approaches has certain caveats.[45–48] In case of the former, it is argued that the adult values do not necessarily reflect the preferences of children.[45–47,49] On the other hand, use of paediatric value set from another country may create differences owing to different socio-cultural and economic context between the reference country and India.[49] However, it is believed that the uncertainties of deriving a QALY estimate using the adult value set from the same country are relatively less as compared to using a paediatric value set from some other country.[48,49] Hence, the Indian Reference Case recommends determining QALYs using adult value set for India, for children aged 4–15 years, till the time the paediatric value set is not available. It is recommended that the paediatric value set for India should be developed in near future and thereafter, the same should be used for estimation of QALYs in children.

The QALYs should be elicited using five level version of the EQ-5D-Y tool for children aged 8–15 years, and EQ-5D-Y proxy for children aged 4–8 years.[50,51] Since the EQ-5D tool is unavailable for children aged <4 years, the Indian Reference Case allows the analysts to present outcomes in terms of DALYs. The disability weights estimated by the global burden of disease study should be used for estimating DALYs.[52] Furthermore, for policy questions where the priorities must be set among the interventions for the same childhood conditions, the researchers may consider using DALYs as the outcome measure. However, when broader resource allocation

decisions need to be addressed, using DALY limits comparability between competing investments because it has been argued ICER per DALY averted is not directly equivalent to ICER per QALY gained.[53] Hence, the use of DALYs should be avoided in such situations as this can negatively impact resource allocation decisions.

Furthermore, where relevant the analysts may present results using clinical outcomes and life years gained in addition to QALYs. For example, while undertaking economic evaluation for diagnostic interventions results may be presented as cost per case diagnosed.

(7) Time horizon

Time horizon is the specified duration of time over which the costs and outcomes for the decision problem are considered.[44] It is very important to select an appropriate time horizon which allows the analyst to capture all important costs and outcomes. The time horizon is dependent on the natural course of the disease and the effect of the intervention. In several cases, it is important to extend the time horizon beyond the duration of the trial period.

Recommendation: The time horizon considered while conducting an economic evaluation should be long enough so that it captures all relevant costs and outcomes. However, care should be taken to avoid unnecessary extension of the time horizon. For interventions influencing mortality and overall survival rates, for example, chronic diseases such as diabetes, cancers, a lifetime time horizon is recommended. Shorter time horizon may be considered in situations when there are no differences in long-term sequelae or mortality, for example, acute conditions such as acute infections, injuries etc. The time horizon should be determined by the natural course of the disease or health condition and the likely impact of the intervention under study. Key stakeholders including clinicians should verify the time horizon as reasonable. It is encouraged to use shorter time horizons in scenario-based analysis while testing uncertainty.

(8) Discounting

To adjust future costs and outcomes to their present values, discounting should be undertaken. Discounting indicates society's rate of time preference whereby people value future costs as less significant in comparison to today's costs and today's benefits as more significant in comparison to future benefits.[44]

Recommendation: Costs and outcomes occurring beyond one year should be discounted to present value using a common annual discount rate of 3%. Discounting at the rate of 3% would facilitate comparison of economic evaluations across jurisdictions as this is the most recommended and applied value globally, and in India.[18,32] Furthermore, to verify the robustness of results the discount rate should be varied from 0% to 5% in sensitivity analysis. In addition, it is recommended to present undiscounted values for costs, health outcomes as well ICERs for each of the different scenarios.

(9) Heterogeneity

Heterogeneity has a significant impact on cost-effectiveness ratios. Unlike uncertainty, heterogeneity is identifiable and known. In general, heterogeneity is considered to be a result of variable population characteristics, such as scenarios where younger populations groups respond better to a given intervention than older populations. This provides reasons to believe that a given intervention is cost-effective only within a certain population sub-group rather than the entire population. It is thus crucial for the researcher to recognise such heterogeneities and classify the population into relevant categories, to perform subgroup analysis. The rationale for identification of subgroups based on differences in relative effect, or baseline risk, or on costs accrued, or any other characteristic should be clearly justified. The ultimate aim of economic evaluation is to inform policies. In a scenario where an intervention is cost-effective only for a particular subgroup, the decision-maker can target the scarce resources to be invested in the population subgroup instead of providing the intervention to the entire population.

Recommendation: The existence of any population heterogeneity should be assessed through undertaking a subgroup analysis while conducting economic evaluations. Ideally it is recommended that the subgroups are identified at the planning stage so that stratified parameter inputs (such as costs, effectiveness, risk, utilities etc.) are available for each of the subgroup under consideration. A post-hoc identification of the subgroups limits the conduct of heterogeneity analysis and introduces decision uncertainty. Furthermore, key stakeholders including clinicians should verify the subgroups identified.

(10) Uncertainty Analysis

Uncertainties in economic evaluation are pervasive due to unavailability of precise estimates. However, to be accountable for the decisions, it is important for the decision-makers to be cognizant of the magnitude of the uncertainty in the results. Uncertainties can result from a variety of causes and may be categorised as parameter, structural or methodological uncertainty.[54]

Recommendation: To account for and determine the impact of the uncertainty present in results of economic evaluation, sensitivity analysis must be undertaken. Broadly the three types of uncertainties–parameter,

structural, and methodological, should be addressed. Probabilistic sensitivity analysis (PSA) is recommended to be undertaken for all analyses. The results of uncertainty analysis should be represented appropriately using cost-effectiveness acceptability curves. In addition, the impact of key structural and model assumptions, and parameters which may strongly influence the results are recommended to be tested using deterministic sensitivity analysis. Furthermore, scenario analysis (including best-case and worst-case scenario) is also recommended to be undertaken.

(11) Equity

The methods used for allocation of available resources against competing priorities are crucial as they determine how much health is generated overall and who receives the benefits and who all are left out. Economic evaluations provide information regarding the costs and effects of a technology. However, for the sake of policy decisions it is crucial to understand the distributional impact of the new technology among various population subgroups in terms of access to services, financial risk protection and health status. Hence, the role of economic evaluations should extend beyond maximizing health and ensuring equitable distribution.

Recommendation: Equity should be evaluated using either a quantitative or a qualitative approach or as an additional evaluative criterion. It is suggested that all lives (and QALYs) should be valued equally irrespective of age, gender, or other socioeconomic characteristics. Where considered appropriate it is recommended to use distributional cost effectiveness analysis (DCEA) for analysing the equity considerations in an economic evaluation.[55] DCEA helps to analyse the anticipated social distributions of costs and outcomes, as well as any possible trade-offs between maximising overall health and eliminating health inequality.[55] Further, extended cost effectiveness analysis (ECEA) may be undertaken to additionally assess the impact of the intervention on financial risk protection or the avoidance of catastrophic health expenditure due to OOP payments. Such an analysis in particular holds relevance in the Indian scenario, where the costs of healthcare may be catastrophic among the poorer quintiles.

(12) Presentation of Results

The way the results of an economic evaluation are reported greatly influences its comprehension and subsequent usability. Key stakeholders including researchers, academicians, patient community, industry groups, and/or policymakers may not trust the most methodologically robust economic evaluation, constructed from the strongest evidence available, if the methods and results are not reported in a clear and transparent manner.

Recommendation: The results should be presented in a clear and transparent manner. Detailed information should be provided with respect to each principle outlined in the reference case. In scenarios where the researchers have deviated from the Reference Case, appropriate justifications should be provided. The results of the economic evaluation should be presented in both disaggregated and aggregated forms. Total costs and total outcomes of the two alternatives should also be presented separately in addition to the cost-effectiveness ratios. Wherever possible, use of graphical representations is encouraged (cost effectiveness curves, tornado diagrams, etc). Threshold analysis may be undertaken wherever applicable. Currently, a formally recognised cost-effectiveness threshold (CET) for India is not available. However, for the purpose of analysis, researchers may use one-time gross domestic product (GDP) per-capita until a CET is determined for India.

Data transparency is also important. The parameters used in the model should be reported clearly and a tabular format may be used. The analysts should discuss the generalisability and transferability of results considering all limitations. It is recommended that the Health Technology Assessment Quality Appraisal Checklist (HTA-QAC) for India, should be used to ensure standardized reporting.[38]

Table 1 provides summary of key recommendations.

Discussion

This paper summarises the recommendations for conduct and reporting of economic evaluations as part of HTA in India, referred to as the Indian Reference Case. The recommendations are intended for any group of researchers interested in undertaking economic evaluations. Additionally, the Reference Case is also expected to assist decision makers, members of technical appraisal committee and reviewers to critically assess the quality of economic evaluations.

The Indian Reference Case builds upon the existing documents. The recommendations for several key principles such as decision problem, study comparator, source of effectiveness evidence, time horizon, heterogeneity analysis, etc., are in line with the existing guidelines.[32] However, other recommendations such as those for study perspective, type of costs to be included, measure of health outcome are tailored to cater to the uniqueness of the health financing mechanisms in India, the researcher capacity, and data availability (Supplementary Table S2).

The Indian Reference Case recommends the cost-utility analysis (CUA) as standard form of economic evaluation. A systematic review of economic evaluations undertaken in India concluded that a variety of analytic techniques were adopted by the researchers, with CEA being undertaken by the majority (64%).[18] The health consequences in a CEA are reported in natural units or in terms of clinically defines outcomes which may not

Principle	Recommendations
Decision problem	Should be clearly stated specifying disease condition, target population, and the interventions being compared.
Comparator	Current practice in use, multiple comparators possible
Perspective	Abridged societal perspective for base case analysis (results should be presented separately for abridged societal perspective as well as healthcare payer perspective). For sensitivity analysis societal perspective should be used.
Effectiveness	Systematic review and meta-analysis (preferred), randomised controlled trials (RCTs), observational studies may be used subject to justifications.
Measuring costs	Direct medical and direct non-medical costs borne by the health system and patients including out-of-pocket expenditure. Indirect costs to be included as part of sensitivity analysis
Health outcome	Quality-adjusted life years (preferred). Disability-adjusted life years (DALYs) may be used in special scenarios. Clinical end points may be used in addition to QALYs but not separately.
Time horizon	Long enough to capture all significant costs and consequences
Discounting	3% for both costs and outcomes; Sensitivity analysis: 0–5%
Heterogeneity	Subgroup analysis
Uncertainty analysis	Probabilistic sensitivity analysis and Deterministic sensitivity analysis including scenario-based analysis.
Equity	Distributional cost effectiveness analysis (DCEA) or extended cost effectiveness analysis (ECEA) may be undertaken

Table 1: **Summary of key recommendations of the Indian Reference Case.**

be comparable across wide range of diseases and intervention types, thus adoption of such evidence for decision making is difficult.[44] Moreover, when the analytic technique is left to the discretion of analysts and not clearly specified, researchers tend to use any of the available techniques resulting in greater variability.[31] Thus, it was considered important to clearly specify the preferred analytic technique. Accordingly, the Indian Reference Case recommends undertaking CUA and reporting results using QALYs gained. This is even more relevant given the fact that quality of life tariff values for EQ-5D-5L, as well as population norms have been published for Indian population.[13]

The Indian Reference Case recommends the use of QALYs as the preferred measure of health outcomes. While more than three-fourths of the previously published Indian economic evaluations have used DALYs as the outcome measure,[18] the recent development of the EQ-5D value set for India, can be seen as a conducive factor for the use of QALYs in future economic evaluations.[13] Furthermore, a vast number of high-income country guidelines, recommend the use of QALYs[32]; thus, using QALYs in the Indian context would increase comparability across evaluations. Nevertheless, the Indian Reference Case does have a provision for the use of DALYs, in situations where the use of QALYs may not be possible due to unavailability of generic instruments to capture QALYs, such as in scenarios where interventions for neonates and infants are being evaluated.

The recommendations on study perspective and type of costs have also been contextualised. While most of the guidelines advocate using a healthcare system or healthcare payer perspective, however, the Indian Reference Case recommends using an abridged societal perspective. Under the abridged societal perspective, direct medical and non-medical costs borne by the healthcare system as well as the patients should be included. Furthermore, the results are recommended to be reported separately using a healthcare system and abridged societal perspective. The rationale for using an overall broader perspective as discussed earlier is that India has a multi-payer system against a single payer system usually existent in most of the high-income countries such as the National Health Service (NHS) in the UK. The costs of services in India are borne by a variety of stakeholders, including the provider (public or private), the external donor and the patient. Also, the absolute share of these costs also varies between the different stakeholders depending on the decision problem. Hence, using an abridged societal perspective which accounts for all relevant costs is recommended.

As it is important to have a reflection of the costs that will be incurred by the healthcare system, it is recommended to report results from a healthcare system perspective as well. In accordance with the study perspective the Reference Case recommends including direct medical and non-medical costs including OOP expenditure in base case analysis and indirect costs in sensitivity analysis. While several countries suggest inclusion of only direct costs, however, in accordance with the study perspective, it is considered important to consider all different types of costs incurred for delivery of a healthcare intervention or programme irrespective of who pays for it. In addition to the recommendation on the types of costs to be included, the reference case also provides recommendation on the source of costs. It is opined that the national repository will provide access to consistent cost information collected using a uniform methodological approach across states and levels of healthcare systems thus making conduct of economic evaluation less time consuming and more consistent. Use of similar cost data repositories has also been advocated in other countries with developed HTA systems such as the UK, Netherlands, and Thailand.[26,56,57]

It is expected that adherence to the Reference Case would enhance the consistency in conduct and reporting, subsequently improving the quality of evaluations and aiding better policy decisions. Previous assessments of impact of adherence to economic evaluation guidelines have documented an improvement in the quality of economic evaluations post dissemination of the guidelines.[58–62] For instance, after the release of first version of the Thai HTA guidelines a significant increase in quality of published studies, ranging from 6 to 53% for individual criteria of economic evaluation was reported.[62] Another study documenting the impact of the Panel reference case using three indicators–discount rate as 3%, QALYs as the outcome measure, and reporting results using ICERs, concluded that the Panel reference case had a positive impact.[58] Similar findings have been reported by Neumann and colleagues, in their assessment on the impact of the Panel reference case on discount rate, QALYs and study perspective.[59] A systematic review comparing the adherence to guidelines in three countries concluded a positive correlation between adherence and quality score.[31] It is thus anticipated that adherence to the Reference Case would produce high quality economic evaluations which are comparable across diseases and interventions. This in turn is expected to increase the use of economic evidence in resource allocation decision making.

However, it is acknowledged that the adherence to the Reference Case may be challenging given the limited researcher capacity and data unavailability amongst other technical considerations. In this regard the HTAIn needs to play a pivotal role in knowledge translation and facilitating uptake of the Reference case. Specialized trainings sessions and workshops to increase the capacity of regional resource centres would be needed. Development of short term and full-time courses on HTA should also be envisioned. A master's programme for health economics and technology assessment (HETA) has also been developed by the HTAIn in collaboration with Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, and National Institute of Epidemiology, Chennai.[63] Additionally, an online course on health economics is being conducted by the PGIMER, Chandigarh since the past few years. In parallel to capacity building, targeted actions for generation of local data repositories would also be beneficial to ensure standardisation across studies and aid compliance with the principles of the reference case. Healthcare information on clinical effectiveness, epidemiology, costs, quality of life, etc. housed in databases or repositories is widely used in high-income countries and is acknowledged to be a useful source of information for HTA studies.[64] Some of these efforts are already in pipeline.[11,12] A national cancer database has been developed which provides information on treatment costs and quality of life segregated by cancer site, stage, and treatment approach.[12] The estimates from this database have been used in recent economic evaluations undertaken for treatment of various types of cancer.[65] Additionally, having regulatory mechanisms in place such as subjecting approval of HTA reports by TAC to adherence to the Reference Case and linking funding of studies to application of the Reference Case, will also be beneficial.

One of the key strengths of the current research is the rigorous methodology adopted to develop the Indian Reference Case. Many existing guidelines are developed based on expert consultations. The Indian Reference Case recommendations are supported by a review of international best practices as well as results of empirical analysis, in addition to the expert consultations. Another important feature of the Indian Reference Case is that it provides detailed guidance to the researchers instead of following a mere recommendatory approach. Furthermore, the reference case is not restrictive and allows for flexibility in special scenarios.

Nevertheless, there a few limitations. First, the Indian Reference Case recommends using a discount rate of 3%, which is justified on the basis to maintain consistency with existing guidelines and aid comparison across studies. However, it is argued that discount rates should be calculated considering social rate of time preference and inflation.[66] Thus, future research should focus on empirical estimation of the height of the discount rate using robust methodologies. Second, while the Indian Reference Case explicitly states QALYs as the preferred outcome measure, however, the possibility for the use of DALYs is not ruled out. It is apprehended that the researchers might use this flexibility, and exercise discretion without proper justifications. While India has recently developed quality of life value set, however, to calculate QALYs the researchers still need to obtain stage specific quality of life weights through primary data collection. On the other hand, the disability weights are readily available through the Global Burden of Disease (GBD) study, which may tempt the researchers to avoid primary quality of life data collection and instead report outcomes using DALYs. A possible solution to overcome this problem is first to have regulatory mechanisms, where in acceptance for use DALY as the outcome measured should be approved by the TAC at the time of protocol development. While this measure will sort out the problem for economic evaluations conducted under the mandate of HTAIn, however, independent researchers might continue to use DALYs. A broader solution to address this issue could be to develop a QoL database, providing disease and stage specific quality of life weights from the Indian settings. One such repository aimed at providing quality of life data for cancer is already being developed.[12] More such disease specific repositories should be targeted in near future. Furthermore, development of paediatric quality of life value set should also be aimed so that utility weights are available for diseases involving children.

Finally, the Reference Case has been designed in accordance with the current best practices, however, with time the methodologies are expected to evolve necessitating the reference case to be updated to address emerging issues.

The Indian Reference Case is expected to provide guidance in the planning, undertaking, and reporting of economic evaluations such that both the analytical approach as well as the presentation of the results is consistent and transparent. Adherence to the Indian Reference case is expected to improve the interpretability, transferability, and quality of future economic evaluations. Also, the Reference Case will allow policymakers to compare all competing evidence in the same way under a common approach. However, considering the evolving evidence and advancements in the field, the responsibility of regularly reviewing and updating the Reference Case document rests with the HTAIn. Furthermore, with the dissemination of the Indian Reference Case there would be a need to generate implementation evidence on the practicality of its use.

Contributors

Conceptualisation of the study: SP, AKA, KR. Data curation: DS. Formal analysis: DS, PB Supervision and validation: SP, AKA. Writing-Original draft: DS, SP. Writing-review & editing: DS, SP, AKA, KR, PB.

Data sharing statement

All the information pertaining to the article have been provided in the main text and Supplementary files.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2023.100241.

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