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The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought

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ABSTRACT

Background: Policymakers in high-, low-, and middle-income countries alike face challenging choices about resource allocation in health. Economic evaluation can be useful in providing decision makers with the best evidence of the anticipated benefits of new investments, as well as their expected opportunity costs—the benefits forgone of the options not chosen. To guide the decisions of health systems effectively, it is important that the methods of economic evaluation are founded on clear principles, are applied systematically, and are appropriate to the decision problems they seek to inform. **Methods:** The Bill and Melinda Gates Foundation, a major funder of economic evaluations of health technologies in low- and middle-income countries (LMICs), commissioned a "reference case" through the International Decision Support Initiative (iDSI) to guide future evaluations, and improve both the consistency and usefulness to decision makers. **Results:** The iDSI Reference Case draws on previous insights from the World Health Organization, the US Panel on Cost-Effectiveness in Health Care, and the UK National Institute for Health and Care Excellence. Comprising 11 key principles, each accompanied by methodological specifications and reporting standards, the iDSI Reference Case also serves as a means of identifying priorities for methods research, and can be used as a framework for capacity building and technical assistance in LMICs. **Conclusions:** The iDSI Reference Case is an aid to thought, not a substitute for it, and should not be followed slavishly without regard to context, culture, or history. This article presents the iDSI Reference Case and discusses the rationale, approach, components, and application in LMICs.

Economic Evaluation and Good Decision Making

Good decisions are those that attempt to maximize benefits and minimize harms. Benefits and harms of a health policy decision are often difficult to identify and measure fully, and so the evidence base for both is rarely complete. The opportunity costs of a decision—the benefits forgone or harm caused as a result of spending limited resources on one intervention and not on another—are even more elusive. Furthermore, decision making in health is inherently value-laden; individual and collective beliefs, needs, and aspirations commonly influence spending priorities.

The International Decisions Support Initiative Reference Case was informed by the Methods for Economic Evaluation Project workshop held at the Bill and Melinda Gates Foundation headquarters in Seattle in June 2013 and subsequent consultation with workshop attendees. A full list of workshop attendees can be found at www.idsihealth.org/knowledge_base/the-reference-case-for-economic-evaluation/. The bulk of this work was completed while the author TW was employed by NICE International, London UK. The following workshop attendees (in alphabetical order) provided substantive contributions to the Reference Case development: Ruth Faden, Director, Johns Hopkins Berman Institute of Bioethics, Baltimore, Maryland, USA; Marthe Gold, Logan Professor and Chair, Department of Community Health and Social Medicine, City College, New York, NY; Carol Levin, Senior Health Economist, University of Washington, Washington, WA; Francis Ruiz, Senior Advisor, NICE International, London, UK; Peter Smith, Professor, Imperial College of London, London, UK; and Anna Vassall, Reader in Health Economics, London School of Hygiene and Tropical Medicine, London, UK.

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To make good decisions, decision makers—whether they are local or national policymakers, clinicians, institutions, nongovernment organizations, or global funding bodies—not only need sound evidence of the likely costs, benefits, and opportunity costs of their choices but also have to filter the evidence through a prism of values, whether their own, those of the agency for which they work, of a particular stakeholder group, or of the society in general.

When used in health, "economic evaluation" refers to a suite of methods for identifying the costs and benefits expected from a health intervention, such as an individual technology or a clinical intervention, a platform for various interventions, public health programs, or a wider service development [1]. Economic evaluation can play an important part in clarifying the likely consequences of a decision (including the opportunity costs), thereby enhancing the quality of decision making [2].

Economic evaluation as a component of health technology assessment (HTA) is gaining increasing attention from decision makers in wealthy and resource-poor countries alike, as well as among global donors. In 2014, the World Health Assembly resolution 67.23 identified HTA as crucial for governments around the world to realize the benefits of universal health coverage, by facilitating the efficient and equitable allocation of health care resources. This resolution used the term "health intervention and technology assessment," which, for the purposes of this article, can be considered synonymous with HTA. This article presents a summary of the International Decision Support Initiative (iDSI) Reference Case [3], which aims to improve the usefulness of information produced through economic evaluation, thereby contributing to good decision making globally.

What Is a Reference Case for Economic Evaluation?

A reference case guides the planning, conduct, and reporting of economic evaluations so that both the approach to the analysis and the presentation of the results are coherent, transparent, and consistent. But more than this, a reference case goes beyond recommendations of good practice methodology and analytics and constitutes an explicit position statement on a range of scientific and social values inherent in the practice of economic evaluation. A major motivation for using a reference case is that it enables institutions or 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.

In 1996, the US Panel on Cost-Effectiveness in Health and Medicine first proposed the use of a reference case as a means of improving quality and comparability in conduct and reporting cost-effectiveness analyses [4]. In 2003, the World Health Organization (WHO) published a *Guide to Cost-Effectiveness Analysis* [5], which introduced a methodology aimed at improving the generalizability of results of economic evaluations globally. In 2004, the UK's National Institute for Clinical Excellence (NICE), which is called the National Institute for Health and Care Excellence since April 2013, adopted a reference case to standardize the analyses used to inform its own decision-making processes [6]. The reference case used by NICE, along with associated methods and process guides, contributes to NICE's ability to foster collective stakeholder buy-in, if not support, for its recommendations on resource allocation decisions and guidance for the National Health Service in England.

The Problem

Economic evaluation is not a simple panacea for the difficult decisions facing health policymakers. It is useful only if appropriate methods are applied, and the results reported with clarity and accuracy. Determining appropriate methods is particularly difficult in countries in which guidelines for undertaking economic evaluation may not have been established, researcher capacity is limited, and reliable data sources may be scarce. Without adequate information about the way an economic evaluation has been conducted, decision makers are unable to judge whether the results are applicable to their decision problem and whether it can usefully assist them to make good decisions.

Inconsistent and nontransparent incorporation of the judgments made when conducting an economic evaluation also limits its ability to contribute to good decisions. For example, if for reasons of advocacy or expediency a researcher conducting an economic evaluation does not compare the intervention in question with all the options feasibly available to the intended decision maker, the analysis may not accurately reflect the decision problem and fail fully to enumerate the relevant costs, benefits, and opportunity costs. The decision maker may understandably reject the analysis as an input to the decision process, or worse, incorporate it and make an ill-informed and potentially suboptimal choice.

Economic evaluations that are not conducted and reported systematically and clearly with a minimum standard of methodological quality have limited transferability [7]. The transferability of an economic evaluation indicates its applicability to different contexts and decisions, and improves the value of an economic evaluation by enabling it to inform decisions beyond the context for which it was conducted. Transferability becomes increasingly important in resource-constrained settings in which the substantial human and financial resources required to conduct an economic evaluation constrain its routine use in decision making.

Developing and using a reference case to guide the conduct and reporting of an economic evaluation of various technologies including interventions and services, programs, and delivery platforms is, therefore, a potential way to consistently improve methodological quality and transferability, and to make the necessary value judgments involved in conducting and using an economic evaluation more transparently.

There is, however, a trade-off between conducting an economic evaluation that can provide useful information for different places and contexts and one that is also sufficiently specific to reflect actual, invariably local, decision problems [8,9]. In addition, promoting consistency in economic evaluation should be weighed against imposing prescriptive methodological rules on researchers, which may constrain the use of methods best suited to the decision problem in light of analytical constraints. When the identities of the decision maker and the population to be affected by the decision remain constant (as with NICE for decisions affecting only the National Health Service in England), transferability and researcher discretion become less crucial and a relatively prescriptive reference case may be applied. These trade-offs, however, become a key consideration if a reference case is to be applied to economic evaluations intended to inform multiple decision makers, populations, and contexts.

The Case for the iDSI Reference Case

The national-level standardization of methods adopted by NICE in England has been implemented elsewhere; to date, mandatory or recommended standards or guidelines for economic

evaluation are available in more than 30 countries [10]. Most of the standards and guidelines are tailored to meet the specific information needs of institutions in high-income countries and, moreover, are designed for predetermined technology types (predominantly medicines and medical devices), constituencies (e.g., a country or province), and payers (e.g., a national health insurer). This burgeoning of standards demonstrates a demand for clarity and consistency of information to support national-level decision making. Nevertheless, many low- and middle-income countries (LMICs) lack the decision-making institutions and processes that articulate jurisdictions' objectives from the funding and delivery of health care and the financial and other constraints that need to be respected. In addition, many policy decisions that have substantial health impact on populations in LMICs are made at a global level, strongly influenced by institutions such as WHO and the UN Development Agencies, partners such as the Global Fund to Fight AIDS, Malaria and Tuberculosis (Global Fund) and the Global Alliance for Vaccines and Immunization, and donors such as the UK's Department for International Development and the Bill and Melinda Gates Foundation (BMGF). Each of these institutions has highly developed internal methodologies for generating information to support its own decision making, but there remains a question: If local-, national-, and regional-level decision makers and global institutions share a desire to improve health, can a common approach to economic evaluation be devised that reliably and consistently supports the decisions required of these different actors?

The iDSI Reference Case has been developed to respond to this challenge. It is not intended to provide a definitive reference case or a standard prescriptive set of methods to be used in all economic evaluations globally. Nor is it suggested that, by using a common reference case, all resource allocation decisions should be made in the same way, incorporate the same types of evidence, or weigh different inputs equally. Rather, the iDSI Reference Case seeks to articulate common principles for the generation of evidence, on the basis of the normative assumption that a health policy decision maker seeks information to facilitate decisions that maximize benefits, with a focus on health outcomes. In this way, the iDSI Reference Case does not seek to specify all the information that should inform a decision or assume that decision making in health is devoid of value judgments. Rather, it enables decision makers to apply personal, institutional, or political value judgments with knowledge of the likely consequences, including the opportunity costs, of applying these to a common substrate: population health.

There are many excellent publications and resources available on best practices for the planning, conduct, and reporting of economic evaluations (e.g., Drummond et al. [2], Gold et al. [4], and Gray et al. [11]). The iDSI Reference Case seeks to build on, rather than replicate, this knowledge. But beyond being merely a good practice guideline, the iDSI Reference Case articulates a set of principles, with sound decision making rather than academic rigor as the ultimate goal, and asks those undertaking economic evaluations to maintain these principles in the planning, conduct, and reporting of their analyses. By avoiding the imposition of specific value judgments and policy parameters, economic evaluations that use the iDSI Reference Case are also encouraged to accommodate the incorporation of local values and parameters into the decision-making process.

The iDSI Reference Case should not be applied inflexibly; rather it should be used to optimize the use of specific methods and existing evidence to produce useful and high-quality analyses. When it is not possible to adhere to particular principles specified in the iDSI Reference Case, analysts are asked to document their reasons. The effective application of the iDSI Reference Case has implications for the processes of decision making as well as for the making of the actual decisions. A detailed exploration is beyond the scope of this article but the general process requires a high degree of consultation with stakeholders and their representatives, as transparent a process as the confidentiality of information permits, and ample opportunity for deliberation over how best to combine and incorporate the various kinds of evidence and to incorporate an appropriate set of social value judgments and trade-offs [12,13].

The Development of the iDSI Reference Case

As a major funder of international development in health, the BMGF is obliged to spend money ethically and wisely. Moreover, the BMGF has an interest in sound decision making, the intelligent use of available evidence, and the pursuit of efficiency and equity in health [14]. To further these aims, the BMGF commissioned NICE International to coordinate an initiative aimed at ensuring that BMGF-funded economic evaluations were conducted and reported with consistently high methodological quality, and could thus become a useful input in decision making in LMICs [15].

As part of this initiative, a review of economic evaluations in LMICs was conducted, looking specifically at those funded by the BMGF. The review found that the BMGF had funded the highest proportion of economic evaluations in LMICs since the year 2000 in the vaccine, malaria, tuberculosis, and HIV/AIDS program areas, but with substantial variation in quality and consistency in both their conduct and reporting. For example, just over a third of the included economic evaluations did not report the time horizon used and half did not explain why particular comparators were chosen for the analysis [16]. The review indicated that a reference case tailored to the needs of decision makers in LMICs, if championed by the BMGF, could improve the overall consistency and quality of economic evaluations, thereby facilitating better decisions, and ultimately, better health.

The subsequent development of the iDSI Reference Case was initiated at a workshop at the BMGF headquarters with a series of email consultations. A pragmatic approach was used to achieve a broad representation from methodologists and those with experience in reference case development, researchers and funders of research in LMICs, and policymakers. Full details of the development process are given in the project report [15].

In partnership with UK's Department for International Development and the Rockefeller Foundation, the BMGF also funds the iDSI, an inclusive network of policymakers, academic units, and think tanks from around the world with the aim of providing coordinated support for priority setting as a means to universal health coverage. Development of the proposed reference case was in parallel with the founding of iDSI, and the initial working title "Gates Reference Case" [17] was broadened to the "iDSI Reference Case" to indicate the broad applicability and nonexclusivity of this global public good for use by decision makers, institutions, and researchers around the world.

The iDSI Reference Case Structure

The iDSI Reference Case has a structure consisting of principles, methodological specifications, and reporting standards (Fig. 1). The principles of the iDSI Reference Case inform corresponding methodological specifications, which, in turn, inform reporting standards. These principles describe the key characteristics of economic evaluations that are fit for purpose, outlining underlying concepts to guide methodological choice, without specifying particular metrics or parameter values. The methodological specifications are a nonexhaustive set of methodological options

Fig. 1 – Structure of the iDSI Reference Case.

that are aligned with a corresponding principle. Although some methodological specifications represent minimum standards of analytical quality (e.g., requiring a systematic evidence search to identify key parameters), many are decision- and context-dependent. This allows some flexibility to ensure that the methods that are appropriate to the decision problem—for example, whether to apply a static model or a dynamic model in an economic evaluation of an intervention in infectious disease, and how nonbudgetary constraints should be characterized. The structure of the iDSI Reference Case is intended to support the following three key objectives:

1. the routine application of fundamental principles by researchers and decision makers in the planning, conduct, and reporting of an economic evaluation to optimize its value in informing good decisions in health;
2. the use of methods that adhere to the same fundamental principles to achieve a minimum standard of methodological quality while remaining appropriate to the context and analytical constraints of the decision problem the economic evaluation is intended to inform; and
3. clear and transparent reporting of economic evaluations to improve their accessibility and usefulness to decision makers and to encourage comparability of both the content and the results with different contexts.

A Framework for Methods Development

A further objective of the iDSI Reference Case is to facilitate economic evaluation methods research, particularly research in LMICs. Its unique structure exposes areas in which there is limited evidence to support definitive guidance to researchers on methodological choices that best enable adherence to the principles, and can therefore best inform local decision making. For example, the methodological specifications for the evidence principle and the constraints principle in the iDSI Reference Case have spurred recent methodological research in these areas [18,43]. It is intended that methods research advancements will feed into future iterations of the iDSI Reference Case, in a continuous cycle of methods development, improving the relevance and applicability of economic evaluation to the needs of local decision makers in light of the constraints facing researchers in LMICs.

Facilitating Capacity Building and Technical Assistance

The iDSI Reference Case is intended to serve as a global public good, and iDSI and other initiatives will provide a potential framework for both external technical assistance and country-led capacity-building initiatives in LMICs. Ethiopia is an example of a country where there is potential for the iDSI Reference Case to be used in this way. Projected to be a middle-income country by 2025 [19], Ethiopia has taken significant steps in strengthening its health care system in recent years, improving the governance and transparency of its operation and extending coverage to an increasing proportion of its population. With a commitment to universal health coverage and an explicit health insurance strategy [20], there is an increasing interest in economic evaluation from both the Federal Ministry of Health and the Ethiopian Health Insurance Agency.

Nevertheless, production and capacity for economic evaluation in Ethiopia remain low. Within the HIV/AIDs program area, a major health priority in Ethiopia, only three costing analyses [21–23] and three cost-effectiveness analyses [24–26] have been published since 1995. The reasons for the limited number of analyses are multifactorial, and include lack of research funding, limited technical capacity, and scarcity of evidence directly relevant to the Ethiopian setting. Nevertheless, the absence of a standardized methodology for conducting economic evaluations to ensure that limited analytic capacity results in high-quality, policy-relevant studies is likely to be contributory [27]. The iDSI Reference Case could be used by local academic units, stakeholders, and government institutions such as the Ethiopian Public Health Institute to develop a national standardized methodology for economic evaluation and provide a basis for future capacity-building initiatives.

Table 1 – The iDSI Reference Case principles.

1	An economic evaluation should be communicated clearly and transparently to enable the decision maker(s) to interpret the methods and results.
2	The comparator(s) against which costs and effects are measured should accurately reflect the decision problem.
3	An economic evaluation should consider all available evidence relevant to the decision problem.
4	The measure of health outcome should be appropriate to the decision problem, should capture positive and negative effects on length of life and quality of life, and should be generalizable across disease states.
5	All differences between the intervention and the comparator in expected resource use and costs of delivery to the target population(s) should be incorporated into the evaluation.
6	The time horizon used in an economic evaluation should be of sufficient length to capture all costs and effects relevant to the decision problem; an appropriate discount rate should be used to discount cost and effects to present values.
7	Nonhealth effects and costs associated with gaining or providing access to health interventions that do not accrue to the health budget should be identified when relevant to the decision problem. All costs and effects should be disaggregated, either by sector of the economy or to whom they accrue.
8	The cost and effects of the intervention on subpopulations within the decision problem should be explored and the implications appropriately characterized.
9	The uncertainty associated with an economic evaluation should be appropriately characterized.
10	The impact of implementing the intervention on the health budget and on other constraints should be identified clearly and separately.
11	An economic evaluation should explore the equity implications of implementing the intervention.

Components of the iDSI Reference Case

The 11 principles of the iDSI Reference Case are listed in Table 1, and the corresponding methodological specifications are presented in Table 2. The transparency, comparators, constraints, and outcome measure principles have generated substantial interest in the development and initial application of the iDSI Reference Case and are described in the following sections. A full description of all the elements of the iDSI Reference Case,

Table 2 – Methodological specifications of the iDSI Reference Case principles.

Principle	Methodological specifications
1. Transparency	• The decision problem must be fully and accurately described • Limitations of the economic evaluation in informing policy should be characterized • Declarations of interest should be reported
2. Comparator(s)	• Current practice in context of decision problem to serve as comparator in the analysis • Best supportive, noninterventional care in context of decision problem should be explored as comparator as additional analysis
3. Evidence	• Apply a systematic and transparent approach to obtaining evidence and to judgments about evidence exclusion • Estimates of clinical effect of intervention and comparator(s) should be informed systematic review of the literature • Single-study or trial-based analyses should outline how these are an adequate source of evidence and should ensure that the stated decision problem is specific to particular context and time of the study or trial • Budget and time allocated to perform an economic evaluation should not determine selection of evidence
4. Measure of health outcome	• Methodological choices include either DALYs averted or QALYs gained • Full and transparent description of method used to calculate the chosen outcome measure
5. Costs	• Estimates should reflect the resource use and unit costs/prices that may be expected if the intervention is rolled out to the population defined in the decision problem • Costs not incurred in study settings but likely if intervention is rolled out should be captured in the analysis • Costs of all resource implications relevant to the decision problem, including donated inputs and out-of-pocket inputs from individuals • Analysis should include estimation of changes in cost estimates due to economies (or diseconomies) of scale
6. Time horizon and discount rate	• Lifetime time horizon should be used in first instance • A shorter time horizon may be used when shown that all relevant costs and effects are captured • 3% annual discount rate for costs and effects should be used in the analysis, with additional analyses exploring differing discount rates • Additional analysis should explore an annual discount rate that reflects the rate for government borrowings • When the time horizon is >30 y, the impact of lower discount rates should be explored in a sensitivity analysis
7. Nonhealth effects and costs outside health budget (perspective)	• Analysis should reflect direct health costs and health outcomes • A disaggregated societal perspective should be used to capture relevant nonhealth effects and costs that fall outside the health budget, to be included in additional analysis; the mechanism of inclusion will depend on the decision problem and context • When external funding or individual out-of-pocket payments substitute for costs that would otherwise fall on a health budget, these costs should be included in the analysis; the impact of excluding these should be explored in sensitivity analyses
8. Heterogeneity	Heterogeneity should be explored in population subgroups, in which subgroup formation should be informed by: • Relevant effect of the intervention differs in different populations • Characteristics of different populations that may influence the absolute health effects • Characteristics that influence direct costs of provision or other associated costs across the constituency Subgroup analysis should always be determined by: • The evidence base regarding differences in relative effect, baseline risk, or other characteristics • Whether the differences have an important influence on costs and effects
9. Uncertainty	The economic evaluation should explore: • Uncertainty in the structure of the analysis • Uncertainty due to source of parameters • Uncertainty due to precision of parameters
10. Constraints	• Budget impact analysis should estimate the implications of implementing the intervention on various budgets • Budget impact analysis should reflect the decision problem and the constituency in which the intervention will be used
11. Equity considerations	There are various mechanisms available for assessing equity implications of an intervention: • The method chosen should be appropriate to the decision problem and justifiable to the decision maker • Equity implications should be considered at all stages of the evaluation, including design, analysis, and reporting

including reporting standards, is available on the iDSI Web site [3].

Transparency

The transparency principle underpins all other components of the iDSI Reference Case, in particular the reporting standards. The need for improvement in the clarity of reporting and alignment of analysis to the stated decision problem in economic evaluations based in LMICs was a consistent theme raised by consultees in the reference case development process. Consultees considered that even the most methodologically robust economic evaluation will not be informative if the decision problem, methods, and results of the economic evaluation are not reported clearly and transparently. Building on existing reporting frameworks [2,28], the transparency principle and corresponding methodological specifications go beyond a requirement for clear reporting. It also seeks an explicit and

consistent link between the stated decision problem and the informational needs of the decision the analysis is intended to inform.

Improved transparency in the conduct and reporting of economic evaluation also aligns with initiatives to address barriers to transferability [7]. Clear and transparent reporting allows research undertaken in one particular context to be applied to the decision making in another, because even when the overall results of the economic evaluation may not be transferable, aspects of the research may still inform analyses in other contexts. Ultimately, however, the transparency principle underscores the primacy of the role of economic evaluations in informing decisions. Clarity and transparency in an economic evaluation enhance not only the transparency of the decision the analysis seeks to inform but also the accountability of the decision maker to the relevant stakeholders.

Comparators

Identifying the comparator against which costs and effects will be measured is critical to ensuring that the analysis both accurately informs the decision problem and is relevant to local decision making.

Comparative incremental analysis against current practice can most accurately reflect the true nature of the decision problem local decision makers are facing. The implications of reporting incremental, rather than average, costs and effects for an intervention have been well established [2,29]. Nevertheless, a limitation of only comparing an intervention with current practice is that if current practice does not represent an optimal use of resources, the resultant incremental cost-effectiveness ratio will not be a good indicator of value for money [2,9]. To address this issue, as a minimum requirement, the iDSI Reference Case requires comparative analysis of therapies currently in routine use (current practice), with additional analysis exploring comparison against best supportive, noninterventional care in the context of the decision problem. This approach will allow the analysis to not only accurately reflect the incremental costs and effects of an intervention but also identify situations in which current practice does not reflect optimal care.

Incorporating the transparency principle, the iDSI Reference Case requires researchers to explain their choice of comparator(s) and how it reflects the decision problem the economic evaluation is intended to inform.

Measure of Outcome

The measure of outcome chosen is critical to the scope of the decision that can be informed by an economic evaluation. The iDSI Reference Case is envisioned as a guide for economic evaluations that are intended to inform decision making in health and address issues of equity and efficiency. Although improving health is not the only source of benefit from health care and public health initiatives, it is likely to be the issue of central concern and so it is appropriate for health outcomes to be the focus in economic evaluations. This means that a measure of health outcome is required that is broad enough to capture the most significant and important aspects of health and can be applied consistently to different types of health technology, interventions, and programs across the population. When the scope of the decision problem is limited to interventions and comparators that impact either length of life or health-related quality of life, consistently using a measure that captures both length and health-related quality of life and is generalizable across disease states allows consideration of opportunity costs for the entire health sector and facilitates comparisons across investment types. Although a disease-specific outcome measure will inform decisions of technical efficiency, it will limit the ability of the decision maker to make reasoned trade-offs between competing investments in different disease states, and can undermine comparability and consistency in decision making.

The disability-adjusted life-years (DALYs) averted and the quality-adjusted life-years (QALYs) gained are measures that meet the requirements of the outcome principle in the iDSI Reference Case. The QALYs gained and the DALYs averted both provide a measure of quality and length of life, and are generalizable across different disease and therapeutic areas. The DALY is the metric most frequently used in economic evaluations in LMICs funded by the BMGF in the vaccination, tuberculosis, malaria, and HIV/AIDS program areas [16]. It is also commonly used in resource allocation decisions in health in LMICs, supported by the Global Burden of Disease analytical series [30] and various WHO programs [31]. The QALY is frequently required by national HTA agencies [32–35] and, in contrast to the DALY, QALYs incorporate estimations of quality of life through survey-based health state valuations.

The benefits and limitations of both the DALY and the QALY have been extensively documented [2,36–38], and researchers will need to exercise judgment in choosing the most appropriate measure(s) for a given economic evaluation. Importantly, both the DALY and the QALY are based on a series of assumptions and simplifications that necessitates judgments about the appropriateness of the methods used to quantify health state preferences and the accuracy of the resultant measures. In addition, the use of DALYs and QALYs implicitly incorporates value judgments such as the additivity of health and ability to compare health across populations and conditions. Researchers should be aware of these judgments and assumptions when conducting and reporting analyses.

Depending on the scope of the decision problem however, the most appropriate outcome measure may sometimes be intervention- or disease-specific, and a generalizable outcome measure may be irrelevant or impractical to calculate. In all cases, a justification of the outcome measure chosen is required. Future iterations of the iDSI Reference Case will provide further guidance for researchers on the appropriate choice and calculation of an outcome measure. The fundamental consideration is that the choice of outcome measure is aligned to the needs of the intended decision maker and that the methods used to calculate the outcome measure are comprehensively and transparently described.

Constraints

Economic evaluation seeks to provide evidential and analytic support to decision making regarding resource allocation in a constrained environment. As such, the objective of enhancing the health of the population (and other relevant measures of benefit such as financial protection) has to be seen against the constraints that apply in the system to achieve these objectives. Various types of constraint exist of which decision makers need to be mindful.

Key constraints relate to resource scarcity, which is an unavoidable reality in all systems, but is most challenging to decision makers in low-income settings. Limits to the financial resources available to a system (budget constraints) should be reflected in any economic evaluation. This involves providing decision makers with estimates of the scale of additional cost (budget impact) associated with a new investment. A good analysis will take this further, however, and seek to quantify the opportunity costs associated with a new investment that requires additional financial resources and, as such, diverts those resources away from other activities. Such displacement will

inevitably have an impact on the actual or potential health (and other benefits) accruing to other types of individuals. The nature and magnitude of these opportunity costs should be a key type of evidence informing the decision. In the context of incremental cost-effectiveness analysis, the measure of opportunity costs can be expressed as the threshold that is used to guide (although not to dictate) whether an incremental cost-effectiveness ratio is acceptable to the system. A cost-effectiveness threshold that reflects opportunity costs directly links the cost-effectiveness of a new investment with its affordability [39]. For new interventions that impose a larger impact on limited financial resources, more valuable alternative activities will have to be displaced to fund them, imposing higher opportunity costs—in effect, equivalent to a lower cost-effectiveness threshold. This "supply-side" conceptualization of the cost-effectiveness threshold that reflects the rate at which the system can at present translate additional resources into health (and other) benefits is appropriate to guide decisions about resource allocation given existing financial resources. It contrasts with other conceptualizations of the threshold that have been posited which are more focused on what funding envelope should be devoted to health care (a "demand-side" concept) [40–42].

Although the implications of the constraints that exist on a system's financial resources are perhaps the most obvious for analysts to present in economic evaluation, the principles remain true for other constraints as well. In LMICs, a particularly important constraint relates to human capital—for example, limits to the availability of skilled clinical staff to deliver particular services. These limits may reflect not only limits to the financial resources needed to fund more staff but also simply the number available, at least in the short-term. With respect to financial constraints, analysts should seek to inform decision makers of the impact of a new investment on the constrained human resource (how many needed vs. how many available), and the magnitude of the opportunity costs (in terms of health and other benefits) involved in diverting them from existing activities. As such, the real (opportunity) cost of a constrained resource may be quite different from its apparent financial cost.

Conclusions

The iDSI Reference Case is the first standardized principle-based methodology for the planning, conduct, and reporting of economic evaluations of health interventions developed specifically with an LMIC focus.

The iDSI Reference Case stresses the primacy of the needs of decision makers to deliver sound decisions, and its principle-based approach provides the flexibility to enable it to be used in different countries, applied to different technologies and interventions, and in support of various decisions. Crucially, the iDSI Reference Case will support decisions aimed at improving population health from within available funding while acknowledging the relevance and trade-offs associated with the incorporation of social values into those decisions. Ultimately though, the iDSI Reference Case is only a tool, and can inform, but not replace, the judgment of accountable decision makers.

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