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The International Decision Support Initiative Reference Case for Economic Evaluation: an aid to thought

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The International Decisions Support Initiative (iDSI) Reference Case was informed by the Methods for Economic Evaluation Project (MEEP) 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 following workshop attendees (in alphabetical order) provided substantive contributions to the Reference Case development: Ruth Faden - Director John Hopkins Berman Institute of Bioethics; Marthe Gold - Logan Professor and Chair of the Department of Community Health and Social Medicine City College New York; Carol Levin - Senior Health Economist University of Washington; Francis Ruiz – Senior Advisor, NICE International; Peter Smith - Professor, Imperial college of London; Anna Vassall - Lecturer, London School of Hygiene & Tropical Medicine

Abstract:

Policy makers 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.

The Bill and Melinda Gates Foundation (BMGF), a major funder of economic evaluations of health technologies in low and middle income countries (LMIC), 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.

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. It draws on previous insights from the WHO, the US Panel on Cost Effectiveness in Health Care, and the UK National Institute for Health and Care Excellence. Comprising eleven 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. This paper presents the iDSI Reference Case and discusses rationale, approach, components and application in LMICs.

Economic evaluation and good decision making

Good decisions are those that attempt to maximise benefits and minimise harms. Benefits and harms of a health policy decision are often difficult to identify and measure fully, 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. Further, decision-making in health is inherently value-laden; individual and collective beliefs, needs and aspirations commonly influence spending priorities.

To make good decisions, decision-makers - whether they are local or national policy makers, clinicians, institutions, non-government organisations, or global funding bodies - not only need sound evidence of the likely costs, benefits and opportunity costs of their choices, but they 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 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 clinical intervention, a platform for a variety of interventions, public health programmes, or a wider service development (Culyer 2014). 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 (Drummond 2015).

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[1] as crucial for governments around the world to realise the benefits of Universal Health Coverage, by facilitating the efficient and equitable allocation of health

[1] World Health Assembly Resolution 67.23 used the term Health Intervention and Technology Assessment (HITA), which for the purposes of this article, can be considered synonymous with HTA.

care resources. This paper presents a summary of the International Decision Support Initiative (iDSI) Reference Case (iDSI 2015a), 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 evaluation 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 (Gold 1996). In 2003 the World Health Organisation published a *Guide to Cost-Effectiveness Analysis* (Edejer 2003*),* 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[2] (NICE) adopted a reference case to standardise the analyses used to inform its own decision-making processes (NICE, 2004). 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

[2] As of April 2013, NICE is called National Institute for Health and Care Excellence, and maintains the same acronym.

Economic evaluation is not a simple panacea for the difficult decisions facing health policy makers. 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 where 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, a decision maker is 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 non-transparent incorporation of the judgements 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 sub-optimal choice.

Economic evaluations that are not conducted and reported systematically and clearly with a minimum standard of methodological quality have limited transferability (Drummond 2009a). 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 where 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 economic evaluation of a variety of technologies including interventions and services, programmes

and delivery platforms is, therefore, a potential way to consistently improve methodological quality and transferability, and to make the necessary value judgements involved in conducting and using an economic evaluation more transparent.

However, there is 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 (Sculpher 2004, Murray 2000). In addition, promoting consistency in economic evaluation should be weighed against imposing prescriptive methodological rules on researchers that may constrain the use of methods best suited to the decision problem in light of analytical constraints. When the identity of the decision maker and the population to be affected by the decision remains constant (as with NICE for decisions affecting only the NHS in England), transferability and researcher discretion become less crucial and a relatively prescriptive reference case may be applied. However, these trade-offs 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 standardisation of methods adopted by NICE in England has also been implemented elsewhere; to date, mandatory or recommended standards or guidelines for economic evaluation are available in more than 30 countries (Eldessouki 2012). The majority of the standards and guidelines are tailored to meet the specific information needs of institutions in high-income countries and, moreover, are designed for pre-determined 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. However, many 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 UN Development Agencies, partners such as the Global Fund to Fight AIDs, Malaria and Tuberculosis (Global Fund) and the Global Alliance for Vaccines and Immunisation (GAVI), and donors such as the UK's Department for International Development (DFID) and the Bill and Melinda gates Foundation (BMGF). Each of these institutions has highly developed internal methodologies for generating information to support their own decision making, but there remains a question: if local, national, 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, based on the normative assumption that a health policy decision maker seeks information to facilitate decisions that maximise 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 judgements. Rather, it enables decision makers to apply personal, institutional or political value judgements 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. Gold 1996, Gray 2010,

Drummond 2015). 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 rigour 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 judgements 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. Where 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 the making of the actual decisions. A detailed exploration is beyond the scope of this introduction but the general character of the process requires a high degree of consultation with stakeholders and their represenatives, as transparent 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 judgements and trade-offs (Chalkidou 2016, Culyer and Lomas 2006).

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 (BMGF, 2015). To further these aims, 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 into decision making in LMIC settings (NICE International, 2014a).

As part of this initiative, a review of economic evaluations in LMICs was conducted, looking specifically at those funded by BMGF. The review found that BMGF had funded the highest proportion of economic evaluations in LMICs since the year 2000 in the vaccine, malaria, TB and HIV/AIDS programme 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 (Santatiwongchai 2015). The review indicated that a reference case tailored to the needs of decision makers in LMICs, if championed by 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 BMGF headquarters and a series of email consultations. A pragmatic approach was used to achieve broad representation from methodologists and those with experience in reference case development, researchers and funders of research in LMICs, and policy makers. Full details of the development process are detailed in the Project Report (NICE International 2014a)

In partnership with the UK's Department for International Development and the Rockefeller Foundation, BMGF also funds the International Decision Support Initiative (iDSI), an inclusive network of policy makers, 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* (NICE International 2014b) was broadened to the *iDSI Reference Case* to indicate the broad

applicability and non-exclusivity 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.

Figure 1 here

The principles of the iDSI Reference Case inform corresponding methodological specifications, which in turn inform reporting standards. The 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 non-exhaustive set of methodological options that are aligned with a corresponding principle. While 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 or dynamic model in an economic evaluation of an intervention in infectious disease, and how non-budgetary constraints should be characterised. The structure of the iDSI Reference Case is intended to support three key objectives:

- the routine application of fundamental principles by researchers and decision-makers in the planning, conduct and reporting of economic evaluation in order to optimize its value in informing good decisions in health;
- 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;

- 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 results to 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 LMIC settings. Its unique structure exposes areas where 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 specification for the Evidence Principle and the Constraints Principle in the iDSI Reference Case has spurred recent methodological research in these areas[3]. 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 LMIC settings.

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 (Moller, 2015), Ethiopia has made significant steps in strengthening its healthcare system in recent years, improving the governance and transparency of its operation and extending coverage to an increasing proportion of its

[3] In press. iDSI Methodological Working Group Reports

population. With a commitment to Universal Healthcare Coverage and an explicit Health Insurance Strategy (Wang 2014), there is an increasing interest in economic evaluation from both the Federal Ministry of Health and the Ethiopian Health Insurance Agency.

However, production and capacity for economic evaluation in Ethiopia remains low. Within the HIV/AIDs programme area, a major health priority in Ethiopia, only three costing and three cost effectiveness analyses have been published since 1995 (Bikilla et al., 2009b, Kombe et al., 2004, Johns, 2014, Asfaw et al., 2012, Bikilla et al., 2009a, FHAPCO, 2012). 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. However, the absence of a standardised methodology for conducting economic evaluations, to ensure that limited analytic capacity results in high-quality, policy relevant studies is likely to be contributory (Asfaw 2015). The iDSI Reference Case could be utilised by local academic units, stakeholders and government institutions such as the Ethiopian Public Health Institute to develop a national standardised methodology for economic evaluation, and provide a basis for future capacity building initiatives.

Components of the iDSI Reference Case

The eleven principles of the iDSI Reference Case are listed in table 1, and the corresponding methodological specifications are summarised 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 below. A full description of all elements of the iDSI Reference Case, including Reporting Standards, is available on the iDSI website (iDSI 2015a).

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 LMIC settings 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 (Husereau 2009, Drummond 2015), 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 (Drummond 2009a). Clear and transparent reporting allows research undertaken in one particular context to be applied to decision-making in another, as even where 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 not only enhance 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 facing local decision makers. The implications of reporting incremental, rather than average costs and effects for an intervention has been

well established (Karlsson 1996, Drummond 2015). However, a limitation of only comparing an intervention to 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 (Murray 2000, Drummond 2015). 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, non-interventional care in the context of the decision problem. This approach will allow the analysis to accurately reflect the incremental costs and effects of an intervention but will also identify where 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 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 programmes across the population. Where 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 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. While 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 or Quality Adjusted Life Years (QALYs) gained are measures that meet the requirements of the Outcome Principle in the iDSI Reference Case. The QALY-gained and DALY-averted both provide a measure of both 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, TB, malaria, and HIV/AIDS programme areas (Santatiwongchai 2015). It is also commonly used in resource allocation decisions in health in LMICs, supported by the Global Burden of Disease analytical series (Murray 1997) and various World Health Organisation programs (WHO, 2010). The QALY is frequently required by national HTA agencies [REF NICE 2013, PHARMAC 2012, CADTH 2006, Thavorncharoensap 2014) 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 QALY have been extensively documented (Anand 1997, Gold 2002, Lipscomb 2009, Drummond 2015), and researchers will need to exercise judgement 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 which necessitates judgements 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 judgements such as the additivity of health and ability to compare health across populations and conditions. Researchers should be aware of these judgements and assumptions when conducting and reporting analysis.

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 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, for example, 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 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 (Claxton 2015). For new interventions that impose a larger impact on limited financial resources, more valuable alternative activities will have to be displaced to fund it, 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 currently 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) (Woods and Revill 2016), (iDSI 2015b), (Culyer 2016).

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 low and middle income settings, a particularly important constraint relates to human capital – e.g. 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 may simply reflect 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 versus 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.

Conclusion

The iDSI Reference Case is the first standardised principle-based methodology for the planning, conduct and reporting of economic evaluations of health interventions developed specifically with a 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 a variety of 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 judgement of accountable decision makers.

Figure 1

Table 1

The iDSI Reference Case Principles	
1	An economic evaluation should be **communicated clearly and transparently** to enable the decision-maker(s) to i**nterpret** 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	**Non-health effects** and **costs associated with gaining or providing access to health interventions that don't accrue to the health budget** should be identified where **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 sub-populations** within the decision problem should be **explored** and the **implications** appropriately **characterised**.
9	The **uncertainty** associated with an economic evaluation should be appropriately **characterised**.
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.

Table 2

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, non-interventional 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 ● Cost 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 costs 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 where 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 ● Where the time horizon is> 30 years, the impact of lower discount rates should be explored in a sensitivity analysis
7. Non-health 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 non-health 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. ● Where external funding or individual OOP 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, where 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 influences 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

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