

NICE International



Bill and Melinda Gates Foundation  
Methods for Economic Evaluation Project (MEEP)

**The Gates Reference Case**  
*What it is, why it's important, and how to use it*

April 2014

A partnership between  
Bill and Melinda Gates Foundation, NICE International,  
the Health Intervention and Technology Assessment Program (Thailand), and  
the University of York, Centre for Health Economics



## What this booklet is about

This booklet is intended for those who use (or who would like to use) the evidence produced from economic evaluation to inform decision making in health, and for those who conduct economic evaluations intended to inform decision making in health. It explains the Gates-Reference Case (Gates-RC), why it is important, and how to use it.

This booklet is a summarized version of the full Gates-RC, which can be found in the Methods for Economic Evaluation Project Final Report, published by NICE International ([www.nice.org.uk/niceinternational](http://www.nice.org.uk/niceinternational)).

## How was the Gates Reference Case developed?

The Bill and Melinda Gates Foundation (BMGF) is one of the largest investors in research on the value of health care interventions in low and middle-income countries (LMICs). In 2013, a novel collaboration known as the Methods for Economic Evaluation Project (MEEP) was established by BMGF to improve the quality and transparency of this research and to guide researchers in undertaking and reporting well-conducted and robust analyses. MEEP was a collaboration led by NICE International including partners from institutions including the Health Intervention and Technology Appraisal Program (Thailand), the University of York, the London School of Hygiene and Tropical Medicine, and the University of Glasgow. An important stage in MEEP was a workshop held at the Bill and Melinda Gates Foundation headquarters in Seattle in June 2013 that was attended by researchers, policy makers, methodologists, and donors. The workshop proceedings were a major part of the Gates-RC development.

A key output of MEEP was the Gates-RC. The Gates-RC document was drafted by Karl Claxton, Paul Revill and Mark Sculpher (University of York), Tommy Wilkinson (NICE International), John Cairns (London School of Hygiene and Tropical Medicine) and Andrew Briggs (University of Glasgow). Its development also benefited from substantive comments from the following people (in alphabetical order):

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## What are the key issues for the Gates Reference Case?

### ***Priority setting decisions in health are unavoidable***

It's axiomatic that resources will always be finite, and as a result, expenditure choices must be made. This means that priorities need to be assigned – some things may not be funded at all, or may need to be delayed in favour of others considered to be of higher priority. As a result, *some benefits will be foregone*.

### ***Priority setting decisions can (and should) be optimized***

When decision-makers assign priorities we would like them to do so as objectively as possible. In order to do this they need to have clarity about the costs and benefits – the *value* – of different options.

### ***How can this be done?***

Economic evaluation methods can provide a systematic approach to relating costs and benefits – and thereby determining *value*.

### ***Are there different ways to do this?***

Yes – but that's part of the problem. Until now there has been a lot of variation in both the approaches and methods used, as well as in the quality of studies. Unfortunately this limits their usefulness – not just for local policy makers, but also for decision-makers in other countries, and for BMGF itself.

### ***Are there ways to make findings clearer and more easily comparable?***

One approach is to develop and deploy a *reference case* – this is the name given to a way of standardizing methods so that both the approach to the analysis and the presentation of the results are more consistent.

### ***What is the value of using a reference case?***

Using a reference case can not only improve the quality of economic evaluations, but can also enable the results of different analyses to be more easily understood and compared – so we can avoid the pitfalls of comparing apples and oranges!

### ***How is a reference case developed?***

There are a number of different ways. The Gates Reference Case (Gates-RC) builds on *eleven key principles* to guide the planning, conduct and reporting of economic evaluations. Each of these eleven principles is supported by a *set of methods and reporting standards* that, *taken together*, make up a *comprehensive template* or guide to undertaking and presenting sound economic evaluations.

This booklet explains *how*.

## PART 1 – Why there is a Gates Reference Case

### Introduction: Good decisions – *better decisions*?

*Primum non nocere* – 'first do no harm' – is universally accepted as a fundamental tenet of health care. Good decisions in health are those that maximise benefits and minimise harms. But in an environment where resources are finite, choices must be made, and activities prioritized. It's an unfortunate reality that in setting priorities there will inevitably be opportunity costs associated with even the most carefully considered decisions. For example, choosing to invest in an intervention that benefits a particular patient group inevitably means less is available to be spent – and therefore benefits will be foregone – in another. Some degree of 'harm' – in the form of unrealized health gains or untreated disease – is unavoidable.

Determining the relative importance of benefits and harms is challenging enough, but decision-making in health is also inherently value-laden, with individual and collective beliefs, needs and aspirations driving different perspectives about priorities in spending. Failing to recognise or consider these values will lead to priority-setting decisions that don't reflect prevailing social values. This means that for decision-makers - whether they are local or national policy makers, clinicians, institutions, non-government organisations (NGOs), or global funding bodies - to make the best possible decisions, they not only need sound evidence of the likely costs and benefits of their choices, but that evidence must also be filtered through a prism of societal values.

*How then can this evidence be obtained?* Economic evaluation when applied to health technologies is a term used for a suite of methods designed to identify costs and resources used in association with a health care intervention, and to then weigh these against the likely outcomes of alternative health policy options – thereby improving resource allocation decisions by enhancing efficiency in health care<sup>†</sup>. Over the past three decades, methods for economic evaluation have gained increasing attention from decision-makers in wealthy and resource-poor countries, as well as among global donors. Importantly, economic evaluation has been identified as crucial for governments around the world to realise the benefits of universal health insurance coverage, by facilitating the efficient and equitable allocation of health care resources.

### Many contexts, multiple methods (or why there's a problem)

While economic evaluation is important for making sound policy decisions about health technologies, it's useful only if appropriate methods are used, and the results reported with clarity and accuracy. If not done well, these analyses can be difficult to interpret and can lead to suboptimal or frankly erroneous decisions. This is a particular risk in low and middle income countries, where guidelines for undertaking these analyses may not have been established, or reliable data sources may be scarce.<sup>1,2</sup> Together with limited expertise, this can lead to economic evaluations that are conducted poorly, or reported inconsistently.

### What's the Bill and Melinda Gates Foundation's role in this?

Established in 2000, the mission of the Bill and Melinda Gates Foundation (BMGF) is to improve health and reduce extreme poverty through a broad ranging series of Global Programmes. BMGF supports its grantees and partners in advancing knowledge, developing innovative approaches, and providing services in areas beset by particular health problems, including HIV/AIDS, maternal and child health issues, and vaccine-preventable diseases.<sup>3</sup>

As part of its mission, BMGF is a well-established funder of economic evaluations in low and middle-income countries (LMICs), utilising these not only in its own decision-making, but also making these available for in-country decision-makers. BMGF is also an advocate for improved decision-making, as well as a stakeholder supporting improved population health at the local level. In each of these roles BMGF's interests are furthered by improving the quality of health economic evaluations.

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<sup>†</sup> Economic evaluation in this context incorporates the term health technology assessment (HTA)

## What is a reference case?

A reference case is essentially a mechanism for enhancing the ability of economic evaluations to inform good decision-making for resource allocation in health, by standardizing methods so that both the approach to the analysis and the presentation of the results are robust and consistent. But more than this, a reference case is a position statement on a range of scientific and social values held by institutions or individuals who want to use economic evaluation to inform their decision making.

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 the quality and comparability in the conduct and reporting of cost effectiveness analyses (CEAs).<sup>4</sup> Seven years later the World Health Organisation (WHO) published a *Guide to Cost-Effectiveness Analysis*<sup>5</sup>, not only to improve the comparability of studies and facilitate consistency in decision-making, but – perhaps more importantly – to increase their generalizability, so that each country need not undertake its own analyses. The use of the reference case approach by decision-makers was subsequently boosted by the adoption of a reference case by the National Institute for Health and Care Excellence (NICE) in 2004 (revised most recently in 2013).<sup>6</sup> NICE's analyses and guidance inform resource allocation in the National Health Service in England and Wales, particularly with regard to new technologies and services.

## What's the case for a reference case?

Put simply, using a reference case can not only support better individual decisions through robust standards for planning, conducting and reporting economic evaluations, but also facilitates more consistent decision-making over time. The use of a reference case enables a meaningful and explicit comparison of the analyses and findings across multiple studies – put simply, it helps avoid having to compare apples with oranges. For example, where studies use different analytical perspectives, cost data will not be directly comparable, even if the interventions and their application are the same. This will be true for comparisons of evaluations of different interventions undertaken within a country as well as for those between evaluations of the same intervention in different countries. A reference case also represents a statement determining what elements of an economic evaluation are important for decision makers, implicitly defining the decision space in which local decisions can operate.

## Are there any disadvantages in using a reference case?

Economic evaluation of health technologies is a rapidly evolving field and there are still some methodological issues about which it's fair to say consensus hasn't yet been reached. As a result, some people believe that prescriptive guidelines for undertaking and reporting evaluations are premature. Some might even argue that progress in the development of methods could be discouraged by the greater use of reference cases.

Promoting the use of a particular reference case also carries some risk that certain practices become 'set in stone', and in this way create barriers for researchers attempting to secure funding for studies that diverge from 'standard' methods. In the UK the Medical Research Council is addressing this by funding (with direct support from NICE) on-going research in methods for economic evaluation.

Finally, the balance of advantages and disadvantages of the use of a reference case is strongly influenced by how prescriptive it is. A highly prescriptive reference case will enhance comparability and may improve quality but risks the application of methods that are inappropriate to the decision problem and the context in which it is being addressed, limiting the ability of the economic evaluation to inform good decisions. A reference case that is less prescriptive may not be adequate to facilitate cross-study comparisons or reliably inform resource allocation decisions. The key issue here is not whether to use a reference case, but how to determine how prescriptive it should be and how to interpret any analyses that diverge from it.

## The case for the Gates Reference Case

To date, mandatory or recommended standards or guidelines for economic evaluation are available in many countries<sup>7</sup>, and the 2003 WHO Guide to Cost Effectiveness provides a recommended framework for generalized cost effectiveness analysis. In addition, there are many excellent publications and resources available on best practice for the planning, conduct, and reporting of economic evaluations. So why has BMGF chosen to develop and promote its own reference case?

BMGF has both a responsibility and a commitment to support and advocate for sound decision-making, the intelligent use of data, and the pursuit of allocative efficiency. And as a major funder, BMGF is obliged to spend money ethically and wisely. As part of this initiative, a review of economic evaluations in LMIC was conducted,<sup>8</sup> specifically looking at those funded by BMGF. The review found that while 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, there was a wide variation in the way that economic evaluations were being conducted and reported in terms of quality and consistency, limiting their usefulness to decision makers.

By developing its own reference case, BMGF has the opportunity to introduce a methodological framework for economic evaluation that reflects its own social and scientific value judgements, but does so transparently and explicitly. That isn't without some risk; it's entirely likely there will be distinct differences between the social and scientific judgements made by BMGF and those of local constituencies.

It's also important to BMGF that economic evaluations are generalizable across different contexts and settings, so that they can inform its own decisions across multiple contexts, while also being useful to other decision-makers. This means that the reference case must support as much generalizability as possible, while maintaining a fundamental "usefulness" or ability to inform good decisions about health and health care on a local level.

## PART 2 – What's in the Gates Reference Case and How to Use It

### The Gates Reference Case – an aid to thinking

The Gates Reference Case (Gates-RC) is a set of [principles](#), [methodological specifications](#) and [reporting standards](#) to support health economic evaluations funded by the Bill and Melinda Gates Foundation (BMGF). The introduction of the Gates-RC is intended to support:

- the routine application of certain fundamental principles by researchers and decision-makers in order to optimize the value of economic evaluation in informing good decisions in health;
- the use of methods that adhere to the same fundamental principles to facilitate comparisons of the quality and relevance of economic evaluations when used to inform decisions in different contexts;
- a minimum standard of methodological quality to ensure that economic evaluations are fit for purpose; *and*
- minimum reporting standards to ensure clarity and transparency of economic evaluations, and to improve the comparability of both the content and results in different contexts.

The Gates-RC should be considered an aid to thinking, by offering a systematic framework of assessment for making decisions. It needn't be applied inflexibly; rather it should be used to optimize the use of specific methods and existing evidence to produce useful and high-quality analysis. By avoiding the imposition of specific value judgements and policy parameters, economic evaluations that use the Gates-RC will also allow local values and parameters to be factored into the decision-making process.

## Components of the Gates Reference Case – the 'building blocks'



The above diagram illustrates the building blocks of the Gates-RC. The reporting standards are informed by methodological specifications, which in turn are informed by eleven principles. The **principles** of the reference case describe how to undertake economic evaluations that are fit for purpose, but don't specify particular metrics or parameter values. The **methodological specifications** are a non-exhaustive set of options that enable the economic evaluation to adhere to the principles. While some methodological specifications represent minimum standards, most are decision dependent and are not prescriptive. 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. Others are specified explicitly (these are denoted as 'stated'), in order to facilitate comparability across multiple analyses – for example, the use of a 3% discount rate for costs and effects in the base case analysis.

The first principle '*An economic evaluation should be communicated clearly and transparently to allow the decision-maker to interpret the methods and results*' underpins the **reporting standards**. The standards mandate the inclusion of clear statements on a range of aspects of the economic evaluation.

### Gates Reference Case Compliance (Gates-RCC)

Economic evaluations may claim compliance with the Gates-RC if the choice of methodology and design follow the principles of the Gates-RC, apply minimum methodological specifications, and are documented according to the specified reporting standards.

Of course it's always important to consider whether the various Gates-RC methodological specifications are appropriate to the particular decision problem at hand. And while methodological variation is encouraged where appropriate, to claim Gates Reference Case Compliance (Gates-RCC) it is necessary either to:

1. present analytical scenario(s) where the stated specifications have been used (the Gates-RC base case), or
2. use alternative specifications, but explain why the Gates-RC specifications were not appropriate and the projected impact of divergence on the results of the economic evaluation.

*Over time it is anticipated that Gates Reference Case Compliance will become a recognized indicator of economic evaluations that are methodologically robust and able to inform sound decisions.*

## Applying the Gates-RC

The principles and methodological specifications are summarized below for ease of use. Readers should refer to the MEEP Final Report for full explanation and detailed specifications.

### 1. Transparency

**Principle:** An economic evaluation should be **communicated clearly and transparently** to allow the decision-maker(s) to **interpret** the methods and results.

#### Base Case Analysis:

- State decision problem using PICO format and describe context of decision
- Outline limitations of analysis in informing health policy
- Declare interests of study authors and source of funding

The aim of an economic evaluation is to inform decisions. However even the most methodologically robust economic evaluation will not be informative if the methods and results of the economic evaluation are not reported clearly and transparently. **Clarity and transparency** in an economic evaluation also enhance the overall transparency of the decision it's used to inform, thereby improving the accountability of the decision-maker to the stakeholders in that decision.

**Clear and transparent reporting** also improves **transferability** of economic evaluations, as research undertaken in one particular context may be used to support decision-making in another, since even where the overall results of the economic evaluation may not be generalizable, aspects of the analysis may still inform analysis in other contexts. A fundamental element of good scientific practice is that results are **reproducible**. Clear and transparent reporting also enhances the capacity of other researchers to reproduce the results of the analysis.

### 2. Comparators

**Principle:** The **comparators** against which costs and effects are measured should accurately **reflect the decision problem**

#### Base Case Analysis:

- Current practice in context of decision problem to serve as base case comparator
- Do nothing comparator should be explored as additional analysis

Identifying the **comparator** against which costs and effects will be measured is critical to ensuring that the analysis accurately informs the decision problem. The **choice of comparator determines the comparative costs and benefits associated with the intervention** under consideration and will therefore drive the incremental cost effectiveness ratio (ICER).

The methods for determining relevant comparators include:

- the interventions currently available to the population as defined in the decision problem;
- 'do nothing' – i.e. comparing the new intervention to best supportive care (no intervention);
- current 'best practice';
- the treatment or practice most likely to be replaced if the new intervention is adopted.

Comparative analysis of therapies currently in routine use should form the base case, with additional analysis exploring 'do nothing' as a comparator as a minimum requirement. Regardless of the choice of comparator, it is imperative that the incremental costs and effects informing the analysis reflect the decision problem and the requirements of the intended decision maker.

Remember: the most appropriate comparator is not always immediately obvious. Comparators may not always be alternative interventions, but can be different ways of administering the same intervention (such as

different regimens or treatment sequences). The place of an intervention in a care pathway will also influence the choice of relevant comparators.

### 3. Use of Evidence

**Principle:** An economic evaluation should consider **all available evidence relevant to the decision problem.**

**Base Case Analysis:**

- Apply systematic and transparent approach to obtaining and using evidence

**Evidence** refers to any information to be used to (qualitatively or quantitatively) inform the design, results and conclusions of an economic evaluation, including the unbiased estimate of clinical effectiveness and the costs and resource use associated with the interventions being compared.

Failure to draw on all relevant and available evidence when undertaking an economic evaluation will potentially introduce bias of unknown direction, limiting the capacity of the economic evaluation to inform a 'good' decision. Some judgement may be necessary as to what constitutes 'all relevant and available evidence'. This judgement must be applied in a systematic and transparent way when designing the economic evaluation, in order to minimise bias. Decision-makers should also assess whether an economic evaluation contains all relevant and available evidence when deciding if it's applicable to the decision problem.

The approach used to consider the relevance and applicability of available evidence to the decision problem should be determined *before* evidence gathering begins.

While the budget and time available for the study are relevant in determining the feasibility of the economic evaluation and scope of the decision problem, these should not influence any determination of the scope of the relevant evidence. That said, while it is important that a systematic review of the literature is undertaken to obtain estimates of the clinical effects of the intervention and its comparator(s), for some other parameters the collection and synthesis of all information may be prohibitively expensive or time-consuming. In these instances a transparent judgement should be made about the likely implications of not including missing information in the economic evaluation. Where feasible, researchers should explore the implications of alternative judgements about the quality and relevance of evidence (e.g. disease natural history or progression and treatment effects). This could include presenting different scenarios that represent different judgements about which evidence ought to be included. The justification for each should be clearly expressed so their plausibility can be properly considered.

Researchers should clearly state when the evidence available to inform aspects of the economic evaluation is weak or unavailable. This allows the decision-maker to make a judgement on the acceptability of the evidence in informing the decision.

### 4. Measure of outcome

**Principle:** 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.

**Base Case Analysis:**

- Disability Adjusted Life Years (DALYs) averted [*stated methodological specification*]
- Alternative generic (e.g. QALY) health outcome measures encouraged in separate analysis

It is important to use a measure of health outcome that is broad enough to capture all socially valued aspects of health and is applicable across investment types. Even where the scope of the decision problem is limited to interventions and comparators that impact either length of life or quality of life, it is still appropriate to use a

measure that captures length *and* quality of life, as this allows proper consideration of the opportunity costs of investing in the intervention. Using a non-disease-specific health outcome measure (i.e. one that is generalizable across disease states) allows consideration of opportunity costs for the entire health sector, and facilitates comparisons across investment types. A disease-specific measure limits 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.

In the Gates-RC, Disability-Adjusted Life Years (DALYs) averted should be used as the measure of health outcome. The DALY provides a measure of both quality and length of life, and is generalizable across different disease and therapeutic areas. This metric is frequently used in resource allocation decisions in health in LMICs, and is the metric most frequently used in economic evaluations in LMICs funded by the BMGF since the year 2000 in the vaccination, TB, malaria, and HIV/AIDS programme areas.<sup>8</sup>

There are other potential disease outcome measures that could be used which would meet this principle, notably the Quality-Adjusted Life Year (QALY) as frequently used in economic evaluations in high income countries. However, the DALY is the outcome measure currently preferred in the Gates-RC as a stated methodological specification to provide continuity with current practice and familiarity to decision-makers in LMICs and to complement large-scale LMICs analyses funded by the BMGF to date. In circumstances where DALYs cannot be estimated, another multi-dimensional metric that captures length and quality of life (such as QALY) can be used, however clear justification of why DALYs could not be utilized should be provided.

## 5. Measurement of costs

**Principle:** 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.

### Base Case Analysis:

- All relevant direct resource use and costs of implementing intervention to be identified, included donated resources and out of pocket payments (see principle 7)

Decision-makers need to know the resource use and costs associated with different options because more costly options will result in benefits foregone (and health opportunity costs), and less costly alternatives can free financial resources for investment in other interventions.

Overall costs of interventions (excluding costs that don't vary between alternatives) should be reported as a key component of the estimate of comparative cost-effectiveness. Where data are available, costs of resource inputs used to deliver interventions should also be reported to help determine what drives the differences in costs. In addition to reporting costs, quantities of resources used should be reported separately from their unit costs/prices, as this can assist decision-makers in assessing not only whether the quantities used are appropriate and reflect practices within their jurisdictions, but also whether unit costs/prices used in the evaluation are still relevant at the time of decision-making.

All relevant resource items involved in the direct delivery of health interventions should be captured as there will always be associated opportunity costs, even if these fall in other jurisdictions (e.g. if a country attracts international funding for the delivery of an intervention). In some cases, decision-makers will also be concerned about the sources of funds.

The average unit costs of an item of resource use may depend upon the scale in which a new intervention is delivered and the range of other interventions delivered alongside it. For instance, the cost of each visit to a clinic nurse may differ with overall patient throughput (scale), as well as whether and how other interventions are delivered at the clinic (scope). Average costs that fall (rise) with increasing scale and scope of delivery are called economies (diseconomies) of scale and scope. Economies of scale and scope may be important and should be incorporated when feasible, particularly when alternatives are likely to differ in their scale and scope of implementation. However, in many cases, data from within a jurisdiction may be inadequate to reasonably establish the nature of these economies. Other social objectives may also be important when

alternatives imply delivery at different scales and in different locations (e.g. if an evaluation involves one comparator being delivered in a community or primary health care setting and another in a hospital). Caution should therefore be used when applying cost functions if these cannot be supported with reliable evidence, or when other non-health effects may also have social value.

Primacy should be placed on the [transparency, reasonableness and reproducibility of cost estimates](#), so that different decision-makers can assess whether results are generalizable to their jurisdictions.

Key considerations:

- Costs should be estimated so that they reflect the resource use and unit costs/prices that are anticipated when interventions are rolled out in real health care settings. Protocol-driven costs in clinical trials should be excluded. Similarly any costs not incurred in clinical trial settings but anticipated in real health care settings, should be incorporated.
- Overall costs of interventions should be reported as well as costs of resource inputs. In addition, whenever possible, it is useful to report quantities of resources separately from their unit costs/prices. In some cases top-down facility level cost estimates provide a useful source of data, particularly if there is not sufficiently detailed and granular resource use and unit cost/price data available.
- Capital and fixed costs can be annualized over the period of implementation, but decision-makers should also consider when costs are likely to be incurred (see also budget impact).
- Where possible cost estimates should be corroborated against costs incurred when implementing the intervention(s) being evaluated (or other similar interventions) in real health care settings, for example using data from feasibility studies or pragmatic trials. This 'reality check' will assist the users in relating the economic evaluation to current practice and costs. Where notable differences between predicted (modelled) and realized costs exist, reasons for these differences should be explored and reported.
- All resource items involved in the direct delivery of health interventions that are expected to differ between alternatives should be costed. This includes donated inputs. While any resource items that do not differ across alternatives can be excluded, care should be taken to ensure that there are truly no significant differences before doing so.
- Economies of scale and scope that are expected with the delivery of interventions should be estimated and incorporated (when feasible). However, these must be based on reliable data from the jurisdiction of concern. Cost functions should not be imposed if unsupported by reliable evidence.
- The means of delivering interventions is not exogenously set – different delivery mechanisms are usually feasible and the choice of delivery mechanism should meet the overall objectives of health systems. Researchers should consider heterogeneity among recipients, impacts on non-health budgets, and equity considerations when using cost functions to evaluate alternative delivery mechanisms.
- Costs should be reported in US dollars and in local currency, and any costs that are estimated in other currencies should be converted to US dollars and local currency. The date and source of the exchange rate used should be reported in addition to whether the exchange rate is unadjusted (real) or adjusted for purchasing power parity (PPP).

## 6. Time horizon for costs and effects

**Principle:** 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 value**.

### Base Case Analysis:

- Lifetime time horizon (or sufficient to capture all relevant cost and effects)
- Discount rate of 3% for both costs and effects [*stated methodological specification*]

An economic evaluation should use a **time horizon** long enough to capture all costs and effects relevant to a **decision problem**. The nature of the interventions and comparators in the decision problem will largely define the appropriate time horizon. The time horizon will often be 'lifetime' – i.e. the natural length of life of the population cohort in which the analysis is undertaken. Confirming whether the length of the time horizon is sufficient can be achieved by monitoring the impact of time horizon changes.

The time horizon should never be determined by the length of time for which evidence is available. Where data aren't available to inform an appropriate time period, some projection of costs and effects into the future will be needed.

When projecting costs and effects into the future, those costs and effects need to be discounted to reflect their value at the time the decision is being made. This ensures that the time preferences of the population that will be affected by the decision are taken into account.

Economic evaluations adhering to the Gates-RC should use an **annual discount rate of 3%** for both costs and effects. While opinions differ as to the appropriate discount rate(s) to be used in economic evaluations, and different constituencies will vary in their time preferences with respect to health and wealth, for the purposes of comparability this is a stated specification. Use of alternative discount rates is nevertheless encouraged where appropriate to the decision problem and constituency, and should be presented clearly with a justification. In cases where the costs and effects are of a particularly enduring nature and a time horizon of more than 30 years is used, the impact of lower discount rates should be explored in a sensitivity analysis.

## 7. Costs and effects outside health

**Principle:** **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.

### Base Case Analysis:

- Reflect direct costs to the health budget and direct health outcomes to patients.
- Include costs incurred by external funders or individual OOP payments where it substitutes for costs that would otherwise accrue to the health budget
- All relevant non– health effects and costs that fall outside health budget to be identified

In addition to health outcomes and direct costs accruing to the health budget, other costs and consequences of interventions may also be relevant, **depending on the context of the decision**. These include wider impacts on families, communities, and other sectors of the economy. They may also include other (direct and indirect) costs such as the cost of accessing health care (e.g. travel, out-of-pocket and care costs), indirect time costs (e.g. relating to the productivity of individuals and informal carers), as well as costs falling on other sectors of the economy.

**Non-health effects and costs that don't accrue to the health budget** may be important because alternative interventions may deliver different non-health effects that have social value. They should therefore be included in the analysis but reported separately, with a justification for the selection of the included non-health

effects, and an explanation of how they may be valued. Primary analyses should only reflect direct costs to the health budget and direct health outcomes. By presenting non-health effects separately, decision-makers can draw their own conclusions on the relative merits of the different effects.

In health systems in which a significant proportion of interventions are funded through [out-of-pocket \(OOP\) payments](#), there may be good reasons to adopt a perspective other than that of the health care provider. Researchers should take care that alternatives don't shift costs onto individuals, and may choose to incorporate direct OOP costs into primary analyses in such cases. Of central concern are the opportunity costs faced in each case and how these are likely to be valued by society (this may also include concern for financial protection).

[Communities often value health and non-health effects differently](#) depending upon who benefits from the intervention (see also Principle 11 - Equity). Similarly, direct health intervention costs may impose different opportunity costs according to who funds a particular intervention. In many LMIC contexts, health interventions rely upon direct funding from different sources (for instance national ministries of health may fund recurrent costs; whereas international donors may fund drugs or certain technologies). In these instances donor funds (including the direct provision of drugs and health care materials) may form a significant proportion of the budget available for health. It would be inappropriate for an analysis to disregard the direct impact of an intervention of donor funds, but it is also important that recognition is made of different sources of funding.

For these reasons, it is recommended that direct costs, health effects, non-health effects and costs that fall outside the health sector are disaggregated so that it is clear who are the beneficiaries and the funders of interventions. This facilitates exploration of health system constraints, budget impacts and opportunity costs, and equity issues. It also allows decision-makers to make judgements on the relative importance of each in their own jurisdictions.

[Non health effects](#) can be valued and presented in different units. Valuing non-health effects monetarily has the benefit that both outcomes and costs can be represented in a common metric, but there are contentious methodological issues relating to how to monetarise outcomes appropriately. Thorough exploration of how to value non-health effects is therefore recommended.

Key considerations:

- The [base case analysis should reflect direct health care costs and health outcomes](#), and should adopt a [disaggregated societal perspective](#) so that the funders and beneficiaries of health interventions can be clearly identified. Inclusion of particular costs and effects within the societal perspective may differ depending on the decision problem and context.
- Direct costs incurred by funders – where these would otherwise fall on government health budgets – should be included in the base case. However, additional analyses should explore the impact of donor funding, and direct health care costs should be disaggregated by funder if it is known that they contribute to different components of the delivery of interventions.
- Out of pocket costs falling on individuals can be included if these are costs that would otherwise fall on the health budget, however the impact of excluding OOP costs should be included in a sensitivity analysis.
- Where there are believed to be important non-health effects and costs falling outside of the health budget, these should be included in an analysis but reported separately, with a clear justification for their selection and a thorough exploration of the ways they can be valued. Any non-health effects and costs that fall outside of the health budget that potentially conflict with other social objectives should be highlighted and discussed. For example, a particular intervention may be expected to have productivity benefits but its adoption may result in adverse equity consequences.
- Decision-makers should be made aware that interventions with positive incremental direct health costs are also likely to impose non-health opportunity costs associated with health interventions that are foregone, insofar as interventions foregone are also likely to have non-health effects. For example, an intervention for HIV/AIDS may have non-health effects but if adopted these may

displace interventions for maternal health that have equal or even greater claims to generating additional elements of positive social value.

- Care should be taken to ensure that non-health effects and costs are not double counted. Double counting can occur where a particular effect (or cost) of an intervention relative to a comparator is attributed to more than one outcome measure – for example, there are debates as to the extent that productivity effects are already captured in quality of life measures.
- Direct health costs should be disaggregated by funder. Both health and non-health effects should be disaggregated by characteristics of recipients and beneficiaries (see also Principle 11 - Equity) and, in the case of non-health effects, the sector or area in which these are incurred.

## 8. Heterogeneity

**Principle:** The cost and effects of the intervention on sub-populations within the decision problem should be explored and the implications appropriately characterized.

### Base Case Analysis:

- Explore and identify significant population subgroups
- Report separate subgroup analysis where heterogeneity relevant to the decision problem exists

It's important to distinguish between uncertainty, variability and heterogeneity. **Uncertainty** refers to the fact that we do not always know what the exact costs and effects will be of an intervention in a particular population of individuals. This remains the case even if all individuals within this population have the same observed characteristics. **Variability** refers to the fact that responses to an intervention will differ within the population or even within a sub population of individuals or patients with the same observed characteristics. **Heterogeneity** refers to those differences in response that can be associated with differences in observed characteristics, i.e. where sources of natural variability can be identified and understood. As more becomes known about the sources of variability the patient population can be partitioned into sub populations or subgroups, each with a different estimate of the expected effect and cost of the intervention, and the uncertainty associated with these. The correct assessment of the cost and effects of providing an intervention across some or all subgroups depends on the effects and costs in each subgroup.

An exploration of heterogeneity enables decision-makers to consider whether an intervention should be made available to groups of individuals with greater capacity to benefit. It means they have the opportunity to make different decisions for different groups of individuals that can improve health outcomes overall given the resources available.

There may, however, be valid reasons not to make decisions based on certain types of observed characteristics. These reasons might include: i) the difficulty and/or cost of maintaining differential access; ii) adverse equity implications; or iii) social values that would preclude differential provision based on certain characteristics. However, even in these circumstances an exploration of heterogeneity can:

- 1) enable decision-makers to consider the opportunity costs (the health foregone) of responding to concerns that would work against differential provision across identifiable groups, thereby enhancing consistency and accountability in the application of social values.
- 2) provide a foundation for exploring the health equity implications of different approaches to the provision of an intervention, and can identify the potential trade-offs between equity objectives and overall health benefits (e.g. for equity reasons it might be considered worthwhile providing an intervention to groups where that provision is less cost effective even though this may reduce overall health benefits because of higher opportunity costs).
- 3) provide a better understanding of the distributional issues associated with an intervention. This can form the basis for further more targeted research and may inform other related decisions.

Since any observed characteristics that affect the health benefits and costs of an intervention are relevant in principle, the exploration of heterogeneity should include subgroups where there is good evidence that the

relative effect of the intervention differs (e.g. pre-specified subgroups within a clinical trial). However, subgroup analysis can be considered when external evidence suggests (and there are good reasons to believe) that relative effects differ between subgroups even where they have not been pre-specified.

However, assessing heterogeneity shouldn't be limited to exploring differences in relative effects between different groups of patients. It should also include exploring characteristics that influence absolute health effects, even where the relative effect is similar, such as differences in baseline risk of an event or incidence and prevalence of a condition. There may also be characteristics that are unrelated to clinical effects but influence the costs of providing care such as geographical location.

The question of which sets of observed characteristics to explore should be informed by

- 1) the evidence base regarding differences in relative effect, baseline risk or other relevant characteristics, and
- 2) whether any differences are likely to have important influences on costs and effects.

The analysis should explain – with respect to these two factors – how the exploration of heterogeneity has been undertaken. An assertion or presumption that certain observed characteristics would not be used as a basis for differential access to an intervention is not sufficient reason to not to explore heterogeneity.

## 9. Uncertainty

**Principle:** The **uncertainty** associated with an economic evaluation should be appropriately characterized.

### Base Case Analysis

- Explore all relevant structural, parameter source, and parameter precision uncertainty
- Probabilistic sensitivity analysis preferred but not explicitly required

Decisions regarding resource allocation in health are unavoidable. All decisions carry a risk that a better course of action could have been selected, and so when making a decision uncertainty must be acknowledged and measured.

All economic evaluations reflect a degree of uncertainty, and it is important that all types of uncertainty are appropriately presented to the decision-maker. These include uncertainty about the source of parameters used in the economic evaluation, the precision of the parameters, and whether models accurately simulate the cost and effects of the intervention and comparators. The characterisation of this uncertainty enables the decision-maker to make a judgement based not only on a likely estimate of the incremental costs and effects of an intervention, but on the confidence that those costs and effects represent reality.

Characterising the uncertainty will also enable the decision-maker to have the option of an informed choice of a course of action that will reduce uncertainty. This could involve delaying implementation to allow for more evidence to be gained. In this situation, appropriately characterising uncertainty will allow the decision-maker to make an informed trade-off of the value of new information, the implications of potentially delaying treatment to patients or individuals, and irrecoverable costs that are associated with implementing funding for an intervention.

There are a many potential selection biases and uncertainties in any economic evaluation, and these should be identified and quantified where possible. There are three types of uncertainty to consider:

- Structural uncertainty – for example in relation to the categorisation of different states of health and the representation of different pathways of care. These structural assumptions should be clearly documented and the evidence and rationale to support them provided. The impact of structural uncertainty on estimates of cost effectiveness should be explored by separate analyses of across a range of plausible scenarios.
- Source of values to inform parameter estimates – the implications of different estimates of key parameters (such as estimates of relative effectiveness) must be reflected in sensitivity analyses (for

example, through the inclusion of alternative sources of parameter estimates). Inputs must be fully justified, and uncertainty explored through sensitivity analyses using alternative input values.

- Parameter precision – uncertainty around the mean health and cost inputs in the model. To characterise parameter uncertainty, probabilistic sensitivity analysis (PSA) is preferred, as this enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. The mean value, distribution about the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. Evidence about the extent of correlation between individual parameters should be considered carefully. Assumptions made about the correlations should be clearly presented.

Where lack of evidence restricts reliable estimations of mean values and their distributions, unsupported assumptions or exclusion of parameters in a PSA will limit its usefulness to characterise uncertainty, and may give a false impression of the degree of uncertainty. For this reason, PSA is not explicitly required in all economic evaluations at this time; however any decision not to conduct PSA should be clearly and transparently explained in the analysis. Future iterations of the Gates-RC will provide further specification on the application of PSA.

## 10. Impact on other constraints and budget impact

**Principle:** The **impact** of implementing the intervention on **health budgets and other constraints** should be **identified clearly and separately**.

### Base Case Analysis

- Report expected budget impact of implementing the intervention on all relevant budgets in the context for the population identified in the decision problem

It is important to determine the net total costs involved in the deployment of a health intervention on a particular scale, as this is also a measure of the value of what must be foregone.

The costs of an intervention (even when capital investment is not required) are unlikely to be evenly spread over time. There will often be high initial costs offset by later health benefits and at times, cost savings. Decision-makers who are responsible for annual budgets must assess the timing of the impact, as well as the magnitude, of the expected incremental costs when deciding if the benefits of an intervention are justified by the health opportunity costs. This becomes especially important when later health benefits or cost savings are uncertain, since implementation will require the commitment of resources that may not be recoverable should subsequent evidence suggest the intervention is not worthwhile (or not cost effective) and should be withdrawn.

In addition to expenditure constraints, decision-makers may be subject to other infrastructural or resource limitations such as limited laboratory capacity or insufficient skilled workers. Decision-makers (at national, regional, or local level) must be able to assess the impact of an intervention in each of these domains to properly determine whether the benefits exceed the health opportunity costs. This may also facilitate some consideration of which constraints have the greatest impact, and the potential value of policies that modify these, such as removing restrictions on the use of donated resources or increasing investment in training health workers.

Since non health benefits and costs do not impact health budgets or other constraints on health care, they should be assessed separately.

Budget impact should be presented in a manner that is relevant to the decision problem and the needs of the intended decision-maker. The budget impact should be disaggregated and reflect the costs to all parties as a result of implementation of the intervention (cost outputs). This includes (but is not limited to) impact on government and social insurance budgets, households and direct out of pocket expenses, third-party payers, and external donors. Budget impact should be projected annually for a period appropriate to the decision problem.

## 11. Equity implications

**Principle:** An economic evaluation should explore the **equity implications** of implementing the intervention.

### Base Case Analysis

- Equity implications of implementing the intervention for the populations described in the decision problem should be reported, however the reporting method is at discretion of researcher or the needs of the decision maker

The equity implications of deploying an intervention within a given constituency are important because resource allocation decisions in health frequently reflect considerations other than efficiency. Important equity considerations may include issues such as whether equal access is given to those in equal need, whether resources are distributed fairly to those with different levels of need, or recognition that interventions such as smoking cessation programmes may simultaneously improve population health but increase health inequalities. Limiting an economic evaluation to a determination of cost-effectiveness across a population as a whole may ignore differences in capacity to benefit and/or in access to care, and may prevent the decision-maker from appropriately considering the differential impacts of a decision on different subgroups within the population.

In adhering to certain principles in the Gates-RC some equity implications will be considered implicitly. For example, exploring heterogeneity may involve a consideration of distributional implications of implementing an intervention. However, adherence to the principles of the Gates-RC will not generally be sufficient to ensure that the equity implications of a decision problem have been adequately explored. For this reason, exploration of equity is a principle that should be addressed in its own right in a robust economic evaluation.

There are many dimensions to assessing the equity implications of a proposed intervention. Methods employed may be qualitative, or may involve the quantitative assessment of distributive impact and expected trade-offs. At the most basic level, an exploration of equity impacts may involve a description of particular groups within the constituency that may be disproportionately affected (positively or negatively) by a decision. Adherence to the equity principle is not, however, simply a matter for reporting of results. Equity implications should be considered at all stages of an economic evaluation, including the design, analysis and reporting stages.

## The Gates Reference Case Principles

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

Principle	Methodological Specifications
1. Transparency	<ul style="list-style-type: none"> <li>● The decision problem must be fully and accurately described</li> <li>● Limitations of the economic evaluation in informing policy should be characterized</li> <li>● Declarations of interest should be reported</li> </ul>
2. Comparator(s)	<p>At a minimum, the following comparative analysis should be undertaken:</p> <ul style="list-style-type: none"> <li>● The intervention(s) currently offered to the population as defined in the decision problem as the base case comparator</li> <li>● A “do nothing” analysis representing best supportive (non-interventional care) for the population as additional analysis</li> </ul>
3. Evidence.	<ul style="list-style-type: none"> <li>● Apply a systematic and transparent approach to obtaining evidence and to judgments about evidence exclusion</li> <li>● Estimates of clinical effect of intervention and comparator(s) should be informed systematic review of the literature</li> <li>● 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</li> <li>● Budget and time allocated to perform an economic evaluation should not determine selection of evidence.</li> </ul>
4. Measure of health outcome	<ul style="list-style-type: none"> <li>● Disability-Adjusted Life Years (DALYs) averted should be used.</li> <li>● Other generic measures that capture length and quality of life (e.g. QALYs) can be used in separate analysis</li> </ul>
5. Costs	<ul style="list-style-type: none"> <li>● 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</li> <li>● Costs not incurred in study settings but likely if intervention is rolled out should be captured in the base case analysis</li> <li>● Cost all resource implications relevant to the decision problem, including donated inputs and out of pocket inputs from individuals</li> <li>● Analysis should include estimation of changes in costs estimates due to scalability</li> </ul>
6. Time horizon and discount rate	<p>Lifetime time horizon should be used in first instance.</p> <ul style="list-style-type: none"> <li>● A shorter time horizon may be used where shown that all relevant costs and effects are captured.</li> <li>● 3% annual discount rate for costs and effects in base case, with additional analyses exploring differing discount rates</li> <li>● Additional analysis should explore an annual discount rate that reflects the rate for government borrowings</li> <li>● Where the time horizon is &gt; 30 years, the impact of lower discount rates should be explored in a sensitivity analysis</li> </ul>
7. Non-health effects and costs outside health budget (perspective)	<ul style="list-style-type: none"> <li>● Base case analysis should reflect direct health costs and health outcomes</li> <li>● 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.</li> <li>● 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 base case analysis, however the impact of excluding these should be explored in sensitivity analyses</li> </ul>
8. Heterogeneity	<p>Heterogeneity should be explored in population subgroups, where subgroup formation should be informed by:</p> <ul style="list-style-type: none"> <li>● Relevant effect of the intervention differs in different populations</li> <li>● Characteristics of different populations that may influence the absolute health effects</li> <li>● Characteristics that influence direct costs of provision or other associated costs across the constituency</li> </ul> <p>Subgroup analysis should always be determined by:</p> <ul style="list-style-type: none"> <li>● The evidence base regarding differences in relative effect, baseline risk or other characteristics</li> <li>● Whether the differences are likely to have an important influences on costs and effects</li> </ul>
9. Uncertainty	<p>The economic evaluation should explore:</p> <ul style="list-style-type: none"> <li>● Uncertainty in the structure of the analysis</li> <li>● Uncertainty due to source of parameters</li> <li>● Uncertainty due to precision of parameters</li> </ul>
10. Budget impact	<ul style="list-style-type: none"> <li>● Budget impact analysis should estimate the implications of implementing the intervention on various budgets</li> <li>● Budget impact analysis should reflect the decision problem and the constituency in which the intervention will be used.</li> </ul>
11. Equity considerations	<p>There are various mechanisms available for assessing equity implications of an intervention.</p> <ul style="list-style-type: none"> <li>● The method chosen should be appropriate to the decision problem and justifiable to the decision maker</li> <li>● Equity implications should be considered at all stages of the evaluation, including design, analysis and reporting</li> </ul>

## Reporting Standard

The decision problem should be stated, clearly identifying:

- Population (description and characteristics) in which the intervention to be used
  - Intervention(s) being evaluated and their Comparator(s)
  - Outcome being assessed (see principle 4)
- The characteristics of the economic evaluation should be stated, clearly identifying:
- Relevance for health practice and policy decisions
  - Constituency that the economic evaluation seeks to inform
  - Intended user(s) of the economic evaluation

The limitations of the economic evaluation should be transparent, including

- Limitations in the design, analysis and results
  - Aspects of the economic evaluation that limit the generalizability of results
- Declarations of interests should be reported including:
- Pecuniary and non-pecuniary interests of the study contributors
  - Sources of funding and non-monetary sources of support

Clear description of comparator(s) that includes:

- Basic descriptive information including setting where comparator is administered
- Statement of availability of the comparator across the population being considered

Differences between mean costs and effects of the intervention and chosen comparators should be reported as incremental cost effectiveness ratios

Describe approach used to obtain included evidence

- Systematic review protocol and evidence search strategies should be made available
- List sources of all parameters used in economic evaluation
- Describe areas where evidence is incomplete or lacking

Clear description of method of weighting used to inform the DALY plus

- Discussion of any important outcomes insufficiently captured by the DALY
- If DALYs not used, provide justification with description of impact of alternative measure.

- Quantities of resources should be reported separately from their unit costs/prices
- Report implications of changes in costs due to scalability of the intervention
- Capital and fixed costs should be annuitized over the period of implementation
- Costs should be reported in local currency and in United States dollars.

State the time horizon over which costs and effects have been evaluated, including additional analyses if different time horizons have been explored.

- If lifetime time horizon is not used, justify why and report impact of different time horizon(s)
- State the discount rate used for costs and effects, and include additional analyses using different discount rates.
- If a 3% annual discount rate is not used, justify why and report impact of different discount rate(s)

Clear description of the result of the base case analysis, plus

- Alternative analyses exploring impact of individual out of pocket payments and external funding should be explored
- Non-health effects and costs that fall outside the health sector should be reported and the mechanisms used to report impact of these cost and effects should be explained and justified
- If non-health effects and costs that fall outside the health sector are not included, reported reasons and estimations of the potential impact of exclusions

Clear reporting of:

- subgroup characteristics, and justification of why particular groups are chosen for subgroup analysis
- evidence base used to determine subgroup specification
- the cost effectiveness of the intervention in the different subgroups
- subgroups with potentially important differences in costs and effects but excluded due to lack of evidence

The effects of all types of uncertainty should be clearly reported, noting impact on final results.

- Uncertainty due to parameter precision should be characterized using sensitivity analyses appropriate to the decision problem.
- The likelihood of making the wrong decisions given the existing evidence should be addressed

Disaggregated and annualized budget impact analysis should be reported that shows budget implications for:

- Government and social insurance budgets
- Third-party payers
- Households and out of pocket expenses
- External donors

The method used to incorporate equity implications should be clearly and transparently explained.

- A minimum level of reporting should include a description of particular groups within the constituency that may be disproportionately positively or negatively affected by a decision to implement (or not implement) the intervention.

## Endnotes

- 1 Al-Aqeel, SA. State of health economic evaluation research in Saudi Arabia: a review. *Journal of Clinicoeconomic and Outcomes Research*. 2012;4:177-84
- 2 Hoque M, Khan J, Hossain S, Gazi R et al. A systematic review of of economic evaluations of health and health-related interventions in Bangladesh. *Cost Effectiveness and Resources and Resource Allocation* 2011;9:12.
- 3 Bill & Melinda Gates Foundation. *What we do - Bill & Melinda Gates Foundation*. [www.gatesfoundation.org/What-We-do](http://www.gatesfoundation.org/What-We-do). (accessed 17 May 2013)
- 4 Gold M, Siegel J, Russell L, Weinstein M. *Cost-effectiveness in Health and Medicine*. (New York: Oxford University Press, 1996).
- 5 Tan-Torres Edejer T, ed. *WHO guide to cost-effectiveness analysis*.: World Health Organisation, 2003.
- 6 National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013: Ch 5 -The Reference Case*.
- 7 International Society for Pharmacoeconomics and Outcomes Research. [www.ispor.org/PEguidelines/index.asp](http://www.ispor.org/PEguidelines/index.asp) (accessed 17 May 2013)
- <sup>8</sup> Review conducted by the Health Interventions and Technology Assessment Program (HITAP), Thailand, and reported in Section One of the Methods for Economic Evaluation Project (MEEP) Final Report. [www.nice.org.uk/niceinternational](http://www.nice.org.uk/niceinternational)



