Defining Appropriate Benefits for Economic Evaluation of Health Care Technologies

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Executive Summary

The Institute for Clinical and Economic Review (ICER – USA), Canada's Drug Agency (CDA-AMC), and the National Institute for Health and Care Excellence (NICE - England) have convened the Health Economics Methods Advisory (HEMA) group to provide independent and critical guidance on new methods and processes for economic evaluation. This first HEMA report focuses on potential extensions to the ***benefits*** considered in economic evaluation.

Economic evaluation used in the field of Health Technology Assessment (HTA) has largely relied on the 'core' elements of net costs and, to measure benefits, Quality-Adjusted Life Years (QALYs) gained for conducting economic evaluation. There have been recent calls for "novel value elements" to be added to this standard approach. These include a variety of concepts such as broadening the perspective regarding which costs and whose benefits should be included, reflecting patients' preferences (e.g., attitudes to risk), incorporating additional costs, equity considerations (e.g., consideration of health inequalities), different ways to reflect the value of innovation, and benefits which may be valued but are unrelated to changes in health outcomes. Many of these ideas have been summarized in the 'ISPOR Value Flower' developed from an ISPOR task force on defining elements of value in health care.

This report sets out and then applies a set of principles to guide HTA organizations in considering whether and how to incorporate a subset of these suggested 'novel value elements' - those associated with benefit measures in economic evaluation. The report has three objectives: 1) to define a set of principles to support HTA organizations' decisions about extending or adapting the measures of benefit in economic evaluation; 2) to appraise recent proposals to extend or adapt benefits used in economic evaluation for HTA; and 3) to apply the principles to these recent proposals with recommendations for HTA organizations. The set of principles are:

- Relevance: additional benefits should be relevant to the responsibilities, objectives and decisions of the HTA organization.
- Valuation: benefits must be aggregated (valued) appropriately and consistently with average preferences of the general population rather than preferences of specific individuals, and avoid double-counting.
- Opportunity cost: any additional benefits need to be reflected in the benefits forgone elsewhere resulting from the funding of more expensive interventions.

We distinguish in-scope from out-of-scope novel value elements proposed in the literature. In-scope elements are those considered to be benefits in that they constitute part of the objectives that decision makers may seek to achieve from the use of their limited resources. These include broad domains related to risk attitudes (e.g., the value of hope and insurance value); process benefits (such as the value of knowing about disease from diagnostics); equity (e.g., giving larger

weight to potential health gains for those subject to unfair health inequalities); and expanding the perspective of economic evaluation (e.g., including productivity effects of treatments). One example, the value of hope, stems from individuals' attitudes to risk. This includes the concept of "prudence", where patients assign greater value to treatments with health outcome possibilities or distributions with long right-hand tails (i.e., large positive outcomes with very small probabilities) compared to treatments without this feature but the same expected (average) outcomes and level of risk. Another example of potential additional benefits is the category of "process utility" benefits such as the value associated with information about future prognosis with no impact on health outcomes.

Out of scope value elements for this report are unrelated to defining benefit (e.g., dynamic pricing). These proposals may be the subject of future reports.

We expand on our principles above, two of which relate to normative positions or value judgements. The first relates to how the benefits of interventions in individuals are characterized. Most HTA bodies – including the three which are the focus for this report – see benefit in terms of the health of the populations for which their health systems are responsible. This is notably different from the ideas underlying some novel value elements which relate to individual benefits expressed as patients' preferences and choices.

The second principle relates to how to aggregate benefits across individuals, which is sometimes referred to as valuing benefits. This is necessary to reflect the inevitable trade-offs to be considered in developing a quantitative expression of overall benefit in economic evaluation, which is essential to inform decisions (e.g., between different dimensions of health and between survival and health-related quality of life [HRQoL]). The standard normative position by HTA organizations regarding this concept is to reflect trade-offs using the average preferences of a representative sample of public preferences in the organization's jurisdiction. Again, this is in contrast with the implied normative position of some of the novel value elements which focus on individual patients' preferences.

The third principle is an evidential requirement rather than a normative position, and this relates to opportunity costs. All health care systems funded collectively, whether via taxation or insurance, impose opportunity costs when they devote additional resources to new medical technologies and other interventions. This is because those additional resources are inevitably taken from interventions and services which could have benefited other patients, and the opportunity costs are the consequent reduction in those individuals' health outcomes.

Proposals regarding new value elements often do not give due consideration to opportunity costs. For example, the incorporation of individual risk attitudes entails a significant departure from the normative position of using average public preferences, moving to an individual willingness-to-pay (WTP) framework where patients' willingness to forgo their own consumption in exchange for

improved health drives the definition of benefit. However, even in insurance-based systems, the need to understand and to reflect opportunity costs (which may result in population-level premium changes and insurance disenrollment) remains necessary and yet may be empirically challenging to reflect individuals' risk attitudes in opportunity costs. Moreover, the limited existing empirical evidence on individual risk attitude to their own health suggests the greatest priority is not given to states with the most severe health, but to those around the center of the range of possible levels of health.

It has been widely argued that equity considerations should be included in benefit measures for economic evaluation. If distributional concerns across individuals (e.g., with different disability status, baseline health, or severity) are considered part of the decision makers' responsibilities, there are multiple frameworks that may be useful for HTA organizations. For example, frameworks using weightings to reflect disease severity or the concept of a "fair innings" are available for HTA organizations to use. Severity weighting approaches that build on the public's preferences regarding equity across people fundamentally differ from novel value frameworks that relate to individuals' preferences for their own health. However, regardless of which approach is taken, HTA organizations still need to manage the implications for opportunity cost of attaching weights greater than one to gains for patients with severe disease as compared to weights less than one for gains for less severe disease.

In considering whether to broaden the perspective of economic evaluation, the implications of difficult trade-offs for decision-makers' responsibilities need to be considered. Perhaps most notably, they will need to be accountable if some new interventions generate positive benefits in terms of wider attributes of social benefit such as productivity but lead to reductions in population health, either directly or through their opportunity costs.

The central aim of this report is to provide guidance to help HTA organizations assess whether additional or alternative benefit measures should be incorporated into economic evaluation. The guidance is grounded in the three principles above. Applying these principles, we have the following recommendations for HTA organizations:

- When considering additional measures of benefit for economic evaluation, HTA organizations should assess these against the principles outlined in this report.
- No additional benefits should be routinely incorporated into economic evaluation until there is an evidential basis to reflect them in opportunity costs. This is essential to ensure comparability and consistency in decision-making, and to avoid inappropriate resource allocation.
- The deliberative process within HTA, which may consider potential additional benefits qualitatively, should not be used in a way that bypasses the consideration of opportunity costs. HTA organizations should consider how the design of their processes, including any pre-specification, may avoid bypassing opportunity costs.

- In private insurance systems, any potential movement towards willingness to pay approaches in benefit design should not be considered a substitute for opportunity costs.
- HTA organizations that have adopted a normative position to use average public preferences to define benefits for economic evaluation should not simultaneously incorporate individual patient preferences, as this lacks a coherent normative basis.
- HTA organizations should provide a clear normative basis and measurement approach when applying 'modifiers' (e.g., for severity) as an expression of equity considerations.
- Risk attitudes for individuals' own health could, in principle, be elicited from the public, but more research is necessary on how to address the risk of double-counting with 'modifiers' such as severity weights in the context of HTA decisions.
- Distributional cost-effectiveness analysis provides a framework for building distributional considerations into economic evaluation but, if used, needs to be used in all assessments.
- If specific benefits associated with the process of care (e.g., the value of information about disease prognosis) are to be included in economic evaluation, further research is necessary to ensure there is no overlap with routinely used health-related quality of life measures.
- If broadening the perspective of economic evaluation to include benefits to the wider economy (e.g., productivity) or other sectors (e.g., education) is considered consistent with decision makers' remits, additional evidence requirements must be considered (e.g., opportunity costs by sector and trade-offs between different outcomes relevant to each sector).

1. Introduction

1.1. Background

Health technology assessment (HTA) has been defined as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle.[7] It is used in many countries to assess and generate evidence to support decisions about what new medicines and other interventions should be funded from the available resources, and at what prices. HTA processes are in place in various jurisdictions with health systems that draw on collective funding through taxation or insurance to provide care and services to specified populations. Some of these jurisdictions use economic evaluation as a quantitative framework as part of HTA given the funding constraints that exist in all systems. In broad terms, economic evaluation in HTA is seeking to establish whether the additional benefits generated by (typically new) interventions can justify calls on limited funding available.

The methods of economic evaluation have developed over time and have always been contentious. In recent years there have been calls for these approaches to incorporate additional or "novel" value elements. These include a variety of concepts such as broadening the appropriate perspective (regarding which costs and whose benefits should be included), reflecting patients' preferences (e.g., attitudes to risk), incorporating additional costs, accounting for equity, including benefits which are unrelated to changes in health outcomes and reflecting implications of funding decisions for innovation. Many of these ideas have been summarized in the 'ISPOR Value Flower' which followed ISPOR (The Professional Society for Health Economics and Outcomes Research) task force on defining elements of value in health care.[8] "Generalized Cost-Effectiveness Analysis" (GCEA) is the term recently used to describe proposals to incorporate these ISPOR Value Flower elements into cost-effectiveness calculations.[3]

Some of these proposed methods are already in place in some jurisdictions, others have been suggested previously, and some are new and are the subject of ongoing research. In this first Health Economics Methods Advisory (HEMA) report, we consider one area where extensions and adaptations in economic evaluation methods have been suggested – what is included in the measure of ***benefit***. Other proposed elements of value may be considered in later reports. Alongside quantitative economic evaluations methods, HTA also typically includes deliberation processes to consider some evidence (see Box 1), but this is outside the scope of this report.

To distinguish the focus of the report from the broader interest in "novel elements of value", it is important to define how the report is using the term "benefit". Built into any economic evaluation is an assumption, understanding, or explicit instruction about decision makers' objectives. That is, attributes of social value that decision makers wish to see achieved from the limited resources available. Inevitably, these social objectives are complex, and it is unlikely that a quantitative

analysis will be able to capture them fully; there are also likely to be trade-offs between them. As such, “benefits" for the purpose of this report can be understood as measurable outcomes that reflect (inevitably, partially and imperfectly) these attributes of social value and the range of authority (remits) of the organizations they represent, and for which they are (at least in principle) held accountable. These attributes are distinct from the resources available to achieve them, so achieving cost savings by the introduction of a new technology is not considered a direct benefit here but can generate benefits by freeing up resources for the management of other patients. There is significant variation between jurisdictions in how fully these attributes are defined in policy and reflected in HTA. Furthermore, there are inevitably multiple potential attributes, so it is helpful to think of a “benefit function” as an aggregation or “valuation” of measurable outcomes using weights reflecting the preferences of a relevant group (e.g., the public, patients, and decision makers).

Box 1. Deliberation in HTA

The focus of this report is quantitative economic evaluation to inform decisions. However, HTA organizations also use deliberation to exchange views and perspectives on “contextual factors” or considerations that expand the evidence beyond quantification in analyses such as comparative-effectiveness and cost-effectiveness analysis.[1] This report was largely focused on quantified benefits as well as their weighting and aggregation, leaving out contextual factors. However, in actual health care priority setting, any benefits that fit within the scope of the principles outlined in this report but cannot be quantified can and often are moved to a deliberative step. Indeed, constructs such as equity in health decision-making and community-level benefits are often considered in HTA deliberation.[2] Some have suggested that additional value elements such as “scientific spillovers” should be discussed in deliberation.[3]

Like changes in weighting and aggregation of benefits, it is important for HTA organizations to acknowledge that movement to the deliberative step constitutes movement away from economic evaluation and into a broader decision process. For example, empirical evidence suggests group perceptions (e.g., “voting panels”) of the value of health technologies and coverage and reimbursement decisions are not always aligned with economic evaluation conclusions.[2,4]

While this broader decision process is out of scope for this report, continued proposals to extend the benefit function may lead to HTA organizations asking how much “weight” should be placed on qualitative value elements (e.g., scientific spillovers) against often quantitative evidence on the cost-effectiveness of new health care technologies.[5] In other words, any deliberative process may acknowledge opportunity cost as a factor, but a major challenge remains in appropriately accounting for the additional unquantified value elements in opportunity costs. Recent good practice recommendations on deliberative practices suggest prioritization as an important step for specifying the scope of deliberation to ensure transparency and consistency in decision making.[6]

Given that economic evaluation supports decisions about how resources are allocated across different indications, patient groups and clinical areas, a key principle is that the benefit function is "generic". This means the changes in benefits associated with new interventions can be compared across disparate conditions, providing a common yardstick of performance of interventions. Importantly, any support for decisions where a new technology costs more than the intervention(s) it is replacing requires economic evaluation to reflect the benefits that could have been generated by using those additional resources elsewhere – in other words, the opportunity costs. A generic benefit function is also necessary so that it applies symmetrically to both the additional benefits of new investments and those forgone by others because of the cost of the new investments. Given the range of decisions HTA organizations need to take over disease areas and time, the definition of a benefit function that is consistent is important.

Inevitably, the specification of a benefit function will be contested – both its constituent parts and the weights - and a social consensus will be impossible. This is consistent with the long-recognized understanding in economics of the impossibility of deriving a "social welfare function" from the preferences of individuals. Economic evaluation has evolved, therefore, by seeking to infer a suitable (but inevitably incomplete) benefit function from decision makers and their organizations. In the field of HTA, the function has centered on health outcomes on the basis that, even if this does not cover the entirety of decision makers' remits, it is likely to be front and center. It has distinguished the potential impact of interventions on survival duration and health-related quality of life (HRQoL). The scope of the former is uncontroversial, although the evidence is often a challenge to generate; what is included in the latter has been a source of debate and there is variation in how HRQoL is measured and its weights determined. The benefit function which has typically brought these two components of health benefit together is the Quality-Adjusted Life Year (QALY). Although this benefit function has been used in numerous evaluations over many years, it has been controversial as would be any defined function. Attempts to address the perceived weaknesses of the QALY have drawn further critiques (See Box 2). [9]

Box 2. Alternatives to the QALY

Attempts have been made to generate alternative measures of health which overcome the perceived limitations of the QALY. We do not address these alternatives formally in this report given they include similar individual measures of health benefit as the QALY (i.e., survival duration and HRQoL) but combined in a way to avoid the multiplicative nature of QALYs.

Alternatives including Equal Value Life-Year (evLY) and Health Years in Total (HYT) change the existing QALY calculation to form an alternative combination of HRQoL and life extension.[9,10] For example, the evLY assigns a uniform value to all extension to life, at the rate equivalent to that of an average individual within the general population. That is, there is no decrement assigned to this period for any impact of the condition, other conditions, or aging, on HRQoL. These are now calculated and reported routinely by ICER alongside cost per QALY estimates. One limitation of the evLY is that it penalizes a treatment that also improves HRQoL more than another intervention during the same period of life extension.

HYT is an additive approach which avoids this limitation by assuming a counterfactual scenario of HRQoL.[9] Specifically, when comparing a new intervention that extends life over an existing intervention, it asks what the HRQoL would have been among patients getting the existing intervention had those patients remained alive. Estimates of HRQoL and survival are then summed up instead of relying on the existing multiplicative assumption of QALYs. The limitations of HYT include implausible assumptions surrounding separation of HRQoL from the life extension component and counterfactual scenarios for HRQoL scores among patients already deceased.[11] Both HYT and evLY cannot provide absolute summary estimates of HRQoL and survival duration for a particular treatment as they rely on outcomes from mutually exclusive alternative treatments to generate incremental cost-effectiveness ratios.

A raft of other alternative measures have been proposed to address different perceived shortcomings of the QALY: SAVEs (Saved Young Life Equivalents) questions the interpersonal comparability of the QALY,[12] DALYs (Disability Adjusted Life Years) aim to quantify the burden of disease within a population,[13] HYEs (Healthy-Years Equivalents) attempts to circumvent the violation of additive separability, and WELLBYs (Wellbeing Years) challenges the relevance of decision utility used to value health states.[14,15] Reviewing each of these in any detail is beyond the remit of this report. Adoption of these measures for HTA has been limited outside specific settings. None has demonstrated empirical evidence that they align with either public or patient preferences, though not all would claim such alignment.

1.2. Aims and Objectives

The aim of this report is to provide a framework to help decision making (HTA) organizations decide on possible changes to the benefit function used in economic evaluation. Although the framework is intended to be broadly applicable across HTA organizations, the focus is on the needs of three bodies: the National Institute for Health and Care Excellence (NICE) in England, Canada's Drug

Agency (CDA-AMC), and the Institute for Clinical and Economic Review (ICER) in the USA. The health systems in which these organizations operate, their roles and responsibilities, and their current preferred methods of deriving benefit functions for economic evaluation differ in various ways (see Table 1), which may shape the extent to which modifications to the benefit function are feasible, appropriate or desirable in each setting.

Table 1. Health Technology Assessment Descriptions

Health Technology Assessment Entity	Description
The National Institute for Health and Care Excellence (NICE)	NICE was formed in 1999 as a national advisory body accountable to the Secretary of State for Health with its functions set in legislation. NICE provides advice to the largely tax-funded funded National Health Service (NHS) in England on the clinical and cost effectiveness of health technologies. The NHS has a budget set by government. When NICE recommends a technology through its technology appraisal or highly specialized technologies program, the NHS must make sure funds are available within 3 months (unless otherwise specified) of the guidance publication. Under its statutory framework, NICE is required to have regard to the broad balance between the benefits and costs of the provision of health services or of social care in England, the degree of need of persons for health services or social care in England, and the desirability of promoting innovation in the provision of health services or of social care in England. This is reflected in NICE's statement of principles.
Canada's Drug Agency (CDA-AMC)	Canada's health-care system is publicly funded and provides universal coverage for hospital and physician services. Coverage for prescription drugs is made up of public and private insurance. CDA-AMC is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in the health care system. CDA-AMC's Drug Reimbursement Reviews provide non-binding recommendations to federal, provincial and territorial public drug plans. Different plans have different mandates and priorities and make their decisions independent of one another.

Health Technology Assessment Entity	Description
Institute for Clinical and Economic Review (ICER)	In the United States, the Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs.

The specific objectives of the report are:

I. To define a set of guiding principles to support HTA organizations' decisions about potential changes in the benefit function used in economic evaluation.
II. To appraise recent proposals to extend or adapt the benefit function used in HTA. Particular attention is given to frameworks such as the ISPOR Value Flower and GCEA, which have shaped much of the current debate. Others are also considered. No attempt is made to be exhaustive regarding these proposals.
III. To apply the proposed principles to these additional benefits and generate recommendations for HTA organizations.

We first set out the purpose of economic evaluation in the context of health care decision making (Section 2). We then propose a set of key principles to be used to determine which benefits are relevant (Section 3). Section 4 provides an overview of proposed additional value elements and classifies these according to the types of issues they refer to and identifies which are of potential relevance to the assessment of benefits. Those elements considered in scope for this report are assessed according to the key principles. Finally, Section 5 concludes with recommendations for HTA organizations when considering additions to the benefit function.

2. Why Is Economic Evaluation Undertaken?

Whether in the context of HTA or more generally, economic evaluation in the field of health is undertaken to support decisions about resource allocation in the face of constraints on expenditure. In some health care systems (e.g., the NHS in England), there are explicit budget constraints, although running time-limited deficits may be possible in some instances. In other systems, decision makers do not face explicit budget limits but there are still limits to the extent to which expenditure can be increased, at least in the short term. In the context of collectively funded health care (whether those funds come from taxation or insurance, or some combination of these), no system has unlimited scope to increase spending.

The consequence of constraints on health system expenditure is that new medicines and other technologies are competing for limited resources, although the details of what resources are available will vary by system. In effect, multiple claims are being made through HTA submissions, on behalf of different groups of patients and other recipients, on health systems' constrained ability to fund. Whenever additional funding is granted to a new technology which benefits one group of patients, there are inevitable negative consequences for the benefits of others as their claim on resources has been weakened.

These negative consequences constitute opportunity costs and can come in different forms, partly depending on the system. In a tax-funded and budgeted system like the NHS in England, additional spend on a new technology will inevitably mean less funding being available to meet the claims of other patients, either in terms of other potentially fundable new technologies or the rules or timing of access to existing care and interventions. In insurance-based systems, opportunity costs can be incurred through different routes such as increased premiums, other out-of-pocket costs such as co-payments, or offsetting reductions in coverage. The Canadian system is a decentralized, federated model where these constraints are primarily realized within the budgets of individual provincial and territorial health systems. While collectively funded, resource allocation decisions and the resulting opportunity costs are incurred at the province/territory level. Regardless of the jurisdiction, evidence on the quantification of opportunity costs associated with increased expenditure is only now (and partially) being reflected in economic evaluation in health.[16]

This reality has clear implications for how benefits are considered in economic evaluation. If the measure of benefit is extended or adapted for a new intervention, this can advantage some patients in the claim made on their behalf. However, to be consistent, that same extended definition of benefit must be applied to other patients who potentially bear the opportunity cost. Hence economic evaluations would need to reflect the extended benefits symmetrically: both in terms of the gains from a new intervention and the benefits forgone by others due to depleted resources. In other words, if benefits are valued differently across populations of patients, some

patients will be advantaged whilst others will be disadvantaged, but this would not be fully reflected in the economic analysis.

3. Principles Guiding Benefits

We propose a series of principles to guide whether a proposed change in the benefit function warrants inclusion in HTA-based economic evaluation as described in Table 2.

Table 2. Summary of Principles Guiding Specific Benefit Inclusion in Economic Evaluations

Principle	Brief Description	Rationale
Benefits must be relevant for the decision-making organization and for the decisions of interest.	This should reflect the statutory, legal or other authorities of the decision-making organization, as well as the expressed objectives and responsibilities of those responsible for decisions. In general, under current approaches, health, as opposed to individual patients' preferences (utility) or happiness, is the key benefit of interest for HTA organizations. Preferences play a role in quantifying health, reflecting key trade-offs in some aspects of HRQoL and length of life.	All three HTA organizations for which this report is developed state a focus on health as opposed to individual patient utility. NICE's charter indicates that its "role is to improve health and wellbeing by putting science and evidence at the heart of health and care decision making" .[17] Canada's Drug Agency (CDA-AMC) describes its primary goal as generating "better health, better patient experience, and better value for Canadians."[18] The Institute for Clinical and Economic Review (ICER) states that the end goal of its work on comparative clinical effectiveness and cost-effectiveness is to "sustainable access to high-value health care for all Americans."[19]
Benefits must be aggregated (or valued) in an appropriate manner.	Current approaches by HTA organizations in general value benefits to reflect the average preferences of the general population in the relevant jurisdiction rather than preferences of specific individuals. Benefits need to be expressed in a consistent way across disease areas.	HTA informs population-level decisions around coverage and reimbursement of new medicines and health technologies.[20] Individual health care decisions are made downstream between physicians, patients, and families. This reflects the current position of the three HTA organizations for whom this report is developed.[20-22] Consistent valuation across diseases is necessary to compare benefits and opportunity costs.

Principle	Brief Description	Rationale
Need to reflect any additional benefit in the assessment of opportunity costs.	Any additional benefit should be reflected not just in the evaluation of new technologies but also in the benefits that would have accrued to current or future patients had additional resources not been devoted to those new technologies.	In resource constrained health systems, policy making involves trade-offs where any allocation of a limited resources involves benefits for some patients and lost benefits for other patients in the system. NICE's principles indicate that "Resources need to be allocated appropriately and fairly. They must provide the best outcomes for the finite resources available while balancing the needs of the overall population and of specific groups".[23] ICER is explicit that it seeks to consider opportunity costs.[20] CDA-AMC state that it adopts a "supply-side" estimate of the cost-effectiveness threshold, which assumes that reimbursing a new technology will displace some other technology or health care service."[21]

3.1. Relevance

As outlined in Section 1, HTA organizations generate guidance for different parts of health care systems. While there is some degree to which these HTA organizations can determine the methods used to produce this guidance, they must be relevant to the needs of the health care systems they impact. A set of remits and constraints, which vary in the extent to which they are explicit, need to be reflected by HTA organizations in their approaches to economic evaluation. This has typically led to a focus on health as the key benefit of interest from these assessments as is apparent in those jurisdictions that use the QALY as the measure of benefit. Here, health is the focus of evaluation not because it enhances the utility of individuals (though it undoubtedly does), but as a socially valuable objective in its own sake. Preferences of the public are typically used to measure health, as is the case when calculating HRQoL weights for QALYs. So, there is some role for the representation of preferences between different aspects of HRQoL and between HRQoL and length of life.

This differs fundamentally from approaches that are more closely aligned with mainstream micro-economic theory, where it is the utility of those individuals consuming interventions that are

paramount. In the context of healthcare decision making, it has been argued that a focus on individual patient utilities may not be appropriate because: it penalizes a patient's adaptation to ill health; there is an unwillingness to treat health differently according to ability to pay; and, more broadly, the standard model of consumer behavior (and associated concepts of individual consumer sovereignty as well as willingness and ability to pay) are not appropriate for health and healthcare.[24,25]

This distinction between utility of individuals versus health as (one of) the benefits of relevance in healthcare is a key normative distinction between what has been termed "welfarism" and "non-welfarism" based approaches.[26] This topic has been subject to significant debate in the health economics literature and, while the details do not require rehearsal here, it does reinforce the need to consider the relevance of any claimed new benefit to the decision making context, how it may relate to these normative concepts of health versus utility, and the degree of consistency with any other benefits advocated for inclusion in economic evaluation.[7,19,24,27-32]

For the three HTA organizations for which this report is primarily developed, the focus on health can be justified because it aligns with explicit institutional mandates or statements of remit (Table 2).

3.2. Valuation

Valuing benefits involves aggregating different types of benefit and making trade-offs explicit within what can be termed a benefit function. This involves subjective judgement, so preferences inevitably shape valuation. As with Section 3.1, there is a clear distinction between valuation approaches that align more closely to mainstream microeconomic theory versus those that purposely depart from it. The former approach holds that the level of utility from different policies be assessed by the affected individuals themselves. However, economic evaluation generally used in HTA and, specifically by the HTA organizations which are the focus of this report, departs from this approach. This is because a normative position has been defined both by using "health" as the primary category of benefit (see Section 3.1) but also in that preferences should reflect the average of a sample of the public. As Brouwer et al state, "in acting as agents for their clients, the public, we do not have to assume that decision-makers are acting as they think the principals whom they represent would act, but rather as they think they ought to act."[24] In both tax-funded and insurance-based systems, arguments can be made that preferences of the public are relevant as a proxy for potential future patients or as a representation of collective views about what should be insured.[33]

The dominant QALY-based approach to economic evaluation recognizes that health comprises both length of life and HRQoL and that, in general, individuals have preferences that lead them to accept trade-offs between these two aspects, and between the dimensions of HRQoL such as physical

functioning, pain and mental health. However, the preferences that this approach seeks to reflect are, typically, an average of those of the general population rather than individual preferences of the patients who actually experience, or may experience, the health benefits in question (although they will be represented among the sample of the public). These normative value judgments are another area that is the legitimate domain of decision makers and the bodies they represent, and their choices can be justified by a range of arguments including not wishing to penalize adaptation to a particular disease or condition, reflecting the preferences of taxpayers, and avoiding vested interests.[34] Hence the principle used here that any additional benefit is valued appropriately is, in part, based on the normative starting point about the use of average public preferences used in most economic evaluation in general and the HTA organizations commissioning this work in particular.

A second aspect of appropriate valuation requires that we avoid the error of counting the same benefit multiple times. This requires us to assess each category of benefit to ensure it does not overlap in full or in part with other types of benefits. Where such overlap potentially exists, accurate measurement methods that facilitate the identification of and control for double-counting are required.

3.3. Opportunity Costs

Economic evaluation is fundamentally concerned with measuring and valuing the benefits of alternative health care technologies and comparing these to their opportunity costs. The latter needs assessment of both the net costs of the new interventions compared to what they seek to replace, and the benefits forgone elsewhere in the health system because of any additional net cost. As presented in Section 2, this means that ***any*** aspect of benefit must be considered symmetrically both for health technologies that are the direct subject of the economic evaluation and for any existing or potential healthcare (or other goods and services if relevant) that is displaced because of additional spending. This is not a normative position but, rather, an evidential requirement of any economic evaluation in the context of constrained expenditure.

Despite the centrality of such evidence to all collectively funded systems, the role of opportunity cost is often underappreciated in HTA, even in relation to publicly funded and explicitly budget-constrained healthcare systems. For example, in Canada HTA practice relies on conventional benchmarks (e.g., CAD $50,000 per QALY). Policy makers should exercise caution around claims that any additional type of benefit applies only to special case new technologies such that the impact on opportunity cost is trivial and may be ignored. Estimates of opportunity cost in the form of the marginal change in health outcomes given a marginal change in expenditure have been generated in several countries, including the UK and USA, and international estimates are also available.[35-38] These are generally based on regression models using aggregate national or international data. As

for much evidence used in HTA, current estimates of opportunity cost are subject to uncertainty and would be improved by additional data collection and further development in methods. Extending measures of benefit before this can be reflected in opportunity cost estimates risks poor decisions and misallocation of resources.

In standard cost-effectiveness analysis, the way opportunity cost is introduced conceptually is usually through a cost-effectiveness 'threshold' against which an intervention's incremental cost-effectiveness ratio is compared to inform a funding, reimbursement or pricing decision. However, these thresholds are often not made public or reflect a range of considerations which may or may not include opportunity costs. This has led to the suggestion that thresholds should be seen as decision norms and distinct from opportunity cost estimates; however, the latter should still be reflected in HTA decisions and available to support transparency.[39]

Although the link between the cost-effectiveness thresholds currently used by HTA organizations and evidence on opportunity cost is uncertain, adapting the benefit function while retaining the existing threshold on the assumption such a threshold reflects opportunity costs would risk making inappropriate decisions. This risk can be illustrated by research which explored the implications of NICE adding productivity to its measure of benefit. Productivity can be added to the estimated additional benefits of a new intervention because of improved health in the indicated population, and this will presumably be expressed in monetary terms. However, any additional cost to the health service due to the new intervention will have negative effects on other patients' health which will also be reflected in productivity, and therefore needs to be included. Otherwise, the analysis is only partial and provides potentially misleading information to decision makers. The extent of the error in such an analysis depends on the magnitude of the productivity effects, but the earlier analysis showed that, when NICE makes decisions to recommend a new technology which imposes additional costs on the NHS and hence involves other patients forgoing health, each lost QALY in opportunity cost is also associated with an average a net productivity effect of £11,600.[35]

The US system in particular deviates from the UK and Canada, with no central insurance or funding system that provides access to healthcare for all citizens; however, opportunity cost remains relevant. Insurance plans in the US can increase premiums or make other changes which impose higher costs on policy holders to cover new interventions, which may lead to the loss of plan members who cannot afford premium increases. Among those who drop coverage, a percentage experience higher mortality and morbidity from lost access, which has been calculated to amount to 10 QALYs lost in population health for every $1 million increase in insurance expenditures (i.e., in the form of pass-through premium increases).[38] Furthermore, the health opportunity cost of increasing health care spending largely falls on vulnerable populations - those most likely to drop insurance coverage when premiums increase. The use of cost-effectiveness thresholds reflecting opportunity cost as a guide for understanding trade-offs, with a strong consideration of additional contextual factors, remains useful to payers in the US system.

Some have argued that cost-effectiveness thresholds should reflect the 'willingness to pay' of those covered by a health system for additional health (i.e., their willingness to forgo their own consumption in exchange for improved health).[40] Sometimes called a 'demand-side' threshold, this assumes that the funding available to systems through insurance premiums, taxation or otherwise, adjusts to reflect those willingness to pay preferences. Such an approach can potentially guide the level of future health expenditure but using it as the basis of a cost-effectiveness threshold for the use of current health care funding is problematic.

4. Additional Value Elements

In this section, we examine proposed additional value elements from the health economics and related literature with a goal of determining their fit within a health benefit function using the principles outlined in Section 3. The literature on additional value elements continues to expand. Therefore, we do not aim to be exhaustive in covering this, but rather to illustrate some examples, mostly from the original ISPOR Task Force,[8] against the principles outlined in Section 3.

The "petals" of the value flower include scientific spillovers, equity, real option value, value of hope, severity of disease, fear of contagion and disease, insurance value, value of knowing, productivity, and family spillovers, in addition to core elements including QALYs and net costs. Recent versions of the value flower have grouped more value elements into four categories: uncertainty, dynamics, beneficiary, and additional elements.[3] We also refer to other concepts of benefit that have been mentioned in the literature. The principles need not be applied solely to existing proposals for additional value elements but also to any emerging in the future.

4.1. Do Proposed Value Elements Relate to Benefits?

We first consider each proposed novel value element (in addition to health as generally expressed in economic evaluation in HTA) and assess whether the proposals relate to benefits for inclusion in economic evaluation. Table 3 briefly summarizes those elements that were considered to meet the scope and the rationale for this thinking. We group these elements into four categories: Risk Attitudes, Non-health Benefits From the Process of Care, Equity, and Perspective. Each category, and different aspects within it, is further described in Sections 4.2 - 4.5, where we apply the principles that were proposed in Section 3.

Table 3. Value Elements in Scope

Domain	Alternative Names and/or Elements Within Domains	Description of the Value in Relation to a Health Intervention	Justification
1. Risk Attitudes			
Outcome Certainty	Value of hope; Value of reducing risk in health outcomes	The value of reducing risk in health outcomes and the potential for favorable outcomes from a health technology.	Incorporating risk attitudes (e.g., risk-seeking or risk-averse) may reveal a sub-set of patients willing to trade-off survival for a small probability of reaching the average survival curve in a general population without their condition.[3]
Risk Protection (Insurance Value)	Peace of mind value; Insurance value; Physical risk protection and financial risk protection; Disease risk reduction	Availability of the technology reduces risk of disease and its unfavorable physical and financial consequences	A medical technology can reduce physical risk for healthy consumers who might get sick in the future. New technologies make illness less unpleasant and thus effectively raise utility. Furthermore, medical technology does not merely create financial risk. Rather, it expands insurance possibilities by converting a previously uninsurable physical risk into a potentially insurable financial risk. Financial insurance value is the incremental gain to risk-averse consumers from gaining access to financial healthcare insurance.[41]
Patient-Centered Health Improvements	GRA-QALY (Generalized Risk-Adjusted QALY)	HRQoL and length of life gains are benefits but the way in which they are calculated differs from standard approaches.	Incorporating risk attitudes of patients into benefits replaces the existing HRQoL weights used in HTA with expected utility as a function of the probability distribution of possible health outcomes along with a HRQoL utility function.

Domain	Alternative Names and/or Elements Within Domains	Description of the Value in Relation to a Health Intervention	Justification
2. Non-Health Benefits from the Process of Care			
Process Utility Value of Knowing	Value of diagnostics; value related to care and delivery of services	Value of informed treatment decisions, reducing uncertainty surrounding a patients' health status. Aspects of interventions not directly impacting health (e.g., information, relationships with providers)	Specific value from diagnostics may reveal future risk of disease and offer patients informed decisions in advance of care. Other aspects of the process of care can impact patients' satisfaction with services but not their health outcomes. Depending on condition, may impact HRQoL in positive as well as negative ways.[3]
3. Equity			
Equity	DCEA (Distributional Cost-Effectiveness Analysis)	Societal preferences for reductions in inequity.	Explicit incorporation of weighting of health benefits across heterogeneous patient populations to potential health gains for disadvantaged populations.
4. Perspective			
Family and Caregiver Spillovers		Patients' family members and friends are also affected by the financial and non-financial burdens of providing care.	Incorporation of the effect of a treatment on caregiver HRQoL and the financial impacts at the family and/or caregiver level.
Community Spillovers		Individuals not infected by an infectious disease can be impacted via behavioral change in response to fear of infection e.g. closing of schools in COVID.	Incorporated into economic evaluation through behavioral impacts, medical costs, and non-medical costs.

Domain	Alternative Names and/or Elements Within Domains	Description of the Value in Relation to a Health Intervention	Justification
Productivity	Work loss, presenteeism, absenteeism, labor market participation	Reduced productivity while at work or reduced ability to go to work.	Disease-specific productivity impacts presenteeism, absenteeism, unemployment, productivity loss due to premature death, and gains in productivity gains from life extension. Differences in productivity are potential positive impacts of health interventions and therefore benefits, even though expressed in monetary units. That is, they are distinct from the cost of resources used to improve health and are only realized because of improvements in health outcomes.

Table 4. Additional Value Elements Out of Scope

Domain	Alternative Names and/or Elements Within Domains	Description of the Value in Relation to a Health Intervention	Justification	Rationale for Exclusion
Dynamic Pricing	Dynamic net health system costs	Price changes both pre- and post-loss of exclusivity for a technology or class of technologies.	In certain monopolist environments, manufacturers may increase prices during a period of exclusivity after initial market approval; oligopolist scenarios reduce the price during patent exclusivity; genericization may be implemented by government entities or because of post-exclusivity competition.3	Relates to how possible price changes over time might be handled in economic evaluation which varies by health system. The proposed inclusion of dynamic pricing is independent of (and involves no change in) the existing benefit function.
Dynamic Disease Prevalence	Stacked cohorts	Technology will impact prevalence of condition over lifetime horizon.	If there are substantial differences in cost-effectiveness between cohorts or if the technology has shared effects.[42]	This is a modelling issue, which changes how net costs or epidemiology evolve over time and involves no change to what is considered in the benefit function.
Option Value	Real option value	The value of a technology to extend life for an average patient to take advantage of future approved technologies. Safrin et al (2024) further distinguish ex ante from ex post.	The concept that health benefits and costs in the future may be impacted by innovation in present day.[3]	This relates to whether the additional benefits associated with keeping patients' options open should count and, if so, how. It does not redefine which types of benefits should be considered.

Domain	Alternative Names and/or Elements Within Domains	Description of the Value in Relation to a Health Intervention	Justification	Rationale for Exclusion
Scientific Spillover	Novel mechanism of action	A new mechanism of action can be of value because it can have positive spillover effects in other clinical areas.	A drug with a new mechanism of action might not in itself be very valuable, but the knowledge that the mechanism works might lead to other more valuable drugs in the future, even to treat very different diseases. The first drug with a novel mechanism of action unlocks the value of the later innovations.[3,8]	This relates to whether the benefits of future R&D in terms of new products because of expenditure on current products should be counted and if so how. It does not relate to which benefits of current and future products should be considered. The case for reflecting such spillovers applies whether the benefit function is defined, for example, in terms of standard QALYs, or QALYs plus productivity and would not change that choice of benefit.
Societal Discount Rate		Standard analyses use a discount rate for costs and benefits. GCEA proposes to use empirically derived societal discount rates based on positive or normative approaches.	The positive approach treats health as an asset whose opportunity cost should be compensated by future returns to health, represented by a risk-free interest rate. Whilst the normative approach utilizes the Ramsey equation to derive a Pareto efficient optimal rate.	No consideration of an alternative or additional items in the benefit function.

Domain	Alternative Names and/or Elements Within Domains	Description of the Value in Relation to a Health Intervention	Justification	Rationale for Exclusion
Adherence		Better adherence generates greater (health) benefits and should be reflected.	Incorporating possible differences in use of a medicine between clinical trials and real-world clinical practice.	The proposal is to consider adherence as a mechanism that generates health benefits; there is no suggestion that improved adherence should be considered as a benefit independently of its impact on health outcomes.
Direct Non-Medical Costs		Incurring direct non-medical costs to accommodate disability and diminished HRQoL.	Additional costs to include may involve travel costs or other costs associated with receiving care but not directly tied to paying for a particular health service or intervention.	This relates to costs rather than benefits.

Several value elements that have been proposed are not relevant to considerations about the benefit function. These elements are listed in Table 4 together with justification for their exclusion.

The overarching principle here is that value elements which do not propose changes to what is included in the benefit function (as described in Section 1) are not within scope for this report. Benefits are the outcomes of interventions and policies which reflect the objectives and responsibilities of the HTA organizations covered by this report and health systems they represent. Rather, these out of scope value elements relate to costs, or different approaches to economic evaluation. Whether these alternative approaches should be used and, if so, how they are implemented are separate questions from what the benefit function should be.

4.2. Individual Risk Attitudes Over Their Own Health

The foundation for several proposed new value elements is that individual risk attitudes should be reflected in assessments of benefits. Those who developed the GRACE method argue that it has implications for the benefits that would be attributed to different scenarios and types of health technologies. The GRACE framework comprises two elements: Generalized Risk Adjusted (GRA) QALYs on the benefits side, and Risk and Severity Adjusted Willingness to Pay (RASA-WTP). The GRA-QALY departs from the standard QALY approach for the assessment of benefits, incorporating individuals' attitudes to risk and anticipating that this will reveal their risk aversion. This contrasts with the standard approach of assuming risk neutrality and is advocated to reflect considerations labelled "Outcome Certainty", "Disease Risk Reduction" and "Patient Centered Health Improvements". RASA-WTP creates a variable WTP threshold with adjustments based on these same risk preferences, according to the severity of the condition and any pre-existing disability.

Diminishing marginal utility is a fundamental economic concept which holds that the amount of utility a consumer obtains from consumption of each unit of a good or service declines as consumption increases. If there is diminishing marginal utility of health, then this implies risk-aversion. If this is reflected in health (as suggested in the GRA-QALY framework), this means that, where the health effect of an intervention is uncertain, the expected (mean) level of health gain used in standard CEA will overestimate the *certainty equivalent* level of health gain. The latter is the level of health gain for certain that is considered equally good as the uncertain distribution of health. With risk aversion, the certainty equivalent is lower than the expected (mean) level, in effect "penalizing" for uncertainty. Where the distributions of health benefits are symmetrical around the mean for both a clinically effective new health technology and its comparator, and less variable for the comparator than the new technology, the expected benefit of the new technology will be lower if incorporating risk attitudes (as per GRA-QALYs) than under standard approaches that assume risk neutrality (standard QALYs). GRA-QALYs penalize higher risk for patient outcomes. (See Box 3, Figure 1).

Whether this will occur in practice is highly technology- and disease-specific but, in general, one might expect that longer periods of clinical experience and opportunity to develop relevant

evidence would tend to reduce the degree of dispersion in health effects (though it is worth noting here that such effects are rarely fully captured in cost effectiveness analyses). Also note that the issue here is not the degree of uncertainty in the sense used in relation to parameters in cost effectiveness analysis, such as the degree of uncertainty in the mean treatment effect, which is resolvable by increasing research sample size.[43] Rather, this is the degree of variability of treatment benefit faced by individual patients. It is this that is likely to reduce with clinical and research experience. In some settings, new classes of targeted treatments and personalized medicine may demonstrate less variability in patient outcomes and, therefore, generate even higher GRA-QALY benefits when compared to existing treatments with greater variability in health outcomes.

A further claimed implication from incorporating risk attitudes into the benefit function is termed the "Value of Hope", which is described in existing literature in two different ways. The first is based on the claim that patients with severe conditions hold risk-seeking preferences.[8] For a new technology with the same mean health but with greater variance than its comparator, the certainty equivalent (GRA-QALYs) of a risk-seeking patient is higher than with standard QALYs: such patients "hope" that they will be in the right-hand tail of the distribution following treatment. A second explanation found in more recent accounts points out that people may be not only be risk-averse but also "prudent" - where a treatment has a right-skewed distribution of health benefits, a prudent individual will prefer this to a comparator treatment that has the same mean and variance but has less of a right hand skew, including a symmetric or left hand skew.[44,45] (See Box 3, Figure 2.) "Prudence" in individual preferences follows if there is diminishing marginal utility but this never becomes negative (there is no level of health beyond which the addition of extra health units leads to a reduction in patient utility). We refer to both cases below.

Box 3: Probability Density Functions of Three Treatments with the Same Expected Health

Figure 1: Two Treatments with Symmetric Distributions with Different variation

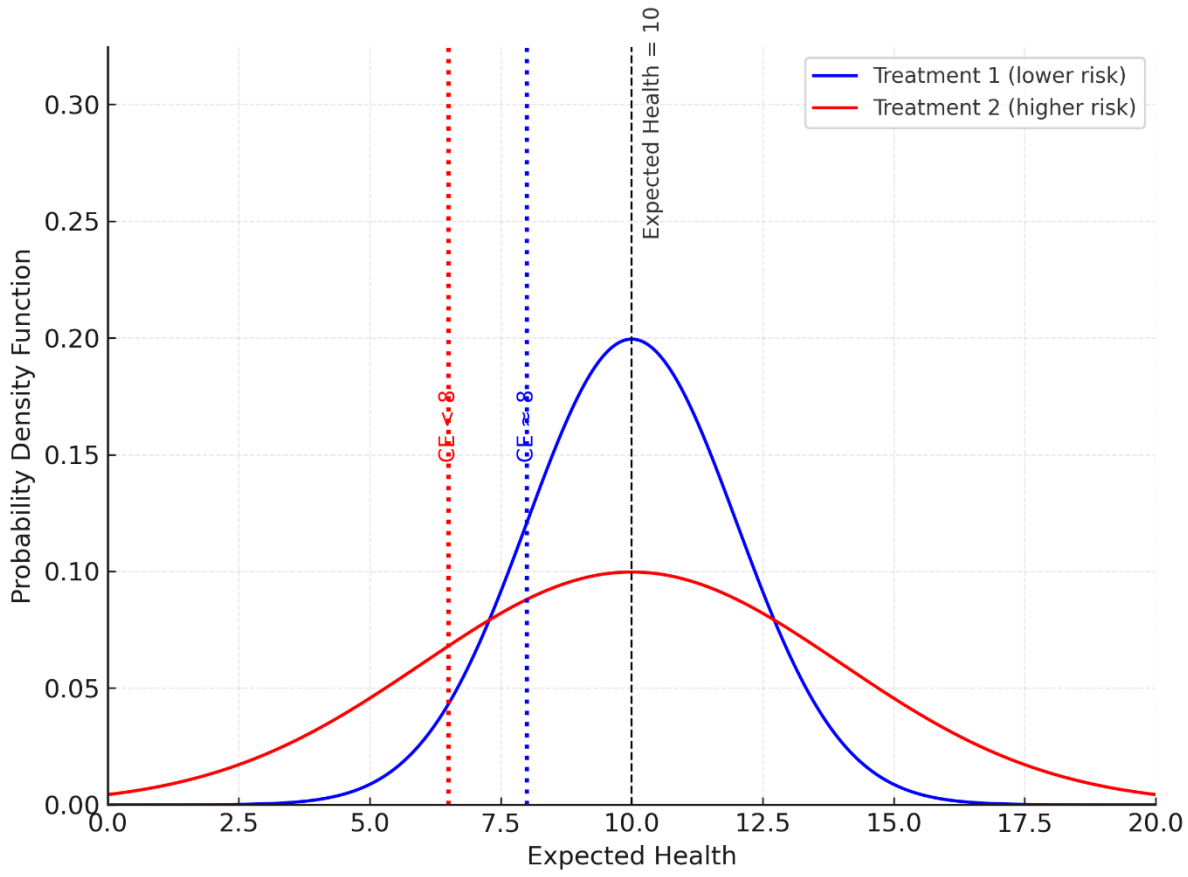

Figure 1 plots symmetric probability density functions of two treatments with the same expected health (here, at 10, measured along the horizontal axis on an arbitrary scale). Treatment 1 in blue has lower variation than Treatment 2 in red, indicating that it is lower risk. For a given risk averse individual, the certainty equivalent of Treatment 1 (shown at 8) is higher than that of Treatment 2, because risk aversion penalizes uncertainty.

Conventional CEA (which uses expected health) does not distinguish between the health outcomes of these two treatments, but GCEA (which uses certainty equivalents) does.

Figure 2: Two Treatments with a Symmetrical and an Asymmetrical Distribution

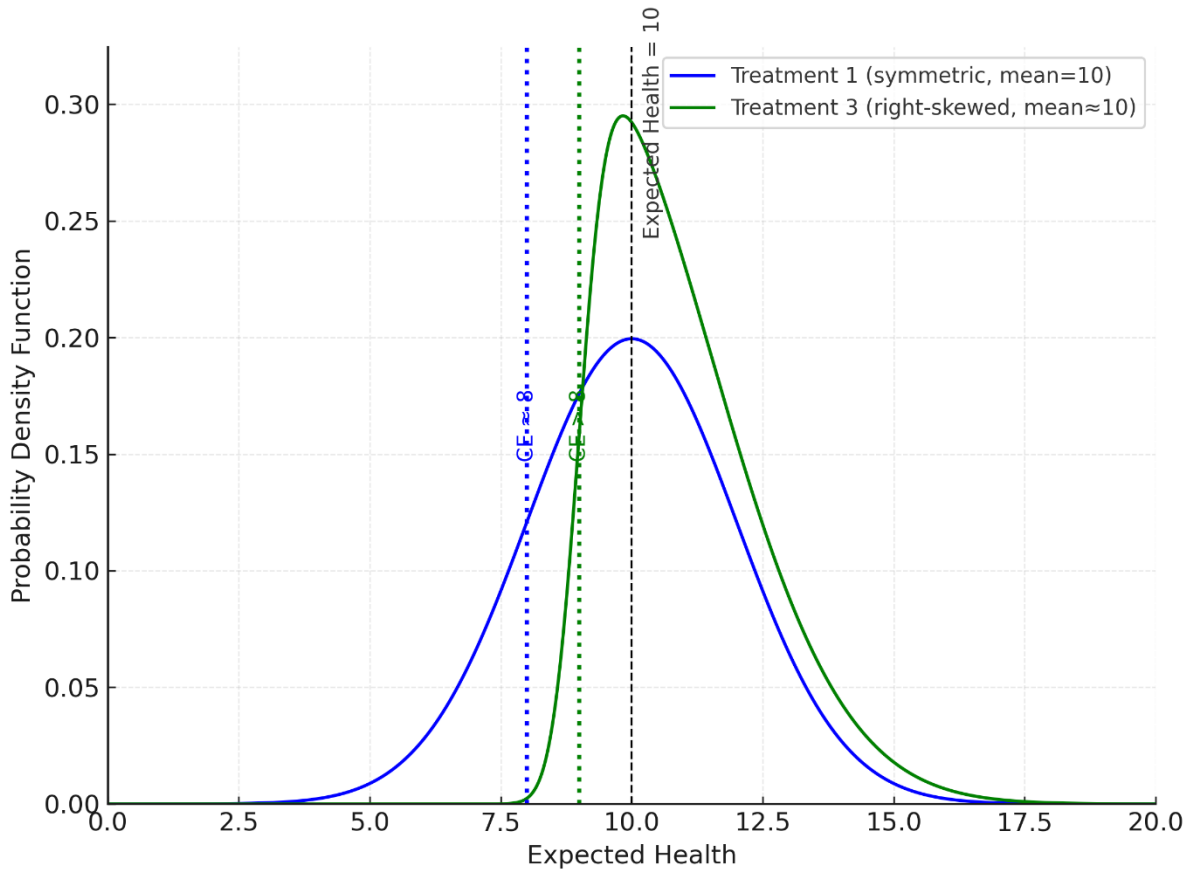

Figure 2 plots the probability density functions of two treatments with the same expected health and the same level of risk. The one in blue is symmetrical and is identical to Treatment 1 in Figure 1. Treatment 3 in green is asymmetrical and is right-skewed – compared to Treatment 1, the density curve has a thinner left-hand tail a fatter right-hand tail, and a taller mode located to the left of the mean. The certainty equivalent of a risk averse and prudent individual for Treatment 3 is higher than 8, because the thinner left-hand tail represents lower chances of outcomes less than 8, while the fatter right-hand tail represents higher chances of better-than-average outcomes. GCEA based on certainty equivalents rewards Treatment 3 for its right-hand skew, relative to Treatment 1. However, as long as the individual is risk averse, the certainty equivalent of any distribution, by definition, remains smaller than the mean (10 in this example).

These figures were developed using the above text as prompts with assistance from ChatGPT, an AI assistant created by OpenAI.

Relevance

The GRACE framework retains health in terms of length and HRQoL at the heart of the assessment of benefits. However, it does still represent a potentially significant departure from standard cost per QALY methods because it seeks to incorporate risk attitudes towards the distribution of health outcomes. "Risk attitude" here refers to reflecting preferences individuals may have (though a variety of standpoints even within this framework can be identified). Decision makers who use HTA are typically assumed to be risk neutral with respect to each decision they make about individual heath technologies because the health of the populations they serve is only marginally impacted by each individual reimbursement decision.

It is important to be clear about the source and basis for claimed preferences since decision makers are unlikely to want to reflect preferences that may be seen as irrational or groundless. We outlined above how the "Value of Hope" has differing explanations. The first is that, given two risky treatment options with the same expected health, patients who are severely ill have a higher certainty equivalent for the riskier treatment option than the one with less risk; that is, they are risk-seeking.[46] But such patient preferences may arise because patients assign a higher subjective probability to treatment success than is objectively warranted (and vice versa). This could equally be termed "desperation" rather than "hope" or seen as the application of subjective probabilities that are likely to result in disappointment or despair once treatment has been provided and its effects become apparent. There are few health care settings where this is likely to be appropriate.

The alternative explanation, where the value of hope stems from the concept of "prudence", has different implications. In this situation, the value of a health distribution is determined not only by its expected value and variance, but also its skew (see Box 3, Figure 2). Specifically, patients assign greater value to health gains from treatments that have long right-hand tails compared to treatments that have the same expected health gain and variance but have a symmetrical or a left-skew distribution even though patients remain risk-averse. For a treatment with variable outcomes, taking risk-aversion into account leads to a lower certainty equivalent than the expected value of health. Taking the value of hope (or prudence) into account increases the certainty equivalent for right skewed distributions of health, partially, but not fully, offsetting the reductions due to risk aversion.

Valuation

Section 3.2 emphasized that standard economic evaluation for HTA focuses on the average preferences of the public regarding health. This is not consistent with the preferences and risk attitudes that individuals hold over their own health as patients or consumers.

In the context of what is referred to as the "value of hope", it is the preferences of individuals assessing the benefits from available treatments for themselves that are proposed for inclusion. For healthcare decision making at the individual patient level, these attitudes are critically important when choosing between a set of available treatment options. But in the HTA setting, conventional economic evaluation takes the normative position that assigns the patient as the relevant source only for describing and measuring health. It is general population average preferences for those health states the approach seeks to reflect, for the reasons highlighted above in Section 3.

In the context of the value of risk protection, the source of preferences is different. Here it is argued that individuals gain peace of mind from having a new health technology covered in their insurance plan. Therefore, it is the risk averse preferences of individuals as purchasers of insurance that form the basis of the claim that there is additional benefit beyond that captured in standard economic evaluation.

Both sources of preferences (patients and consumers of insurance) differ from the standard approach where it has been considered that health care decision makers seek the average preferences of the general population over the domain of health, consistent with the explicit remit set by government for bodies such as NICE. Of course, the attitudes to risk that may be exhibited by individuals acting as patients, or potential patients in the context of diagnostics or screening, or consumers of insurance may also be apparent when considering general population preferences for health.

Furthermore, in publicly funded systems, the magnitude of health care funding is determined via a political system that reflects the preferences of the general population, albeit imperfectly. The value to individuals of knowing they have health coverage, the extent of that coverage and, in addition, the "caring externalities" from the coverage for others are all captured, in principle, through this system. The assessment of individual therapies using cost-effectiveness analysis takes place as a distinct stage given prior decisions about funding.

Even if risk attitudes of individuals over their own health were deemed appropriate in principle, measurement is challenging. One study to attempt this recruited nationally (US) representative samples of community members and conducted thought experiments based on hypothetical health scenarios using a simple one-dimensional scale from 0 – 100, each lasting one year.[47] Participants were asked to consider, from the standpoint of a patient in a health state below full health, choices between a treatment with a certain health gain versus a risky health option that has two equal

probability outcomes. Such choices are complex, and several simplifications and limitations are reported by the authors. Most notable among these is the need to simplify health to a single composite quality of life 0-100 scale, although people may have different risk attitudes depending on the dimension of health. One may also ask whether participants could distinguish between health states rating, for example, 21, 24, 27 or 29 on the 0-100 scale from each other, to answer the choices meaningfully.[48]

The issue is further complicated by their finding that the US general population utility function for health is S-shaped: risk-seeking in very poor health which becomes more risk-averse as health increases, with an inflection point around 0.485.[47] This implies that the greatest marginal benefit in terms of GRA-QALYs (or the value of hope) comes not from states with the most severe health scores, but with those around the center of the range of possible scores.

Few other relevant studies have been conducted. Attema et al. provide an example of work conducted using a small sample set in the Netherlands.[49] The work of Mulligan et al. would require replication and extension in different populations for use in other jurisdictions (where relevant), validation of the findings and consideration of issues such as the relevant population for each purported element of benefit (for example, whether patient samples are also needed), further consideration of attitudes in the face of losses versus gains and, potentially, the development of multi-attribute descriptions of health but without rendering these experiments infeasible for respondents. Furthermore, given the empirical evidence suggesting that utility function over their own survival may also be S-shaped, the implications of non-constant marginal utility over life years (and possible interaction with HRQoL) needs to be explicitly considered.[50]

Opportunity Costs

In principle, opportunity costs could be estimated to reflect risk preferences and to be consistent with a measure of benefit like GRA-QALYs. However, such research would need to reflect clear methods to measure and value these outcomes more generally.

4.3. Benefits from the Process of Care and the Value of Knowing

A further category of benefit which is not routinely included in economic evaluation for HTA relates to aspects of the process of health care which, despite not generating a change in health outcomes, might be something over which individuals have preferences. One example of this, taken from the ISPOR Value Flower is the “value of knowing”. The context for this putative benefit is diagnostics which provide information to make judgments regarding a person’s disease or condition. The information they provide impacts decisions about how the person is to be managed, and changes in treatment decisions may in turn lead to changes in health outcomes and costs captured in

conventional cost-effectiveness analysis. The value of knowing is predicated on the idea that, separately, patients may derive benefit from the information diagnostics provide aside from its instrumental value in promoting changes to decisions that promote health. This could include, for example, enhanced opportunity to make personal and family plans. In some cases, this information may cause disbenefits, where for example the knowledge of the condition causes distress, there is no effective treatment, or the information is incorrect.

Other examples of the concept of process benefits or process utility have been discussed in the economic evaluation methods literature. Researchers have estimated the process utility of individuals for a range of factors such as the mode of treatment delivery (e.g., oral versus injection), waiting times, continuity of care, and the degree of information given to patients about treatment options. Methods such as willingness to pay and discrete choice experiments have been used to quantify process utility relative to other attributes such as health outcomes.[51,52] Donaldson and Shackley examined what they termed "reassurance value" arising from knowledge of a test, in the context of antenatal screening for cystic fibrosis.[53]

Relevance

There may be relatively few situations where the impact of a component that is considered part of the process of care is not associated with measurable impacts on HRQoL. Other examples might be seen as good practice delivery standards that should be universally required for all health care services (for example, the provision of sufficient information to patients to allow informed decision making, the communication style of clinicians or distance to travel) rather than characteristics distinguishing options to be considered in HTA.

The inclusion of "pure" process benefits is likely to be contentious in resource constrained systems because the implications for HTA would be that some degree of health gain can, in principle, be sacrificed to promote process benefits. At the extreme, this could lead to the funding of some interventions, for example a diagnostic for a condition that has no available treatment, which has no positive health gain at all.

Valuation

The distinction between the process of care and health outcomes can be blurred. Needle phobia, for example, can cause measurable impacts on discomfort, anxiety and usual activities for prolonged periods and, therefore, could be captured, at least partially, through standard measures of HRQoL. Broader aspects of HRQoL have been developed that more explicitly incorporate factors that overlap with those that could be considered part of the process of care. For example, the EQ-HWB-9 includes items such as "having control over day to day life", although interestingly items more specifically related to care such as "independence in decision making" and "feeling valued and respected" that were considered as preliminary themes do not appear in the final EQ-HWB-9

instrument.[54] The ICECAP instruments include domains such as independence, choice and preparation (in the palliative care setting).[54,55] This development of more sensitive instruments for assessing HRQoL may be seen as part of the improvement of methods that responds to the need to capture process benefits in a more generalizable manner than in many of the studies of process utility itself, which tend to be setting specific.

In any case, there is a challenge to avoid double counting of these aspects of benefit that may already be captured, albeit imperfectly, in existing HRQoL measures.

Opportunity Costs

The feasibility of ensuring that the extent of these process benefits is reflected in the measure of opportunity cost depends in part on the methods that are adopted to capture these non-health benefits. For example, a process utility study might give an estimate of the relative value respondents place on process components versus health gains, but such estimates are very context specific and tend not to be generalizable to other disease areas or technology types, making it problematic to measure process benefits forgone from displaced services.

4.4. Equity

As outlined previously, the policy objective of economic evaluation used in HTA by those organizations which are the focus of this report is to maximize population health using a benefit function with estimates of a treatment's impact on length and aspects of HRQoL. Such an approach is entirely focused on efficiency, while people often value equity, particularly in health. Recent literature on equity in HTA has aimed to incorporate such preferences by applying various weights to health gains in economic evaluation.[56]

The socioeconomic gradient in health is where various measures of health are positively correlated with socioeconomic status, and this persists in many populations, is often recognized as being caused by socioeconomic mechanisms largely beyond individual control, and is typically regarded as unjust, unfair or inequitable.[57] People may consider the reduction of the social gradient of health as a good outcome, so an extra health gain should be given to the socioeconomically disadvantaged. The benefit function may capture this through two distinct mechanisms: an aversion to the inequality in health per se (in other words, reducing a health inequality is good, regardless of who benefits from this); and/or a dislike of the socioeconomic inequality per se (in other words, the extra health gain should be given to the socioeconomically disadvantaged, even if their baseline health was no worse than the population average). These are not mutually exclusive and can be combined.

It is important to emphasize that priority for those with low health because of individual preferences for their own health is distinct from, and cannot be used to proxy for, priority for those with low health because of normative distributional preferences across the health of different individuals in society. Notwithstanding this, after noting the qualitative and deliberative manner in which HTA organizations have considered equity, Mulligan et al (2024) state that, based on neoclassical economics, "empirically measured utility over HRQoL could be used to support a more principled microeconomic approach to the analysis of welfare and inequality" (p.22).[47] Indeed, individual utility over HRQoL can inform who would gain the most utility from the extra HRQoL gain. But note that this does not capture the shape of the benefit function or normative distributional preferences.

The benefit function used in economic evaluation for HTA by the three HTA organizations is a function of health, and it is agnostic about the level of utility people derive from their own health. In its simplest additive form, it does not distinguish between a QALY accruing to individuals from different socioeconomic groups, and is therefore distribution neutral. The implied equity stance is that everybody's QALY is treated the same. This can be extended in two ways, both of which rely on normative social preferences.

The first extension is to allow for inequality aversion – this is where health-related social benefit is increasing in population health but can also be decreasing in health inequality. Under inequality *aversion*, as the relative importance given to health inequality increases, the extra health benefit would improve health-related social benefit more if it was given to those with worse health. (In theory, a benefit function could be inequality *seeking*, so that it is increasing in population health and increasing in health inequality, but this would not be politically viable.) Degrees of inequality aversion can be captured by an inequality aversion parameter elicited from members of the public.[58-60]

The second extension to the benefit function is to allow for asymmetry – this is where the health of different population subgroups is given different weighting, because of who they are (rather than because of their health). The benefit function for conventional CEA is *symmetric* – the social benefit of this distribution is insensitive to any correlation between socioeconomic status and levels of health. On the one hand, if the benefit function is asymmetric in favor of the socioeconomically disadvantaged, then social benefit will improve more if the extra health benefit was given to them, not because they have worse health but because of their socioeconomic status (for instance, because socioeconomic deprivation is a matter of social justice). It is also possible that the benefit function is asymmetric in favor of the socioeconomically advantaged: then health-related social benefit will improve more if the extra health benefit was given to them, notwithstanding their already better health, because of their socioeconomic status (for instance, because they will be more productive and make more tax contributions by being healthy). Degrees of asymmetry are captured by an asymmetry weight.

Relevance

The above framework applied to CEA has been the theoretical basis of Distributional Cost-Effectiveness Analysis (DCEA).[61-63] DCEA takes health, measured in terms of QALYs, as the benefit, and can include two types of weights. "Indirect equity weights" are a function of inequality aversion and background health distribution, while "direct equity weights" are fixed weights applied to specific subpopulations independently of their levels of health.

The application of indirect equity weights to reflect inequality in health may be within the remit of health care systems. For instance, the "fair innings" weights are an example of indirect equity weights and penalizes inequality in expected lifetime QALYs.[64] The fair innings argument assumes that there is a reference level of lifetime health ("a fair innings") that everybody is entitled to, so that health gain to different people can be given fair innings weights based on the level of their expected lifetime QALYs relative to this reference. Health gain to those who are unlikely to achieve the fair innings will be weighted above 1, while health gain to those who are likely to achieve (or have already achieved) the fair innings will be weighted below 1. This is a form of severity weighting where severity is defined as shortfall in expected lifetime QALYs.

The application of direct equity weights is more contentious. Because direct equity weights apply independently of the background health distribution, it amounts to using the health care system to correct for social injustices (e.g., income inequality) or to penalize socially undesirable behavior (e.g., smoking). Whether these lie within the remit of the health care decision maker may be debatable.

Current HTA practice has already recognized the greater weight decision makers place on improvements to populations with worse baseline health as compared to the population average. For example, NICE has explicitly incorporated modifier weights for severity in its decisions, defining it in terms of shortfalls in prospective QALYs given current age (albeit currently with no empirical basis to do so) but has stopped short of including approaches such as DCEA with indirect inequality aversion weights as routine in the reference case analysis.[65]

NICE has also introduced modifiers for drugs for rare diseases ("highly specialized technologies"). However, the weighting is designed as an increasing function of the size of health gain, rather than the rarity of the condition (or poor baseline health), and it is unclear what equity consideration it is designed to address.

Each approach has limitations that should be acknowledged by HTA organizations.

Valuation

The value of the fixed extra health gain to any group of patients in worse baseline health relative to the value of the same health gain to another group of patients in better baseline health depends on

the specification of the relevant benefit function and its parameter values. This is ultimately a matter of interpersonal distributional justice, and as such, they must not be based on how individuals value their own health.

There is a growing literature eliciting distributional preferences from members of the public to estimate the parameters of the benefit function.[58,59] Most empirical studies elicit aversion to health inequality across socioeconomic groups, but as aversion to other types of health inequality are explored, there will be a risk of double-counting. For example, people may regard health inequality across urban, rural, and very remote areas as unfair. But if regional health inequality aversion parameters and socioeconomic health inequality aversion parameters elicited separately are both included in a DCEA, this is likely to involve some double-counting, given the likely correlations between the two factors.

Opportunity Costs

If decisions about the funding of new interventions are to include equity weights which reflect decision makers' aversion to inequality, then this should also apply to resource allocation in health more generally, hence it should be reflected in the estimates of benefit forgone when new interventions limit funding to other activities. Some research has been undertaken in the UK suggesting that NHS expenditure changes generated greater health impacts on the most socioeconomically deprived, giving some indication that the opportunity cost of more costly new interventions could increase inequalities.[66] However, other research suggests NHS hospital expenditure is neutral in terms of inequality.[67] This is an area in which more research is needed.

Given that health care resources are constrained, applying a weight larger than 1 to the health of the socioeconomically disadvantaged (or any other) group requires applying a weight smaller than 1 to at least one other group. This also means that the application of equity weighting (or the implementation of DCEA) should not be optional only for interventions that reduce health inequality, but consistent across the board.

Furthermore, for HTA organizations, there should be an acknowledgement that there are limitations on any approach that weights or does not weight health outcomes; and this may have implications for decision making around coverage and reimbursement, e.g., upweighting severity may demonstrate technologies for severe conditions as more valuable than technologies for less severe conditions.

4.5. Broadening the Perspective of Economic Evaluation

Some proposed additional value elements may imply a broadening of the perspective of economic evaluation, beyond a simple focus on health-related benefits and costs falling on the health care system. One element of the ISPOR Flower proposes analyses consider "spillovers" to caregivers and family of the costs and health effects of interventions. Another is dynamic effects of infectious diseases on future cohorts of individuals other than those who are subject to, for example, initial treatments for or vaccination against those diseases (this is called "community spillover" in the GCEA framework). Considering spillovers to such individuals in terms of *costs* falling on individuals (patients, carers, family) would require a widening of the cost perspectives used by some HTA organizations, including NICE and CDA-AMC. However, reflecting the spillover effects in terms of *health effects* of interventions is, in principle, *already part* of recommended methods for economic evaluation by HTA organizations such as NICE. In other words, once decisions are taken by HTA organizations about an appropriate benefit function to support their decisions, there is no issue in principle about counting intervention effects on such benefits regardless of on whom they fall. The challenge has been more practical, however, in generating suitable evidence quantifying such spillovers and to ensure these are causally related to the interventions under evaluation.

In thinking about the appropriate benefit function for economic evaluation in HTA, there have long been debates about whether benefits beyond those generally associated with the remit of health systems should be incorporated. A prominent example is the impact of interventions on productivity, and this has also been part of the ISPOR Value Flower. This can be understood as the causal effects of treatments and other interventions, typically because of improved health for those receiving interventions or through spillovers, on the value of what individuals contribute, or produce, net of the amount they use or consume. There is an extensive literature on how such effects can be measured covering, for example, implications for absenteeism, presenteeism and early retirement, but also considering informal work such as childcare. Much has also been written about how productivity can be quantified in monetary terms or through the QALY.[26] Despite the extensive research, productivity is not formally considered by many HTA organizations, including NICE. Currently CDA-AMC is piloting the use of a broader perspective in some evaluations.[68] ICER includes productivity effects in its 'modified societal perspective'. A key challenge with combining costs falling on health care and productivity effects expressed in monetary terms is that opportunity costs of changes in productivity are quite different from changes in health expenditure. In other words, when net productivity is expressed in monetary terms, expressing these as offsets to the incremental cost of a new intervention ignores the fact that this does influence health system resources. There are strong arguments, therefore, to express productivity effects (and any other broader impacts) separately from healthcare sector costs.[69]

Broadening the perspective of economic evaluation through the benefit function could consider several other consequences of interventions. These can be seen as the implications of interventions

and policies for the benefits that decision makers who are responsible for resource allocation in other sectors consider part of their objectives or remits. Examples include the impact of public health policies on criminal justice objectives and the effects of medical interventions for children's mental health or neurodevelopmental conditions on educational outcomes. The consequences of how health care is produced for the system's carbon footprint is another example which has recently been considered by HTA organizations, although these effects may more appropriately be seen as choice of perspective in costs rather than benefits.

There are major evidential challenges to extending benefits to include productivity and other consequences of health to wider social value attributes. Quantifying the effects of interventions on productivity and other outcomes outside health could involve collecting data in prospective or retrospective studies alongside traditional health outcomes. Research has been undertaken on standardized ways to measure, for example, productive activities and work participation.[70,71] Standardized ways of collecting potentially relevant outcomes in, say, education and criminal justice, are less well developed. An alternative to directly quantifying the effects of interventions on these types of benefit is to estimate how they change as health outcomes vary. This would also need to consider other characteristics of the recipients of interventions such as age, sex and clinical diagnosis. This indirect approach was used in the work undertaken in the UK on net production.[72,73]

Relevance

While this range of consequences of changes in health for some subgroups of the population for these wider social value attributes may be important to broader policy objectives, their relevance to the remit of health care systems is debatable. In general, it would be expected that policy makers in health are held accountable for the quality and access of health services and health outcomes for patients and the population, rather than impacts on the broader economy or meeting the objectives of other sectors like education. Furthermore, broadening the benefit function in HTA to encompass the *implications* of improvements in health for other social objectives would suggest some prioritization of those subgroups of the population who are the focus of those objectives. The most obvious example is that, if enhancing productivity net of consumption were to become part of the benefit function informing HTA decisions, this would effectively prioritize the working age population who, on average, generate more net production, even allowing for informal work activities. This is likely to raise challenges for health systems in terms of the fairness of their objectives and decisions.

Valuation

Expanding economic evaluation to include these non-health social value attributes has been undertaken in many published studies. Typically, however, this has been implemented by monetizing these extended benefits and including them as if they were costs or savings which is problematic as explained above for productivity: mixing resource costs and monetized (dis)benefits

is arguably inconsistent with the aim of economic evaluation in HTA to support decisions about how to enhance health benefits from resources available to the system. An alternative approach to incorporating these wider benefits would be to represent them directly in the benefit function. This would use some measure of preference or elicited weights from a relevant group to express trade-offs between health outcomes and, for example, gains in productivity or education outcomes. In effect, this requires HTA organizations to be transparent about how they set the 'rate of exchange' in how they value health against these other broader objectives.

Another way to handle these wider benefits in HTA presents them separately from the measure of health benefit. This disaggregated approach to implementing a broader perspective has been called cross-sectoral economic evaluation. It effectively works from the principle that decisions made in the healthcare sector will focus on health-related benefits but recognizes that other public bodies and sectors of the economy have different benefit functions (even if not defined) which reflect their remits and responsibilities. The same logic can apply to the wider costs/savings associated with those sectors. The "impact inventory" was developed by the Second Panel on Cost Effectiveness in Health and Medicine to support this approach to economic evaluation.[33] This was extended by Walker et al to include distributional considerations and opportunity costs.[69] From a decision-making perspective, this *extended impact inventory* can support wider discussions between decision makers across different areas of policy about making some resource allocation decisions jointly.

Opportunity Costs

As for all other potential additions to benefit functions in economic evaluation for HTA, if such benefits are relevant to those new interventions which are subject to HTA, they are potentially relevant to those interventions and services from which resources are taken to fund the new technologies. So, a widening of the benefit function needs to be reflected in the measure of opportunity cost. In principle, empirical estimates of opportunity costs with these wider benefits are feasible. Indeed, some work has been undertaken of this nature. Claxton et al, quantified the net production associated with the health opportunity cost of NICE's appraisal decisions.[35] This area of research, however, is underdeveloped. It would benefit from improvement in methods and data and need to be extended if these broader measures of benefit were to be routinely adopted in HTA.

5. Conclusions and Recommendations

The central aim of this report is to provide guidance to help HTA organizations assess whether additional or alternative benefit measures should be incorporated into the benefit function they use for economic evaluation. The guidance is grounded in three principles: (i) benefits must be relevant to decision makers given their remit; (ii) benefits must be aggregated (or valued) in an appropriate manner; and (iii) benefits must be incorporated symmetrically with opportunity costs. Applying these principles, we have the following recommendations for HTA organizations:

- When considering additional measures of benefit for economic evaluation, HTA organizations should assess these against the principles outlined in this report.
- No additional benefits should be routinely incorporated into economic evaluation until there is an evidential basis to reflect them in opportunity costs. This is essential to ensure comparability and consistency in decision-making, and to avoid inappropriate resource allocation.
- The deliberative process within HTA, which may consider potential additional benefits qualitatively, should not be used in a way that bypasses the consideration of opportunity costs. HTA organizations should consider how the design of their processes, including any pre-specification, may avoid bypassing opportunity costs.
- In private insurance systems, any potential movement towards willingness to pay approaches in benefit design should not be considered a substitute for the explicit consideration of opportunity costs.
- HTA organizations that have adopted a normative position to use average public preferences to define benefits for economic evaluation should not simultaneously incorporate individual patient preferences, as this lacks a coherent normative basis.
- HTA organizations should provide a clear normative basis and measurement approach when applying 'modifiers' (e.g., for severity) as an expression of equity considerations.
- Risk attitudes for individuals' own health could, in principle, be elicited from the public, but more research is necessary on how to address potential double-counting with 'modifiers' such as severity weights in the context of HTA decisions.
- Distributional cost-effectiveness analysis provides a framework for building distributional considerations into economic evaluation but, if used, needs to be used in all assessments.
- If specific benefits associated with the process of care (e.g., the value of information about disease prognosis) are to be included in economic evaluation, further research is necessary to ensure there is no overlap with routinely used health-related quality of life measures.

- If broadening the perspective of economic evaluation to include benefits to the wider economy (e.g., productivity) or other sectors (e.g., education) is considered consistent with decision makers' remits, additional evidence requirements must be considered (e.g., opportunity costs by sector and trade-offs between different outcomes relevant to each sector).

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