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PRACTICAL APPLICATION

The Broader Opportunity Costs in the Broader Cost-Effectiveness Analysis Framework

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Abstract

Background The traditional cost-effectiveness analysis framework usually takes a healthcare system perspective, where the aim is to maximise population health from a fixed budget allocated to healthcare. Extensions to this framework have been suggested, including: (i) incorporating impacts that fall outside the healthcare sector; (ii) accounting for outcomes beyond health; and (iii) assessing equity considerations. Several alternatives have been proposed that serve these purposes, for example, the extended "impact inventory", the "beyond-the-QALY" approach and the distributional cost-effectiveness analysis.

Objective This paper aims to develop a comprehensive framework that incorporates into the cost-effectiveness analysis framework some of its most advocated extensions and provides a means of arriving at a unidimensional cost-effectiveness analysis result measure.

Methods Building on previous work, I proposed a framework that explicitly incorporates the full extent of the opportunity costs that arise when new dimensions and distributional concerns are included in cost-effectiveness analyses. A hypothetical example is provided as a way of illustration.

Results Operationalising the proposed framework requires system-wide representative values and/or robust estimates concerning: (i) selecting dimensions; (ii) measuring opportunity costs associated with each dimension; (iii) quantifying equity weights and percentages of beneficiaries and losers meeting equity considerations; and (iv) attaching monetary values to dimensions measured using a non-monetary metric.

Conclusions Extending the cost-effectiveness analysis framework entails extending the measurement of the opportunity costs of funding decisions. This implies populating an ambitious puzzle that in some cases poses fundamental conceptual and empirical questions. Potential routes of further research that might facilitate such undertaking are proposed.

1 Introduction

Economic evaluations in health are aimed at informing on the relative merit or value of alternative courses of action [1]. These analyses allow the comparison of the benefits associated with a new health technology and the costs imposed by its introduction. The scope and nature of benefits and costs considered relevant in a given analysis depend upon the objectives and the perspective of the decision makers commissioning the evaluations [2].

Key Points for Decision Makers

The need to widen the scope of the traditional cost-effectiveness analysis framework is increasingly advocated, but the intrinsic implications upon the relevant opportunity costs are often overlooked.

The proposed conceptual framework explicitly incorporates into the cost-effectiveness analysis framework some of the most advocated extensions and their associated opportunity costs.

The parameters needed to operationalise the proposed framework are identified and potential routes of further research that might facilitate such undertaking are proposed.

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Most commonly, benefits are quantified using a measure of health outcomes, such as quality-adjusted life-years (QALYs), while the quantification of costs is expressed in monetary terms. Measuring benefits and costs using different metrics turns the comparison of gains and losses into a challenging and complex task.

There have been two main approaches to resolve this issue. One approach is to monetarise health outcomes, by attaching a monetary value to health gains. This procedure is framed under the cost-benefit analysis and it is grounded in welfare economic theory [3]. Under this framework, the comparison of gains and losses becomes a matter of whether the benefits of the intervention expressed in monetarised health gains are larger than the monetary costs associated with the intervention, i.e. whether the intervention yields a positive net *monetary* benefit. The second approach involves translating the costs associated with the new intervention into a measure of the forgone health that will be necessarily forsaken as the resources required to fund the new intervention would no longer be available for its best alternative use. This approach is grounded on the notions of opportunity costs and resource scarcity [2, 4]. Under this latter perspective, the relevant comparison becomes whether the health gains associated with the new technology are larger than the health likely to be forgone due to the additional costs falling on the system, i.e. whether the intervention yields a positive net *health* benefit.

While some authors have pointed out the advantages of using the net benefit approach [5], most analysts present economic evaluation results using incremental cost-effectiveness ratios (ICERs) instead. To draw any conclusion, ICER values need to be compared to a benchmark, also known as cost-effectiveness threshold (CET). In such cases, the monetary value of a unit of health gained (which is the input required to compute the net *monetary* benefit) and the cost per unit of health displaced (which is the input required to compute the net *health* benefit) might be viewed as alternative CETs to which to compare the estimated ICERs.

Therefore, these two perspectives on the CET, i.e. the societal monetary value (which is usually denoted v) and the opportunity cost value (which is usually denoted by k), have often been regarded as alternatives and most authors have only taken one perspective into account. However, Brouwer et al. articulated a framework that allows the integration of both elements in decision making [6]. These authors first identified different decision rules depending on the objective function and the perspective taken by decision makers. Under the most common decision-making scenario that takes an extra-welfarist and healthcare system perspective, the relevant benchmark is defined by k, the health opportunity cost CET. In contexts where a degree of flexibility in the allocated budget is assumed and the goal is to maximise social welfare from a broader societal perspective, the relevant benchmark is given by v, the societal CET. However, Brouwer et al. went one step further and identified that even when budgets are fixed and the intervention costs fall directly on the healthcare sector, v will be relevant next to k, if analyses were to take a broader perspective and incorporate other societal costs and/or other benefits beyond health outcomes. To conclude, the authors outlining this framework emphasised that in this broader decision-making context, both v and k are relevant.

The need to widen the scope of the cost-effectiveness analysis (CEA) framework is increasingly advocated [7]. The main reason is that the traditional single-sector unidimensional analysis arguably ignores important dimensions relevant in decision making. Some of the most advocated extensions involve: (i) including impacts that fall outside the healthcare sector; (ii) accounting for outcomes beyond health; and (iii) incorporating equity considerations. Several frameworks have been proposed that serve these purposes. For instance, Walker et al. [8] have extended the approach first developed by the Second Panel on Cost-Effectiveness in Health and Medicine in the United States [9], named the "impact inventory". This framework aims at incorporating costs and outcomes falling on different sectors and decision makers (e.g. health, criminal justice, education), and, although less explicitly, might also accommodate other CEA extensions that are addressed in more depth in other frameworks. For instance, Brazier and Tsuchiya [10] have discussed several approaches to extend the traditional QALY framework to capture outcomes beyond health, and the need to formally incorporate information about the equity impacts of health technologies into CEAs has led to the development of the distributional CEA [11].

This paper builds on the conceptual framework proposed by Brouwer et al., but the framework is further extended to simultaneously account for the advocated extensions to traditional CEAs and their associated opportunity costs. While these extensions could potentially be introduced in the framework proposed by Walker et al. [8] (and some of them explicitly are), the aim of this paper is to go one step further and formally and explicitly identify the parameters needed to operationalise the proposed broader CEA framework and to suggest potential routes of further research that might facilitate such undertaking. This paper also contributes to the debate of when and how expanding the scope of CEAs is appropriate by identifying the specific assumptions underpinning the traditional CEA framework and those of some proposed attempts to widen its scope. This highlights that, in some cases, broadening the CEA framework without considering the associated broader opportunity costs makes implicit assumptions that are harder to justified than those of traditional CEAs.

1.1 Extensions to the Single-Sector Unidimensional CEA Framework

It is often argued that CEAs should take a societal perspective that incorporates effects that fall outside the health system, such as those that might impact on patients and their relatives and on the society. Authors advocating for this approach claim that this perspective is required to reach optimal decisions at the social level, as decisions based on restricted single-sector perspectives are most likely suboptimal [12]. The conflicts that might arise between strict healthcare sector analyses and broader societal analyses have led some authors to suggest the adoption of a two-perspective approach as a standard [13]. However, in the CEA empirical literature, the social perspective is not applied in the vast majority of the studies, and among those that do, it is often limited to including productivity costs, ignoring other relevant intersectoral aspects [14]. As mentioned above, current proposals for incorporating societal-level effects include the impact inventory [8, 9].

A second extension considered in this paper is specifically related to extending the outcomes associated with health interventions [15]. It is widely recognised that health, commonly quantified using QALYs, does not encompass all the outcomes that are relevant for decision making. This is true even when the focus is on informing decisions taken from a healthcare and related sectors perspective. The reason being that there might be aspects associated with the use of health services that matter to patients (and their carers) that go beyond direct impacts on health [10]. However, the problem is even more pronounced when the goal is to inform decisions that take a multi-sectoral perspective. Particularly for the latter, some authors have proposed the use of well-being instruments, including measures of happiness and life satisfaction, as these might provide a common outcome measure to be used across sectors [16, 17]. Others have proposed complementary, rather than alternative, instruments that capture benefits associated with the receipt of care that are not assessed in quality-of-life instruments routinely applied in CEAs. One example is the ICEpop Capability Measure (ICECAP), which was developed to assess people's capability in terms of what they "can do" and what they are "able to be" [18]. This instrument has been found to measure different constructs and provide largely complementary information to that elicited by the most commonly applied quality-of-life measures, such as the EQ-5D [19, 20]. More recently, a new instrument that encompasses health and well-being aspects has been developed, the EQ-Health and Wellbeing (EQ-HWB), which is currently in experimental version status [21].

Concerning the third potential extension that involves incorporating equity considerations, the current approach in most health technology assessment bodies is not to incorporate distributional considerations into CEAs. Instead, the assessment of the fairness of the distribution of costs and benefits is often considered deliberatively within decision making. However, there is a need to understand the value that societies attach to providing care for specific treatment or patient groups, such as those advocated for orphan drugs [22], and to formally incorporate identified relevant equity aspects within CEAs [11]. In line with this, the National Institute for Health and Care Excellence in England has recently updated its methods manual for conducting a health technology assessment to incorporate the severity weights [23]. Similarly, in the Netherlands, the relevant CET varies from €20,000 to €80,000 per QALY depending on the severity of the condition under evaluation [24]. However, this approach has been criticised for not taking a symmetrical account in applying a higher weight to the health gains of the beneficiaries of the intervention and to the health decrements of the losers bearing the opportunity cost [25]. A more comprehensive approach applying direct equity weights under a net health benefit approach is described in Paulden and McCabe [26]. In their paper, the authors emphasised that the same equity weights ought to be applied to patients who meet the equity consideration and whose health would be forgone if the technology was adopted.

The approach proposed by Paulden and McCabe [26] in the context of equity weights emphasises one implication that is often overlooked: any step taken towards extending the traditional CEA framework in any of the directions described above has intrinsic implications on the relevant opportunity costs arising from funding decisions. These new dimensions of opportunity costs that fall on 'invisible' members of the society ought to be measured equally to those falling on the individuals targeted by the intervention [4, 8, 27]. This implies that when adding new dimensions and distributional concerns to the evaluations undertaken, the values of v and k might not be relevant, or might not be enough, to inform whether the gains associated with a new intervention are larger than its associated losses. Identifying the parameters that are required for the broader CEA framework to be capable of providing a symmetrical account of gains and losses associated with an intervention is thus the first step to accomplishing this difficult task. In the next section, a conceptual framework for the broader CEA that incorporates their broader opportunity costs is outlined.

2 Conceptual Framework

2.1 Starting Point

Starting from the narrower healthcare perspective, where the aim is to maximise population health from a fixed budget allocated to healthcare, the decision rule to deem a technology as

cost effective implies that (using the net health benefit and the ICER approach, respectively):

$$\Delta B_{\mathrm{H}} - \frac{\Delta C_{\mathrm{HC}}}{k} > 0 \text{ or } \frac{\Delta C_{\mathrm{HC}}}{\Delta B_{\mathrm{H}}} < k, \tag{1}$$

in which, ΔB_{H} is the incremental benefit associated with the intervention measured in health units, ΔC_{HC} are the associated incremental healthcare costs, and k is a measure of the health opportunity cost, reflecting the cost effectiveness of displaced resources. As pointed out above, this decision rule is equivalent to stating that the health gains associated with the new technology ought to be higher than the health likely to be forgone owing to the additional costs falling on the healthcare budget. The estimate of the health forgone can be measured by $\frac{\Delta C_{\mathrm{HC}}}{k}$, when k represents the health opportunity costs of healthcare funding decisions. In practice, measuring forgone health at each decision may not be practical, if only because it often remains unknown what services might get displaced. Therefore, k has been proposed to be empirically proxied by the marginal cost effectiveness of current healthcare spending [28]. Under the decision rule presented in Eq. 1, k is the relevant CET value to which to compare the ICER of the technology. This approach relies on the assumption that the only objective for decision making is to improve health, that everyone's health gains have the same value, and that there are no relevant effects outside the healthcare sector or, if there are, they ought to be ignored.

Brouwer et al. [6] show the decision rule in contexts whose goal is to maximise social welfare from a societal perspective and when assuming that there is a degree of flexibility in the allocated budget. This is presented in Eq. 2 (using the net monetary benefit and the ICER approach, respectively):

$$v\Delta B_{\mathrm{H}} - \Delta C_{\mathrm{T}} > 0 \text{ or } \frac{\Delta C_{\mathrm{T}}}{\Delta B_{\mathrm{H}}} < v, \tag{2}$$

in which ΔC_{T} are the incremental total costs associated with the intervention, including incremental healthcare costs (ΔC_{HC}) and other broader costs (such as direct costs incurred by patients, informal care, and productivity losses, denoted by ΔC_{c}), and v is a measure of the societal monetary value of health. This decision rule is interpreted as indicating that for a technology to be deemed cost effective, the incremental benefits of the intervention expressed in monetarised health gains ought to be larger than the total incremental monetary costs. In these decision contexts, v is the relevant CET determining whether a technology is cost effective. However, this approach makes no consideration of the role of limited budgets, ignoring the existence of opportunity costs likely to fall on the healthcare budget.

The two-perspective approach proposed by Brouwer et al. (and that was first outlined in Claxton et al. [29]) reflects a situation where the societal perspective is considered relevant but the healthcare budget is assumed to be fixed:

$$v\left[\Delta B_{\mathrm{H}} - \frac{\Delta C_{\mathrm{HC}}}{k}\right] - \Delta C_{\mathrm{C}} > 0. \tag{3}$$

In this framework summarised by Eq. 3, the monetary value v is attached to the net health gain associated with the intervention (the term in brackets). In this decision context, for the intervention to be deemed cost effective, the monetarised net health benefits ought to outweigh the broader incremental societal costs. To arrive at any conclusion, information on both v and k is required.

However, the authors proposing this approach already pointed out a limitation of this framework. The authors noted that if the displaced resources were also associated with broader societal costs or gains, then ΔC_{c} should reflect the net change on these broader impacts of the new intervention compared to the displaced activity. To explicitly capture these wider opportunity costs, the decision rule presented in Eq. 3 needs to be expanded.

2.2 A Conceptual Framework for the Broader CEA and Its Broader Opportunity Costs

A conceptual framework is proposed in this section using a notation that is defined in the text as it appears. The notation is also summarised in Table 1 for quick reference. An illustrative example is provided throughout for the hypothetical introduction of a new technology in a healthcare system.

Starting with this illustration, consider a new vaccine that was able to produce a health gain of ΔB_{H}= 1000 QALYs but imposes an incremental cost of ΔC_{HC} =€50 million on the healthcare system. If the estimate of the health opportunity cost was k_{H}= €25,000/QALY (that is, for every €25,000 displaced from the healthcare system, an average of one QALY is lost), then following Eq. 1, the net health benefit associated with the programme would be equivalent to: $1000 - \frac{€50M}{25{,}000} = 1000 - 2000 = -1000$ QALYs. If broader societal costs, outcomes beyond health and/or equity weights were not incorporated in the evaluation, this intervention would not be deemed cost effective, irrespective of any other regard, including the monetary value of a unit of health, denoted by v_{H}. Assuming that the latter is estimated at €30,000/QALY, the intervention is estimated to produce a net monetary loss amounting to €30 million.

Table 1 Notation and illustrative example

Parameter	Description	Illustrative example
ΔB_H	Incremental health gains (in QALYs)	1000 QALYs
ΔB_W	Incremental (health and) well-being gains (in QALYs)	2500 QALYs
ΔB_{Ca}	Incremental capability gains (in "ICECAPs")	800 "ICECAPs"
ΔB_T	Incremental productivity gains (in units of time)	1000 years
ΔC_{HC}	Incremental healthcare costs (in €)	€50,000,000
ΔC_E	Incremental education costs (in €)	€−1,000,000
k_H	€ per unit of health displaced in the healthcare system	€25,000/unit
k_W	€ per unit of (health and) well-being displaced in the healthcare system	€20,000/unit
k_{Ca}	€ per unit of capability displaced in the healthcare system	€100,000/unit
k_T	€ per unit of productivity displaced in the healthcare system	€200,000/unit
k_E	€ per unit of education costs displaced in the healthcare system	€−100/unit
v_H	Monetary value of a unit of health	€30,000
v_W	Monetary value of a unit of (health and) well-being	€40,000
v_{Ca}	Monetary value of a unit of capability	€60,000
v_T	Monetary value of a unit of productivity	€20,000
e_H	Equity weight applied to special consideration (e.g. severity)	1.7
p_H^G	Proportion of health gains associated with the intervention that meets special consideration	1.0
p_H^L	Proportion of health displaced associated with the intervention that meets special consideration	0.1

ICECAPs ICEpop Capability Measures *QALYs* quality-adjusted life-years

2.2.1 Introducing External Effects

Moving now towards the first extension discussed, which implies incorporating broader effects falling outside the healthcare sector. As a way of illustration, I consider the implications of incorporating productivity losses and costs falling on the education sector,[1] which are now introduced in Eq. 4.

$$v_H\left[\Delta B_H - \frac{\Delta C_{HC}}{k_H}\right] + v_T\left[\Delta B_T - \frac{\Delta C_{HC}}{k_T}\right] - \left[\Delta C_E - \frac{\Delta C_{HC}}{k_E}\right] > 0. \quad (4)$$

Incremental productivity of patients, and possibly of informal caregivers, is added to Eq. 4 as a potential additional benefit derived from the intervention, measured in terms of units of time. Incorporating this dimension in the analysis implies measuring the direct impact on productivity among the individuals targeted by the intervention, denoted by ΔB_T, and the indirect impact on productivity among patients bearing the opportunity costs associated with the funding decision. For the latter, a measure of rate of changes in productivity per change in health system spending is required; this is captured by k_T. The impact on the costs falling on the education sector that might be associated with some health interventions are also added in Eq. 4, and measured in monetary terms, denoted by ΔC_E. Note that this incremental value might be positive if the intervention imposes a financial burden on the education sector, for example, such as a health programme that is delivered at schools, or negative if the intervention reduces educational costs, for example, by reducing the costs associated with special needs education. Displacing resources from the healthcare system might also have an indirect impact on the education sector. To account for this, we need an estimate of the rate of changes in education costs per change in health system spending. This is included in Eq. 4 by k_E. Alternative methods of arriving at such estimates are suggested in the discussion section. Aggregating the additional dimensions incorporated into Eq. 4 to arrive at a single measure implies translating all dimensions into a common metric. To do so, the monetary value of a unit of health, v_H, and the monetary value of a unit of productivity, v_T, are now required to conclude whether the intervention might be viewed as cost effective.

Following on the vaccine example, let us consider that estimates of the opportunity costs of displacing healthcare services in terms of its impact on productivity (measured in years) and education costs (measured in euros) were available

[1] Note that this paper takes what Walker et al. [8] named as the "within-dimension" approach, where we first estimate the average population-level impact in each dimension, and then we aggregate across dimensions, as opposed to the "within-individual" approach, which implies aggregating first within individuals across all dimensions, and then aggregating across individuals. The former approach is likely to reflect the most common data availability contexts, as individual-level information across all dimensions might not be often available.

and estimated at k_T = 200,000€/year and $k_E = -100$€/€, respectively. These two stylised hypothetical values have no empirical basis. A monetary value of a unit of productivity is assumed to be estimated at 20,000€/year, based, for instance, on average annual salaries.[2] If the vaccination programme was associated with an increase in productivity of, say, 1000 years and was able to save, say, € 1 million to the education sector by reducing costs associated with special needs, the result obtained when substituting the values in Eq. 6 is: $30,000\left[1000 - \frac{50M}{25,000}\right] + 20,000\left[1000 - \frac{50M}{200,000}\right] - \left[-1M - \frac{50M}{-100}\right] = 30,000[-1000] + 20,000[750] - [-0.5M] = -30M + 15M + 0.5M = -14.5M$.

Therefore, in this example, including productivity and education costs also yields a negative net monetary benefit, although in this case is reduced from €30 to €14.5 million. However, note that the result would be different if these dimensions were added but their associated opportunity costs, alongside health opportunity costs, were ignored. In such a case, the analysis would lead to the conclusion that the vaccine programme is a cost-effective use of healthcare resources yielding a positive net monetary benefit of €1 million ($=30,000[1000] + 20,000[1000] - [50M] - [-1M] = 1M$).

2.2.2 Introducing Outcomes Beyond Health

New outcome measures may be complementary or alternative to the traditional QALY approach. In the event that an alternative dimension, considered to be a more universal outcome measure, was to substitute the health measure, the analysis would be equivalent to the traditional decision context, but the new universal measure of outcomes would substitute the estimate of ΔB_H. For example, if ΔB_W was a measure of broader incremental impacts on the (health and) well-being of the population associated with an intervention, the decision rule that mirrors that in Eq. 1 (ignoring now external effects) would take the following form:

$$v_W\left[\Delta B_W - \frac{\Delta C_{HC}}{k_W}\right] > 0. \quad (5)$$

It is important to note that in such a case, the relevant input to reach a conclusion about the cost effectiveness of the intervention no longer is reflected by the health opportunity costs of the funding decision, which was denoted by k_H. The relevant input should now reflect the opportunity costs in terms of the new outcome measure, i.e. in terms of (health and) well-being, denoted k_W.

[2] Note that, alternatively, productivity might be measured and directly enter the equation in monetary terms as a cost/saving dimension.

In our illustrative example, if we assume that this value was €20,000 per unit (that is, for every €20,000 imposed on the health system, on average one unit of [health and] well-being is lost in the population), and that the number of (health and) well-being units associated with the introduction of the hypothetical vaccine were 2500 units, then the estimated net gain would be: $2500 - \frac{€50M}{20,000} = 2500 - 2500 = -0$ units. In this case, the intervention would be at the margin of being considered cost effective. This conclusion is irrespective of the monetary value that might be attached to the unit of (health and) well-being, denoted by v_W.

Different data requirements would arise if health outcomes were complemented with another measure capable of capturing aspects beyond direct health impacts that are also associated with the use of healthcare. As discussed, an example might be a "capability" measure, quantified through an instrument such as ICECAP. However, when considering this dimension, it is important to ensure that changes in capabilities are independent of changes in health to avoid double counting. When incorporating this dimension into the CEA framework (ignoring again any external effects), the decision rule becomes:

$$v_H\left[\Delta B_H - \frac{\Delta C_{HC}}{k_H}\right] + v_{Ca}\left[\Delta B_{Ca} - \frac{\Delta C_{HC}}{k_{Ca}}\right] > 0. \quad (6)$$

Several new elements are added to inform decision making now, namely, (i) the impact of the intervention on individual capabilities (these can be the patients' and/or their caregivers'), denoted by ΔB_{Ca}, (ii) the opportunity costs in terms of capabilities associated with introducing the new intervention and reflected by k_{Ca}, and, particularly when there are net gains in one dimension and net losses in another, (iii) a social function capable of aggregating both dimensions based on the monetary values attached to a unit of health and to a unit of capability, v_H and v_{Ca}, respectively.

Considering our illustrative example, let us assume that the vaccine is capable of generating not only 1000 QALYs in the targeted patients but also 800 units in terms of capability in (to avoid potential doble counting) the people who care for the affected patients. If a value of k_{Ca} was known, and estimated at €100,000 per unit of capability, and the monetary values attached to a unit of health and to a unit of capability were estimated at €30,000 and €60,000, respectively (similar figures were obtained in an empirical study [30]), the result of this evaluation yields the following outcome: $30,000\left[1000 - \frac{50M}{25,000}\right] + 60,000\left[800 - \frac{50M}{100,000}\right] = 30,000[1000 - 2000] + 60,000[800 - 500] = -30M + 18M = -12M$.

In this example, there is a net loss in the health dimension and a net gain in the capability dimension. The values of v_H and v_{Ca} are decisive in concluding whether the intervention is considered cost effective.

In our example, the aggregated result leads to a negative net monetary benefit, so the vaccine would not be considered cost effective. Note that if we were to add this new dimension, but ignore their associated opportunity costs, alongside the health opportunity costs, the analysis would yield a different conclusion. The vaccine would be considered cost effective and estimated to produce a net monetary benefit of €28 million $(=30,000[1000]+60,000[800]-[50M]=28M)$. It is worth noting that this illustration provides a particular example that avoids double counting, as we have assumed that improvements in capabilities apply only to caregivers, not patients. A more cautious approach should be considered if wishing to incorporate changes in health and capabilities within an individual patient.

2.2.3 Applying Differential Weighting to Outcomes

The last step of this conceptual framework consists of introducing distributional considerations by the means of equity weights, following a similar approach to that outlined in Paulden and McCabe [26]. We assume, for simplicity, that the weighting is applied in a binary manner, so that health gains meet or do not meet the equity requirement, and that a higher weight is applied to health gains that occur in "severe" conditions. Assuming a larger number of groups complicates the illustration but leads to the same conclusions. To operationalise the equity weighting, the following inputs are required: a measure of the quantitative value of the additional weight attached to health gains for severe conditions, denoted by e_H, and the proportion of health gains associated with the intervention that meets the severity condition, denoted by $p_{\mathrm{H}}^{\mathrm{G}}$. The health gains associated with the intervention would then be weighted by the factor $\overline{w}_{\mathrm{H}}^{\mathrm{G}}=(p_{\mathrm{H}}^{\mathrm{G}}*e_{\mathrm{H}})+((1-p_{\mathrm{H}}^{\mathrm{G}})*1)$. Acknowledging that a proportion of health displaced by the costs of the intervention might also meet the severity condition, denoted by $p_{\mathrm{H}}^{\mathrm{L}}$, implies that the calculation of forgone health ought to also be weighted by the factor $\overline{w}_{\mathrm{H}}^{\mathrm{L}}=(p_{\mathrm{H}}^{\mathrm{L}}*e_{\mathrm{H}})+((1-p_{\mathrm{H}}^{\mathrm{L}})*1)$. Equation 7 describes the decision rule in this context (ignoring external effects and outcomes beyond health):

$$v_{\mathrm{H}}\left[\left(\Delta B_{\mathrm{H}}*\overline{w}_{\mathrm{H}}^{\mathrm{G}}\right)-\left(\frac{\Delta C_{\mathrm{HC}}}{k_{\mathrm{H}}}*\overline{w}_{\mathrm{H}}^{\mathrm{L}}\right)\right]>0. \tag{7}$$

To illustrate, consider that all the health gains associated with the hypothetical new vaccine meet the severity condition, and that health gains that occur in severe conditions have a 70% higher value than other health gains, that is, $p_{\mathrm{H}}^{\mathrm{G}}=1$ and $e_{\mathrm{H}}=1.7$. If one-tenth of the expected losses in health that would result from displacing health resources occurred in people who also meet the severity requirement (i.e. if $p_{\mathrm{H}}^{\mathrm{L}}$ =0.1), the net weighted health benefit associated with introducing the vaccine becomes: $[(1000*1.7)]-\left[\left(\frac{50M}{25,000}\right)*(1.07)\right]=[1700-2140]=-440$ QALYs.

The vaccine would thus not be deemed cost effective if opportunity costs were accounted for in a symmetrical manner to the benefits associated with the intervention. However, note that if opportunity costs were ignored and equity weights were applied only to the beneficiaries of the intervention, the vaccine would yield a positive net monetary benefit estimated at €1 million $(=30,000[1000*1.7]-[50M]=1M)$.

2.2.4 Generalizing the Conceptual Framework

The above sections have illustrated the implications of moving towards a broader CEA framework, the consequences of ignoring opportunity costs in the conclusions drawn and the input requirements that arise if opportunity costs were to be appropriately accounted for. These data requirements are summarised in Fig. 1, where the parameters identified in this proposed conceptual framework are generalised and are also related to the specific examples shown in the illustration.

As Fig. 1 indicates, the first step involves the identification and measurement of all the dimensions that are considered relevant. These are denoted by ΔB_j and ΔC_h, where j indicates the dimensions of benefits and h is the dimensions of broader costs, over and above healthcare costs. The second step in this framework allows for the net impacts on these dimensions to be measured. This requires estimates of the opportunity costs that arise owing to the additional costs falling on the healthcare budget. These are denoted by k_j, k_h, depending on whether they relate to a benefit or a cost dimension. The third step of this framework allows the application of symmetrical equity weights to the dimensions of benefits considered relevant. The specific weights are denoted by e_j^i, where j represents the benefit dimension and i denotes the population subgroup whose gains are applied relative weights. Information on the proportion of gains associated with the intervention and the proportion of losses due to displacement that meet the equity conditions are also required; these are denoted $p_j^{i,G}$ and $p_j^{i,L}$, respectively. The final step of the framework implies the aggregation of each of the benefit and cost dimensions into a single measure, for which information on the monetary value of dimensions measured in a non-monetary metric are needed; these are denoted by v_j.

The generalised decision rule in this broader conceptual framework is summarised in Eq. 8:

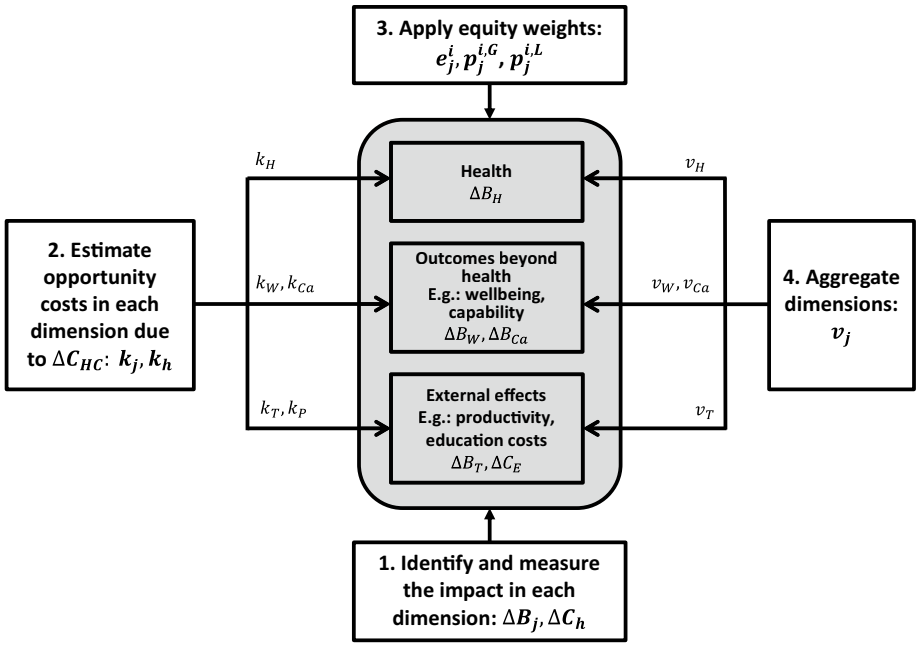

Fig. 1 Summary of generalised conceptual framework

$$\sum_j v_j \left[\left(\Delta B_j * \overline{w}_j^G \right) - \left(\frac{\Delta C_{\mathrm{HC}}}{k_j} * \overline{w}_j^L \right) \right] - \sum_h \left[\Delta C_{\mathrm{h}} - \frac{\Delta C_{\mathrm{HC}}}{k_{\mathrm{h}}} \right] > 0, \tag{8}$$

where $\overline{w}_j^G = \sum_i p_j^{i,G} * e_j^i$ and $\overline{w}_j^L = \sum_i p_j^{i,L} * e_j^i$. This decision rule implies that for an intervention to be deemed cost effective, the sum of monetarised equity-weighted net benefits ought to be larger than the sum of the net broader costs imposed by the intervention.

Some authors have suggested that not all costs are equally important in making healthcare decisions, and therefore that there might be an argument for also weighting costs in economic evaluations [13]. Weighting cost dimensions is not included in this conceptual framework, but this could potentially be introduced. However, if different weights were to be applied to costs that fall inside and outside of the healthcare system, one might also need to consider the likely inter-dependence of the production functions that create those costs. We return to this issue in the discussion section, as inter-dependences might be expected across many of the parameters of this framework.

Note that the data requirement imposed by the proposed conceptual framework have dramatically increased when compared with the data requirements in decision-making contexts defined by Eqs. 1 and 2 above. Furthermore, the conceptual and methodological challenges to arrive at robust estimates of the parameters identified in this framework are diverse and complex. The next section proposes a series of further research venues that might facilitate such an undertaking and highlights the implications of ignoring the broader opportunity costs that arise when extending the scope of the traditional CEA framework.

3 Discussion and Conclusions

The proposed framework has identified the steps and data requirements of moving from a single-sector unidimensional analysis to a broader framework that considers the full spectrum of the associated opportunity costs arising from funding decisions. The framework outlined is particularly relevant for decision-making contexts characterised by limited flexibility in the allocation of funding, implying that the direct opportunity costs of incorporating new health technologies fall primarily into the healthcare budget.

The conceptual and data requirements of such a framework are demanding, requiring system-wide representative values and/or robust estimates concerning: (i) selecting and measuring the dimensions included in the analyses; (ii) the opportunity costs associated with each of the dimensions included in the analyses; (iii) the equity weights and the percentages of beneficiaries and losers meeting equity considerations; and (iv) the monetary values attached to dimensions measured using a non-monetary metric. I now discuss potential routes to move toward each of these directions and highlight the assumptions underpinning analyses ignoring the opportunity cost implications of widening the scope of CEAs.

Identifying the dimensions that ought to be included in CEAs is a context-dependent task but it needs to be defined according to a consistent and socially legitimate criterion. While decision makers might be seen as responsible for

defining the scope and making the implicit social value judgements underpinning this task, analysts can support this undertaking in scientific and principled ways [2]. Therefore, an obvious starting point would consist of reviewing and interpreting the vast literature that has explored this particular issue in theoretical and empirical studies. Based on this, and informed by their expertise, analysts can guide this process to ensure that decisions on which, and how, incorporate dimensions are based on "good" science, are legitimate, mitigate the risk of double counting, respond to social demands, are a result of a considered process that avoids political convenience and are in line with the core principles underpinning the health system in question[3] [2]. There have been several exercises that have used qualitative and/or mixed-methods approaches to elicit the view of different stakeholders regarding dimensions to be incorporated in, for example, multiple criteria decision analyses [31] or some other forms of consensus frameworks for particular types of technologies, for example, for vaccination programmes [32]. However, for the framework proposed in this paper, the goal would be to identify a set of dimensions that will then consistently and systematically be applied in CEAs of health technologies undertaken in a given setting, and to ground this selection not only on the view of specific decision makers and particular stakeholders, but also on a checklist regarding the conceptual justification and the empirical evidence supporting its introduction. Similar consultation processes have been undertaken, for instance, on the last methods review conducted by the National Institute for Health and Care Excellence [33].

In the second step of the framework, estimates of the opportunity costs associated with each dimension included in the analyses are required, i.e. k_j, k_h. Identifying and measuring the expected losses associated with a specific funding decision is often unfeasible, and, as a result, there has been pathbreaking work conducted in England aimed at empirically estimating the average marginal effect of health spending on health outcomes [28]. This work was followed by similar studies in Spain [34], Australia [35], the Netherlands [36, 37], Sweden [38], South Africa [39], China [40] and the USA [41]. There are methodological challenges in these analyses [42], but in some countries their corresponding estimates are increasingly being used to draw conclusions on the cost effectiveness of health technologies [43]. Incorporating wider dimensions implies that estimates of health losses are just one (potential) source of opportunity costs, and similar studies ought to be undertaken to measure the average impact of health spending on other outcomes. The design of such studies can be informed by previous work exploring health impacts, although the assessment of the opportunity costs related to, for instance, external effects is argued to be significantly more difficult in scope than estimating the health opportunity costs of healthcare spending [29]. Therefore, there is a call for more comprehensive data and more sophisticated methods. An alternative route worth exploring is the use of multipliers that might capture the ratio of displaced outcomes in the additional dimensions relative to displaced health, similarly to the approach proposed by Al-Janabi et al. in the context of family health spillovers [44]. In the case of, for instance, education costs, this would imply estimating the impact on educational costs due to changes in population health that are, in turn, a result of changes in healthcare spending. The value of $\frac{1}{K_E}$ could then be approximated by $= \left[\frac{\partial C_E}{\partial B_H}\right]\left[\frac{\partial B_H}{\partial C_{HC}}\right]$, where the first term measures the marginal impact of health on educational costs, and the second term measures the marginal effect of healthcare spending on health. The complexity of arriving at such estimates means that the uncertainty around these proxy parameters is likely to be large, but this uncertainty can and should be characterised in CEAs.

I now consider the implications of ignoring the opportunity costs that arise when incorporating additional dimensions into CEAs. Potentially, there are two alternatives to formally assessing and incorporating proxy estimates of opportunity costs in CEAs, each of which underpins different assumptions. The first is to include additional dimensions but to ignore their associated opportunity costs (i.e. the standard approach in CEAs taking the societal perspective). This approach implicitly assumes that interventions under evaluation might have impacts on the incorporated dimensions, but that displaced healthcare has no impact on such dimensions, which is very unlikely the case. In practice, this assumption implies a procedural injustice, in which "patients who could benefit from the technology being appraised have 'voice' in the process [45], while those who could be harmed (through displaced healthcare funding) do not" [27]. Furthermore, it might lead to an overestimation of the net benefits associated with new interventions.

The second option is to ignore wider effects altogether (i.e. the standard approach in CEAs taking the healthcare system perspective). Interestingly, in the latter, the underpinning assumption is not, as it has been wrongly pointed out, that health technologies have no external effects, or that these effects ought to be ignored. Instead, the implicit assumption is that the intervention impacts on additional dimensions are compensated with the losses in these dimensions expected because of displacement. In other words, it assumes that the impact of the intervention on the additional

[3] For example, analysts have already pointed out a potential conflict between the incorporation of productivity costs in economic evaluations and the egalitarian principles many countries adhere to [13, 57]. The reason being that incorporating productivity costs might favour technologies that are targeted to paid productive members of society over others. As a possible solution, some authors have suggested incorporating lost production related to unpaid work [57].

dimensions is not substantially different to the average effect of existing interventions at the margin. The extent to which this latter assumption is reasonable might form the basis to decide whether incorporating wider effects is appropriate, noting that their potential exclusion does not imply the absence of such effects, but rather that they are similar to the expected effects of displaced care.

Identifying equity weights and the proportion of beneficiaries and the proportion of losers meeting the equity considerations is the challenge associated with the proposed third step. To identify the equity criteria and to arrive at specific equity weights, a similar approach conducted in parallel to that outlined in step 1 might be considered, complemented with empirical societal elicitation studies as explained in the following paragraph. Measuring the proportion of losses that would be entitled to such weights will require exploring the prevalence of the relevant equity criteria in the general population, or, in a more sophisticated endeavour, to explore the characteristics of the average displaced gains, such as in the analysis conducted by Claxton et al. [46].

Note again that while any of the aforementioned approaches can only approximate the average expected impact on invisible members of society, ignoring this impact makes again an even stronger assumption, i.e. that displacing health spending has no effect on individuals elsewhere who also meet the equity considerations. Traditional CEAs that do not incorporate equity weights do not necessarily imply that everyone's health has the same value, but might rather reflect that the proportions of health gains that meet the equity considerations are no different to the proportions of health losses that also meet such considerations. This might not be an unreasonable assumption in specific circumstances.

Finally, to provide an aggregated CEA measure to inform decisions, information on the trade-offs across dimensions not expressed in monetary terms is needed. In cases where markets exist, market values would serve this purpose, such as the use of wage rates to measure the value of productivity. When markets do not exist, elicitation exercises using discrete choice experiment techniques that might be complemented with willingness-to-pay methods in samples of the general populations can be used to assess and measure the relevant trade-offs individuals are willing to make across dimensions. Moreover, these can also be conducted to elicit the potential equity weights, if any, that might be attached to particular population groups according to societal preferences. These exercises are methodologically complex and some have pointed out the difficulties of arriving at a social aggregation function with a broad consensus and social legitimacy [8, 29]. However, in the health economics literature, there is a vast body of empirical research aimed at eliciting the monetary value of health outcomes (see the recent review identifying 53 studies in [47]) and there is an even longer tradition in environmental economics, with published methodological standards for monetary valuations of environmental impacts [48]. Other routes that might be worth pursuing involve the use of the well-being valuation approach, as conducted by Himmler et al. when estimating the monetary value of health and capability well-being [30], or the methods proposed by Phelps [49], who specified utility as a function of income using estimates of relative risk aversion. The alternative to providing an aggregation function consists of resting decision making on disaggregated information and on deliberative processes often characterised by competing interests, and where 'invisible' patients do not have a voice and are not included in any discussion panel.

As noted, one further challenge in estimating the parameters required for the proposed framework relates to the interdependences expected among them. This means that, for instance, setting a specific value for the monetary value of health might have implications on the current or future value taken by the marginal productivity of the healthcare system. Empirically estimating the relationship between these parameters is currently challenging, but to begin exploring this issue, one recommendation would be to regularly update the estimated parameters to account, not only for changes over time, but also for the inter-dependences among them.

There are other alternative frameworks that have also attempted to comprise several dimensions into decision making (e.g. cost-consequence analyses [50], the extended CEA [51], the original impact inventory framework [9]), multiple criteria decision analyses [31, 52], and social returns of investment analyses [53]) or have focussed on related issues such as incorporating the consequences of diminishing returns and risk aversion over health (the Generalized Risk-Adjusted Cost-Effectiveness [GRACE] approach [54]). However, these frameworks either fail at providing an aggregated measure, focussing instead on displaying outcomes in a disaggregated manner or fail at accounting for opportunity costs, both related to health and/or to any other dimension, or they fail at both. In addition, some of these previously proposed frameworks involves qualitatively eliciting values from specific stakeholders at each decision-specific context, and are at a high risk of double counting [55]. In contrast, the proposed framework seeks to provide an alternative based on empirical evidence to methods requiring decisions to be based on the value judgements of a small number of stakeholders, different at each decision, which introduce arbitrariness, subjectivity and inconsistency into decision making, and that most often ignore "the patient not in the room" [56].

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