PharmacoEconomics (2019) 37:119–130
https://doi.org/10.1007/s40273-018-0749-8

LEADING ARTICLE

Future Costs in Cost-Effectiveness Analyses: Past, Present, Future

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Published online: 26 November 2018

Abstract

There has been considerable debate on the extent to which future costs should be included in cost-effectiveness analyses of health technologies. In this article, we summarize the theoretical debates and empirical research in this area and highlight the conclusions that can be drawn for current practice. For future related and future unrelated medical costs, the literature suggests that inclusion is required to obtain optimal outcomes from available resources. This conclusion does not depend on the perspective adopted by the decision maker. Future non-medical costs are only relevant when adopting a societal perspective; these should be included if the benefits of non-medical consumption and production are also included in the evaluation. Whether this is the case currently remains unclear, given that benefits are typically quantified in quality-adjusted life-years and only limited research has been performed on the extent to which these (implicitly) capture benefits beyond health. Empirical research has shown that the impact of including future costs can be large, and that estimation of such costs is feasible. In practice, however, future unrelated medical costs and future unrelated non-medical consumption costs are typically excluded from economic evaluations. This is explicitly prescribed in some pharmacoeconomic guidelines. Further research is warranted on the development and improvement of methods for the estimation of future costs. Standardization of methods is needed to enhance the practical applicability of inclusion for the analyst and the comparability of the outcomes of different studies. For future non-medical costs, further research is also needed on the extent to which benefits related to this spending are captured in the measurement and valuation of health benefits, and how to broaden the scope of the evaluation if they are not sufficiently captured.

Key Points for Decision Makers

When an intervention prolongs life, this leads to additional costs in added life-years. Including the additional medical costs in economic evaluations is required, under reasonable assumptions, to allow optimal decisions, both from a healthcare and societal perspective.

Knowledge on how to estimate future (unrelated) medical costs has improved. Important challenges for their systematic inclusion in economic evaluations are changing pharmacoeconomic guidelines to allow or prescribe inclusion (rather than exclusion) and lowering the practical difficulties for doing so.

The inclusion of future non-medical costs is hampered by both theoretical and empirical challenges. The benefits of future non-medical consumption and productivity may currently not be comprehensively and systematically included in cost-effectiveness analyses. This is a requirement for including these costs.

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1 Introduction

Cost-effectiveness analyses are increasingly used to guide pricing and reimbursement decisions in healthcare [1]. The analytical approach most frequently applied is a cost-utility analysis, wherein outcomes are quantified in quality-adjusted life-years (QALYs). The results of the analysis are typically summarized in an incremental cost-effectiveness ratio (ICER), the ratio of additional costs to additional benefits of a new intervention compared to an appropriate alternative. A fundamental issue within a cost-effectiveness analysis, which is unresolved to date, is the extent to which future costs should be included in the ICER [2, 3]. Future costs (also referred to as 'survivor costs') are the costs that arise during the life-years that would not have been lived without a life-extending intervention. These costs are typically classified into future related medical costs, future unrelated medical costs, and future non-medical costs.[1]

Future related medical costs are costs for treatments in life-years gained that are directly related to the disease that is being treated with the life-extending treatment. When, for instance, an intervention to treat a heart-attack successfully extends life, costs for routinely visiting a cardiologist thereafter would count as future related medical costs. Future unrelated medical costs are only a consequence of the life-extending intervention through its effect on life expectancy. Costs for treating a broken leg or severe influenza after surviving a heart attack would be examples of these costs. Future non-medical costs comprise future net non-medical resource use. These future non-medical costs can be obtained by subtracting productivity gains as a result of the ability to work longer when life is extended from the costs of non-medical consumption during the life-years gained. Examples of such future non-medical consumption costs are travel expenditures and costs for housing and food during the life-years gained.

Although none of the future costs would arise without the life-saving intervention, not all of these costs would generally be included in cost-effectiveness analyses of life-prolonging interventions. The exclusion of some of the costs can be justified by the perspective adopted by the decision maker. The aim of a decision maker adopting a healthcare perspective, for example, is typically assumed to be the maximization of health or health-related utility under the constraint of the healthcare budget. Broader welfare implications including future non-medical costs are then generally ignored. In contrast, a decision maker adopting a societal perspective is typically assumed to aim to maximize social welfare, often described as some (weighted) aggregation of individual welfare, under the constraint of total societal resources.[2] For such a decision maker, broader welfare economic implications beyond healthcare are relevant, and are generally taken into account in an economic evaluation [4].

The extent to which future costs should be included in a cost-effectiveness analysis, considering the decision maker's perspective, has been frequently debated [2, 5–21]. Although progress has been made, diverging approaches and viewpoints continue to exist in both theoretical and practical contributions in this area. To contribute to appropriate methods, to increase validity, consistency, and comparability of results, our aims in this article are threefold. First, to highlight past theoretical debates and empirical research on the inclusion of future costs in a cost-effectiveness analysis; second, to clarify which issues within these debates are unresolved to date; and third, to indicate future research needed in this area.

2 Future Medical Costs

In this section, we discuss the inclusion of future medical costs. We start with the discussion of the theoretical debates and then elaborate on the empirical research.

2.1 Theoretical Debates

In the development of methodological guidance for cost-effectiveness analyses, mathematical models have played an important role. For instance, the decision rule to adopt an intervention only when the ICER is lower than a cost-effectiveness threshold has been derived from a mathematical model with a clearly defined objective and several constraints [23]. Such models have also been developed and used to address the question whether future costs should be included in cost-effectiveness analyses.[3]

Van Baal and colleagues [19], for instance, set up a mathematical model describing a decision maker who wants to

[1] Future non-medical costs could also be categorized into future related and unrelated costs, to the same degree as future medical costs. However, in concordance with previous literature, we will not make this distinction and label all these costs here as future non-medical costs.

[2] Note that adopting a societal perspective is not synonymous with taking a welfarist approach, which restricts welfare information to solely (individual) utilities. Extra-welfarism, allowing broader definitions of welfare including for example capabilities, is fully compatible with taking a societal perspective [22]. Hence, the issues addressed in this article are relevant for both approaches.

[3] In these models, future medical costs are specified as related or unrelated on a cost level (expenditures conditional on survival, which do not change with an increase in the quantities of the intervention consumed, are unrelated). In practice, future medical costs are typically specified as related or unrelated on the level of the disease to be treated.

maximize QALYs given a fixed healthcare budget. They concluded that both future related medical costs and future unrelated medical costs should be included in a cost-effectiveness analysis to maximize the number of QALYs gained from available resources. The explanation is that given a fixed healthcare budget, life-prolonging interventions necessarily result in a lower budget per person for healthcare in the future. Hence, life-prolonging interventions have real health opportunity costs by leaving less budget for others. Excluding future unrelated medical costs therefore leads to an underestimation of the opportunity costs of life-extending interventions. As a consequence, ignoring these costs could result in care being adopted that is actually less cost effective than the care that it displaces or prevents from being funded. Hence, inclusion of future unrelated medical costs can lead to different decisions and ultimately leads to more (health) benefits.

For decision making from the societal perspective, several competing mathematical models have been proposed that have implications for the inclusion of future medical costs. The assumptions underlying these models are typically of major importance for the interpretation and real-world relevance of the results. For instance, Garber and Phelps [5] developed a model from which the welfare-optimizing decision rule included future related and unrelated medical costs in the ICER. However, according to their model, future unrelated medical costs could be excluded without affecting the relative ranking of cost effectiveness of alternatives. This makes exclusion possible provided practice is consistent and the value of the cost-effectiveness threshold appropriately adjusted [5]. Crucial assumptions in their model that were required to arrive at these conclusions were that earnings and consumption profiles (both medical and non-medical) do not vary by age and that at every age individuals exactly consume what they produce. These assumptions are difficult to justify, given the observed age patterns in healthcare use and net resource use [6, 24]. Furthermore, the trade-off between improvement of quality of life and improvement of length of life was not properly accounted for in this model. This is relevant because interventions that only increase quality of life are not affected by the inclusion or exclusion of costs in life-years gained (as survival is unaffected). Ignoring future costs for life-prolonging interventions thus distorts their comparison to interventions that improve quality of life. This leads to biased decisions in favor of life-prolonging interventions.

Meltzer [6] constructed a more general model with less restrictive assumptions, and, based on that, concluded that the welfare-optimizing decision rule necessarily includes both future related medical costs and future unrelated medical costs in the ICER. As future unrelated medical costs can vary under different conditions, excluding these may affect the relative ranking of cost effectiveness of alternatives, and consequently lead to different decisions on the care to provide.

Later, Lee presented a model implying that the welfare-optimizing decision rule need not include future unrelated medical costs. Furthermore, including these costs would, according to this model, lead to suboptimal outcomes for society [14]. His model was subsequently criticized because it employed similar assumptions as Garber and Phelps by ignoring survival probabilities in the budget constraint. Therefore, ignoring this essentially implies that these costs were not meaningfully included in the model to begin with [15]. Feenstra and colleagues [16], in response to Lee, showed that proper inclusion of the probability of survival in the budget constraint, and thereby capturing the increase in future unrelated medical expenditures as a necessary consequence of increased life expectancy, leads to the conclusion that future unrelated medical costs should be included in a cost-effectiveness analysis. These results support the results earlier found by Meltzer [6, 15].

Conversely, some have argued that new treatments should be evaluated in isolation (excluding both costs and benefits of unrelated care) [4, 25]. In this line of reasoning, it is claimed that future unrelated medical care is not a necessary consequence of the life-prolonging intervention because no irreversible commitment to obtain future unrelated care is made when adopting it [4]. Although intuitively appealing, the commitment argument does not provide a rationale why we should include lifetime consequences of a decision in terms of healthcare use for related diseases (like the cardiologist's visits in the introduction) but not for unrelated diseases (like the broken leg). For both disease categories, it is often unclear what the exact commitments will be in the future (although it is likely that there will be commitments). More importantly, van Baal and colleagues demonstrated that consistently excluding the costs and benefits of unrelated care in general pushes the ICER upwards and results in suboptimal decisions [12]. The reason for this is that unrelated medical care is usually a mix of different interventions and the cost effectiveness of unrelated medical care will then be some sort of average return to healthcare expenditures, which on average is lower than the threshold. If indeed future unrelated medical care is cost effective, the inclusion of both costs and benefits can never push an ICER above the threshold.

It should also be emphasized that although the inclusion of future unrelated medical costs has been disputed, the benefits related to this spending are generally already included in cost-effectiveness analyses. The quality of life and life expectancy upon which estimates of benefits of life-prolonging interventions are based are typically observed in patients also receiving unrelated medical care. This implies that the benefits of unrelated medical costs are projected in the estimations of the QALY gains of a life-extending

intervention. Childhood vaccination may, for example, prevent early death. However, quality of life and expected survival in added life-years depend on the provision of unrelated healthcare during these years and estimates thereof typically obtained in people receiving unrelated care. To exclude costs but include benefits of unrelated future medical care would of course be inconsistent.

In that context, Nyman developed rules for internal consistency to determine which costs should be included in a cost-effectiveness analysis given the benefits included. These rules require that all costs required to produce projected benefits should be included, as well as those that are causally related to the intervention, even when they do not yield additional benefits. Given current practice, internal consistency thus requires that future unrelated medical costs should be included because benefits thereof are captured in the projected QALY gains [7, 12].

It needs to be noted that internal consistency could also be achieved by excluding both costs and benefits of unrelated care. Doing so however requires disentangling related and unrelated costs and benefits, which is practically difficult, if not impossible [12, 20]. Benefits from interventions would then for example need to be estimated under the assumption that patients would not receive any unrelated care. It appears highly difficult to practically estimate the quality of life of patients under such assumptions. Furthermore, it is not always clear or known which costs are actually related or unrelated [26, 27]. Additionally, if the aim of an economic evaluation is to meaningfully inform healthcare decision makers, inclusion of future unrelated medical costs and their benefits seems most appropriate (also referred to as the external consistency argument) [2, 12, 20]. To illustrate this, take the example of childhood vaccination. It seems rather inconceivable that people who live longer because of childhood vaccination would be denied standard future care on that ground. Nor is it clear how one would estimate their life expectancy and quality of life without future care, or what the practical relevance would be of doing so.

Summarizing, the theoretical work in this area suggests that under the most reasonable assumptions it is necessary to include both future related medical costs and future unrelated medical costs in the ICER to obtain optimal decisions, in line with the decision maker's objectives. This conclusion holds, regardless of the perspective that is adopted by the decision maker. Inclusion is optimal as well as internally and externally consistent.

2.2 Empirical Research

Practical difficulties in the estimation of future unrelated medical costs and the burden that having to include these costs may place on analysts have been mentioned as arguments not to include these costs in a cost-effectiveness analysis [3, 25, 28]. However, methods have been developed to facilitate the estimation of future medical costs, which was possible given the knowledge on the effect of aging on healthcare expenditures [29]. It would be an unsurmountable task to predict the risk of all unrelated diseases and link these predictions to costs to estimate future unrelated medical costs. Therefore, rather than modeling all these individual diseases explicitly, the starting point for the estimation of future unrelated medical costs is typically estimates of medical spending by age, which comprise spending on all sorts of diseases [6]. Such an approach is similar to how economic modeling studies usually deal with other causes of death, as well as estimates of quality of life by age (which are included to deal with the fact that mortality risk increases with age and quality of life generally decreases) [30]. Age- and sex-specific per-capita medical spending can then be linked to survival curves to estimate future unrelated medical costs. In general, there is no correction for the fact that per-capita spending includes spending for related diseases unless the related disease(s) represent a large part of health spending. For instance, several modeling studies focusing on smoking and obesity do correct per-capita spending for the cost of related diseases when estimating future unrelated medical costs [31–33].

Further refinements in estimating future medical consumption have been made by taking into account the observation that healthcare spending is usually concentrated in the last phase of life [34, 35]. This also typically affects how age influences medical expenditures because part of the effect of aging may be owing to the costs of dying (and older people have higher probabilities of dying) [36]. Given that everybody only dies once, the impact of unrelated medical costs on the ICER is less strong when one accounts for the higher spending in the last year of life [34, 37].

In the Netherlands, a tool was developed that facilitates the inclusion of unrelated medical costs in a standardized manner, accounting for the high spending in the last year of life and allowing for the correction for costs of related diseases [35]. For other countries, such tools do not yet exist but estimates of spending by age, sex, and disease have been produced for several countries, which would allow the creation of such a tool or other comparable guidance, also for those countries. For instance, several studies have illustrated how to estimate future unrelated medical costs for the UK [19, 38–40].

Of course, the exact nature and height of future healthcare spending is uncertain, and increasingly so when it is further ahead in the future. A common assumption in studies addressing future unrelated medical costs is that future spending patterns resemble current healthcare spending patterns. While this is an assumption that need not completely hold, it seems a reasonable starting point for estimation (and better than estimates of zero) and is consistent with the

types of assumptions commonly made in practical economic evaluations. In these evaluations, for instance, the estimates of the impact of individual interventions on future health and healthcare also assume the current standard of care [20].

Estimates of the impact of including future unrelated medical costs for specific patients and treatments have revealed that the inclusion of future unrelated medical costs can significantly affect the cost effectiveness of interventions [12, 19, 26, 41–45]. These findings refute the argument that future unrelated medical costs are negligible and can therefore be ignored [25, 28]. Moreover, these studies revealed large differences in the changes in ICERs as a result of inclusion depending on the age of the patients, following from the pattern that healthcare consumption is typically higher for people at higher ages. As a result, including the future unrelated medical costs has more impact when people reach higher ages.

Textbox 1 describes an example of a Dutch study in which including future unrelated medical costs significantly affected cost-effectiveness estimates. During the submission process of the new intervention, Dutch pharmacoeconomic guidelines were updated and future unrelated medical costs had to be included. Because of this, a full analysis was performed both including and excluding future unrelated medical costs, [46] highlighting the impact of inclusion.

Textbox 1: Future unrelated medical costs and the cost effectiveness of LCZ696 Most patients with chronic symptomatic heart failure with reduced ejection fraction are treated with angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers. When ACEI are not tolerated, patients may receive angiotensin receptor blockers. However, if patients remain symptomatic, ACEI should be replaced by the angiotensin receptor neprilysin inhibitor sacubitril/valsartan (LCZ696). A global health economic model was adopted to reflect the Dutch societal perspective, to determine the cost effectiveness of LCZ696 in comparison to treatment with ACEI in adult patients with chronic heart failure with reduced left ventricular ejection fraction in the Netherlands, based on an average age of 75 years.

The analysis displayed a quality-adjusted life-year (QALY) gain from LCZ696 compared to ACEI of 0.33. With total incremental costs (excluding future unrelated medical costs) of €5839, the incremental cost-effectiveness ratio (ICER) was estimated on €17,600 per QALY. The increased longevity of 0.39 life-year because of LCZ696 caused additional discounted medical costs, unrelated to heart failure, of €2950. The inclusion of future unrelated medical costs increased the ICER with €8891 (€2950/0.33) to €26,491 per QALY gained.

In the Netherlands, cost effectiveness is judged against a threshold ranging from €20,000 to €80,000, for which the height depends on the principle of proportional shortfall. For this treatment, a threshold of €50,000 applied. The intervention was thus cost effective both before and after inclusion of future unrelated medical costs. However, the increase of the ICER with over 50% shows that the effect can be large. (See [46] for more details.)

3 Future Non-Medical Costs

In this section, we discuss future non-medical costs. As already mentioned in the introduction, these costs are only relevant for the societal perspective. We follow the same structure here as for the previous section, starting with the theoretical debates, following with empirical research.

3.1 Theoretical Debates

Some of the mathematical models highlighted above in the discussion of the inclusion of future medical costs have also played a key role in the debate on the inclusion of future non-medical costs. Generally, comparable conclusions were drawn regarding the inclusion. For instance, in the welfare-optimizing decision rule derived from the model by Garber and Phelps [5], future non-medical costs could be included or excluded without affecting the relative ranking of cost effectiveness. This conclusion strongly depended on the restrictive assumptions underlying the model. Using less restrictive assumptions, Meltzer [6] found that the welfare-optimizing decision rule necessarily includes future non-medical costs. Leaving these out would affect the relative ranking of cost effectiveness of alternatives, which could consequently lead to suboptimal decisions and outcomes.

In terms of internal consistency, it should be noted that Meltzer implicitly assumed that in cost-effectiveness analyses, utility measures are used that capture the full welfare benefits, also those of non-medical consumption and productivity (leisure). However, QALYs are intended to measure health-related quality of life. The internal consistency rules, proposed by Nyman, specify that the ICER should only include costs for which the related benefits are also captured (or when these are causally related though do not yield additional benefits) [7]. One may wonder whether QALYs capture the benefits related to non-medical consumption.

From a theoretical point of view, QALY optimization would only be compatible with welfare maximization (with broader costs and benefits beyond health also implicitly considered) under strict assumptions rarely met in practice [47].

Empirically, different views exist on what actual benefits are captured in the quality-of-life weights that are assigned to the health states. Standard gamble and time-trade-off exercises are typically used to derive these weights. Although the most frequently used questionnaires used do not explicitly mention non-medical consumption [7], it is not clear what consumption level the respondents implicitly assume when answering the questions.

Some argue that people expect non-medical resource use to remain unaffected to the current level [9, 11]. Another view is that people at least consider the non-medical resource use needed to stay alive, such as daily food intake. Such assumptions have not been empirically verified. It is also good to emphasize that even if minimal consumption levels to stay alive are not considered by respondents in health-state valuations, they are still required to obtain the quality of life that is measured from the questionnaires and should thus be counted as a cost [10, 41]. This could also be stated for other non-medical consumption, which to a certain extent produces health in the same manner as medical care. Considerable gains in life expectancy in many Western countries were for example the result of interventions outside the healthcare sector (clean water, sewerage, healthier and safer foods, road safety) [48].

Available experiments suggest that respondents inconsistently include impacts on productivity and leisure in health-state valuations, if not explicitly requested to do so. The latter is uncommon in practice. The influence of spontaneous inclusion of these impacts on health-state valuations varied [49], although it was typically small and often insignificant, especially on average valuations, suggesting that these impacts would better be valued separately. Explicit instructions (to exclude these effects) could improve consistency in terms of what respondents include in health-state valuations.

Adarkwah and colleagues investigated the impact of instructions on including the impact of ill health on the utility of consumption and leisure in health-state valuations [50]. Explicit instruction to consider this utility did not influence valuations. In contrast, spontaneous consideration in the group without explicit instruction led to significantly lower valuations. From this, one could derive that currently the non-health benefits of interventions are not systematically captured through common health-state valuations. However, because relatively few studies have been performed in this area, with varying results, further research is needed to gain more insight into the extent to which people consider the broader welfare implications that result from ill health.

Besides being internally consistent, the information a cost-effectiveness analysis provides to decision makers should also be externally consistent; the information should entail the policy-relevant consequences of adopting an intervention. In line with this, Lundin and Ramsberg argue that rather than following the QALY, which costs (and benefits) to include should be determined by the welfare theoretic foundations underlying a cost-effectiveness analysis [11]. This is related to the argument by Richardson and Olsen that the scope of the analysis should be consistent with the aims of the decision maker and preferences of society [9]. According to Nyman, because the aim of healthcare interventions is mainly to increase health, a focus on health-related quality of life as an outcome would be sufficient [51]. These arguments, however, are more related to the issue of how to conceptualize the societal perspective appropriately [52] than to the specific issue of inclusion of future costs.

Nyman has later argued that the welfare implications of non-medical consumption and productivity (leisure) are already known to be positive, and can therefore be safely ignored. He argues that, unlike for medical consumption, people can and do weigh benefits of non-medical consumption and production against its costs, and make deliberate and appropriate decisions whether to consume, and to work or enjoy leisure instead [17, 51]. Whether this is a sufficient argument to exclude these costs from evaluations remains to be seen, as the welfare effects may still differ between interventions (even if often positive). Meltzer also demonstrated that decisions will be affected when consumption or productivity are excluded when having an effect on welfare.

3.2 Empirical Research

Several studies have estimated net non-medical resource use, for inclusion in cost-effectiveness analyses [6, 41–45, 53]. For this, productivity costs were estimated using the human capital approach (in economic evaluations, the friction cost approach sometimes is also used to calculate productivity costs in 'normal' life-years [4]). For consumption, these studies used either data from household expenditure surveys [44, 53] or data on earnings to extract consumption costs as disposable income minus savings [42]. Age patterns of per-capita consumption and average earnings (as a proxy for productivity) were used for these estimates [6, 43–45].

Different views exist regarding how to handle transfer payments when estimating future consumption costs and productivity. Lee [14] argued that net resource use should be calculated by net dissavings, implying that not only earnings from productivity should be included, but also other sources of income such as private and public pension payments and asset income. This argument was refuted by Meltzer [15], explaining that transfer payments are not relevant when analyses are performed from a societal perspective. This is consistent with how transfer payments are treated in a traditional cost-effectiveness analysis from a societal perspective (as transfers not costs) [54].

Net resource use (consumption minus production) is typically positive in younger ages, negative in middle ages, and again positive in older ages. This means that only in people of 'working ages' does production normally exceed consumption. For example, it was shown that for the Danish population, production exceeded consumption from ages 24–62 years [42]. Other research found comparable patterns [41, 43–45]. The difference between age groups is typically owing to higher (paid) work force participation among younger people. Note that in these studies, data on household consumption were used to derive per-capita consumption but economies of scale within households were not addressed. Economies of scale can be important when the goal is to estimate the costs of non-medical consumption resulting from living longer because preventing death in a multi-person household would result in less additional consumption than preventing death in a single-person household. Additionally, to date, studies have not yet used the friction cost method when estimating production gains in life-years gained. This would likely result in lower productivity gains at a societal level from the prolonged life of patients (owing to the possibility of replacement), hence a less often negative net resource use. It needs to be noted that unpaid work is not accounted for in these calculations.

More generally, in comparison with the inclusion of the future medical costs, there is less experience with the inclusion of future non-medical costs. An example of the difference in cost effectiveness when future non-medical costs are either included or excluded based on a Swedish study can be found in Textbox 2. Because of a change in the Swedish pharmacoeconomic guidelines, this study obtained ICERs both including and excluding future non-medical costs [55].[4]

Textbox 2: Future non-medical costs and the cost effectiveness of pomalidomide Patients with multiple myeloma who have progressed following treatment with both bortezomib and lenalidomide have a poor prognosis. In this late stage, patients are often left with best supportive care. Pomalidomide is an anti-angiogenic and immunomodulatory drug for the treatment of multiple myeloma.

The cost effectiveness was estimated of pomalidomide as an add-on to best supportive care in patients with relapsed and refractory multiple myeloma in Sweden, based on an average age of patients of 64 years. The analysis displayed a quality-adjusted life-year (QALY) gain from pomalidomide of 0.74 and increased longevity of 1.21 life-year.

The incremental cost-effectiveness ratio (ICER) [without future non-medical costs] was estimated to be €56,682 per QALY. Including future productivity gains (which were negligible owing to the fact that most life-years are spent in retirement in this patient group) lowered the ICER with €457 to €56,225 per QALY. When consumption costs in added life-years were included, this increased the ICER with €28,642 to €84,867 per QALY gained.

Despite the relatively high ICER, the treatment was granted reimbursement by the Swedish authorities. (For more details see [55].)

4 Practical Relevance

4.1 Pharmacoeconomic Guidelines

Which costs are actually considered in a cost-effectiveness analysis largely depends on the requirements in country-specific pharmacoeconomic guidelines.[5] These guidelines generally prescribe the inclusion of future related medical costs (typically referring to these as 'direct medical costs') in the reference case, the standard format for a cost-effectiveness analysis. However, they often pay no further attention to the inclusion of future unrelated medical costs or explicitly require the exclusion of these costs. In jurisdictions in which a societal perspective is adopted, it is generally required to include future productivity costs (or gains) and the future costs of non-medical consumption related to the intervention (such as informal care and traveling expenditures). Other non-medical consumption is rarely mentioned in the guidelines. Consistent with these prescriptions, empirical studies found that in practice, future unrelated medical costs and future non-medical consumption costs not related to the intervention are rarely included in economic evaluations [41, 56].

Some countries recently changed their guidelines regarding the inclusion of future costs. For instance, Dutch guidelines, which prescribe adopting a societal perspective, traditionally did not require the inclusion of future unrelated medical costs. This changed in 2016, when inclusion of these costs became mandatory. However, still no specific attention is paid to future non-medical consumption that is not related to the intervention [57]. In 2013, Swedish guidelines, adopting a societal perspective, were changed to specifically (and uniquely) prescribe the inclusion of future costs as total consumption (medical and non-medical) minus

[4] Numbers are based on table IV in [55] and in euros. Consumption costs in this study comprised both medical and non-medical consumption. Using the proportions from the original estimates [53], it can be derived that of the €28,642, the increase as a result of future non-medical consumption costs would be approximately €25,896 ((1-(13,623/142,074))*28,642), and the increase as a result of future non-medical costs would be €2746.

[5] For an overview of country-specific pharmacoeconomic guidelines, see https://tools.ispor.org/peguidelines/.

production in life-years gained [58]. However, the guidelines were changed after criticism was voiced from the public and patient advocacy groups on the inclusion of future costs [59]. It was stated that it would be investigated how these costs should be handled in the future [60, 61]. In the revised versions from 2015 [62] and 2017 [63], only the inclusion of future related medical costs and additional productivity in life-years gained is required and not future unrelated medical and consumption costs. In contrast, the second US Panel on Cost-Effectiveness in Health and Medicine in 2016 [64] recommended the inclusion of all future costs, contrary to the first US Panel in 1996 [28]. While the recommendations of the Panel are not official requirements, they have shown to be influential [65].

In the debates on the inclusion of future unrelated medical costs, the influential National Institute for Health and Care Excellence guidelines [66], which apply in England and Wales, are often discussed. These prescribe taking a healthcare perspective. To date, however, National Institute for Health and Care Excellence guidelines exclude future unrelated medical costs from the analysis. It has been argued that National Institute for Health and Care Excellence should change its guidelines in this context because the exclusion of future unrelated medical costs is inconsistent with the aims of the analysis [2, 20, 21, 27, 29]. Counterarguments mainly relate to ethical concerns regarding the potential distributional impact of including these costs [26, 29].

Summarizing, in general, guidelines still typically are silent or prescribe the exclusion of future unrelated medical costs and future non-medical costs not directly related to the treatment. However, first signs of adjustment towards inclusion of, at least, future unrelated medical costs appear to be showing. The inclusion of future non-medical costs not directly related to the treatment may follow, but seems more contested.

4.2 Ethical Concerns

As illustrated by the examples in the textboxes, the inclusion of future unrelated medical costs and future non-medical costs can have a substantial impact on final ICERs. Consequently, including these costs in cost-effectiveness analyses in practice may affect funding decisions. In general, the impact of the inclusion of these costs is larger when life-years gained are spent in relatively poor health (implying a lower denominator and thereby increasing the ICER). Note that while the total number of life-years gained is relevant in terms of budget impact, it typically has a limited impact on the ICER. Further, even if the number of life-years gained is small, the impact of future costs can still be substantial.

Additionally, including future unrelated medical costs and future non-medical costs results in different decisions on what care to provide, and thus has distributional consequences. Including future unrelated medical costs may, for instance, disfavor interventions targeted at the elderly (because non-medical expenditures are typically higher at higher ages, which increases the impact of including future unrelated medical costs) and people already in ill health or with already higher healthcare expenditures. On the ground of such ethical concerns, it has been argued to exclude future costs from a cost-effectiveness analysis [4, 26, 29, 67]. Acknowledging the relevance of these issues, it has also been argued that ignoring real costs is not an appropriate or useful answer to ethical questions [3, 27, 68]. One may even wonder whether ignoring real opportunity costs, that will have consequences on others, is an ethical strategy. Furthermore, ignoring real costs endangers the credibility and usefulness of outcomes from a cost-effectiveness analysis [27]. Equity issues need to be dealt with, preferably based on all relevant information in deliberative decision-making processes. In light of the information provided, decision makers may for instance wish to use a higher threshold for care focused on specific groups of patients [69].

The question of how to appropriately incorporate ethical concerns into the decision-making process is an important matter in this context. One method is through an appraisal phase in which ethical concerns are dealt with explicitly, while being fully informed on all relevant costs and effects [27]. This may also be facilitated by incorporating societal distributional preferences into the ICER or threshold, by assigning higher weights or values to health gains for specific groups in the population [65]. Another option is to use a multi-criterion decision analysis. In this approach, formal methods are used to identify and score the various factors considered relevant to a decision [1]. All such methods do require initial inclusion of information on all relevant costs and benefits.

5 Discussion

5.1 Future Medical Costs

The theory and practical possibility of including future medical costs in a cost-effectiveness analysis has significantly developed over the past years. Most (relevant) economic models revealed that optimal outcomes require considering all current and future medical costs, regardless whether these are related or unrelated [6, 15, 16, 19]. Although some models yielded opposite results [5, 14], the assumptions underlying these models are too restrictive to be relevant in practice. Furthermore, other arguments against the inclusion of future unrelated medical costs (e.g., future unrelated medical costs are not a necessary consequence of an intervention or that future unrelated treatments should be evaluated on their own) have been refuted [19, 20].

It has also been explained that projected benefits from interventions require the provision of future unrelated care

and that costs thereof should also be considered in economic evaluations to be internally consistent [7, 12]. Furthermore, external consistency requires both the benefits and costs of future unrelated care to be included for the analysis to be most informative for the decision maker. It has additionally been argued that ethical issues (e.g., inclusion may disadvantage specific patient groups) should be dealt with explicitly and informedly, and cannot justify systematically ignoring real costs.

Most pharmacoeconomic guidelines nevertheless still do not require the inclusion of future unrelated medical costs. This may be because of some 'status quo bias', wish for intertemporal comparability of results, and practical concerns about difficulties of estimating these costs. It may also simply reflect the fact that guidelines are normally based on well-established and accepted viewpoints, which implies they follow (with some lag) on from theoretical developments.

It must also be noted that it is not only the cost effectiveness of the new intervention for which additional inclusion of future unrelated medical costs would be relevant. Additionally, this issue matters for the determination of the threshold against which the cost effectiveness is judged. For instance, within a system with a fixed healthcare budget, when funding a new healthcare intervention implies displacing health sector activity elsewhere, the threshold represents the cost effectiveness of displaced care. The future unrelated medical costs should also be considered in the estimates of the threshold to more accurately represent the opportunity costs. Recent estimates of such a threshold in the Netherlands illustrated how this can be achieved [70].

5.2 Future Non-Medical Costs

For jurisdictions adopting a societal perspective in economic evaluations, with the aim to optimize societal welfare, future non-medical costs are relevant to consider as well [6]. This is typically not done in practice nor prescribed or encouraged in guidelines. Concerns about the benefits captured when quantifying outcomes in QALYs reiterated the debate on the appropriateness of including these costs because internal consistency requires that only costs are included when benefits thereof are also included [7]. Several authors discussed the extent to which welfare implications beyond health are measured and valued in QALYs [49, 50].

A point that has not yet received any attention in the discussion in this context is to what extent people take into account the non-medical benefits when they provide monetary valuations of QALY gains. These valuations are usually obtained using willingness-to-pay exercises and are one possible source of determining the threshold value at which health technologies are considered too expensive [71]. Further research in this area is needed. If such research shows that relevant aspects of benefits beyond health are indeed not systematically and comprehensively measured and valued in current economic evaluations, one could take this to imply that the associated costs can also be ignored. However, if the aim is to improve overall societal welfare, a more appropriate response might be to investigate how the scope of economic evaluations can be broadened to include the relevant benefits as well as costs.

Although internal consistency is a fundamental premise (considering that all transactions have both a cost side and benefit side) [17], internal consistency is not a sufficient criterion. The information a cost-effectiveness analysis provides should also be externally consistent. It needs to inform the relevant decision maker by providing information on all relevant consequences of adopting an intervention. It can be argued that interventions in healthcare primarily aim to improve health-related quality of life. However, welfare implications beyond health (care budgets) can also be relevant for decision makers. This is, by definition, true for decision makers who aim to optimize societal welfare, defined in a relevant welfarist or extra-welfarist approach [6].

One might also argue that decision makers in principle taking a healthcare perspective would not wish to be left completely ignorant about the 'welfare externalities' their decisions might have. In such cases, a separate account of broader societal impacts may be provided. In either case, the inclusion of future non-medical costs would be warranted. A two-perspective approach could facilitate a full account of impacts, while indicating where these impacts fall. Recently, the second US Panel on Cost-Effectiveness in Health and Medicine argued in favor of using such a two-perspective approach, detailing impacts from both a healthcare perspective and from a broader societal perspective [64], as was proposed before [72]. With such an approach as standard, non-medical costs could systematically be included in economic evaluations in healthcare. This leaves open the possibility for decision makers to weight certain impacts more than others and to explicitly address distributional consequences related to the inclusion of specific elements.

However, given the questions regarding whether, how, and to what extent the benefits beyond health related to future non-medical costs are adequately captured in current economic evaluations, it would be premature to advise to simply include these costs. For now, it might be advisable to include these costs separately in a cost-effectiveness analysis. Then, at least the decision maker is provided with more comprehensive information regarding societal costs that follow from a new intervention.

6 Future Research

Regarding future unrelated medical costs, further research could be aimed at reducing practical objections in terms of difficulties in estimating future unrelated medial costs, by standardizing methods and estimates across and within

jurisdictions. This will improve both the applicability of inclusion and the comparability of outcomes. Translating the large body of research on the economics of aging into tools and reference tables that can be used by practitioners of a cost-effectiveness analysis seems one clear way forward. Furthermore, estimates of future unrelated medical costs could be improved by taking into account changes in healthcare expenditures over time as presently these estimates are typically based on the current standard of care.

For future non-medical costs, further research should be conducted regarding the question of whether relevant benefits are already captured in current outcome measures, and, if not, how this could be assured. To facilitate inclusion, research is also required on the development and improvement of methods for the estimation of future non-medical consumption costs. For instance, by accounting for economies of scale in household consumption and by investigating the relation between non-medical consumption and health status. Furthermore, research should focus on how to standardize estimation methods across jurisdictions applying the societal perspective, to broaden the applicability and comparability of outcomes.

7 Conclusion

When an intervention prolongs life, additional costs in the added life-years are incurred. To allow optimal decisions, both from a healthcare and societal perspective, including the additional related and unrelated medical costs in economic evaluations is required. Knowledge on how to estimate future (unrelated) medical costs has improved, also allowing inclusion in practice. Inclusion of these costs would presumably benefit most from lowering the practical difficulties and the burden on the analyst of including these costs in a cost-effectiveness analysis, as well as guidelines prescribing or at least encouraging inclusion rather than prescribing exclusion.

For future non-medical costs, the conclusion is less clear. The benefits of future non-medical consumption and productivity may currently not be comprehensively and systematically included in a cost-effectiveness analysis. Therefore, the appropriate technique to include future non-medical costs requires further attention, both theoretically and empirically. Research in this area is encouraged. Ultimately, this should contribute to optimal decision making in healthcare to obtain the most favorable outcomes for society.

Author contributions Linda M. de Vries was primarily responsible for reviewing the literature and writing the manuscript, in cooperation with Pieter H.M. van Baal and Werner B.F. Brouwer. All authors read, edited, and approved the final manuscript.

Funding No sources of funding were received for the preparation of this article.

Compliance with ethical standards

Conflict of interest Linda M. de Vries, Pieter H.M. van Baal, and Werner B.F. Brouwer have no conflicts of interest that are directly relevant to the contents of this article.

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