# Making sense of cost-effectiveness analyses in respiratory medicine: a practical guide for non-health economists

Job F.M. van Boven[1,2], Susanne J. van de Hei[1] and Mohsen Sadatsafavi[3]

**Affiliations**: [1]University of Groningen, University Medical Centre Groningen, Groningen Research Institute for Asthma and COPD (GRIAC), Dept of General Practice and Elderly Care Medicine, Groningen, The Netherlands. [2]University of Groningen, University Medical Centre Groningen, Dept of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands. [3]Faculty of Pharmaceutical Sciences, the University of British Columbia, Vancouver, BC, Canada.

**Correspondence**: Job F.M. van Boven, University of Groningen, University Medical Centre Groningen, Groningen Research Institute for Asthma and COPD (GRIAC), Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: j.f.m.van.boven@rug.nl



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## Introduction

We live in a world of great advances in respiratory care, but at the same time, we are facing increasing budget constraints. In such a world, the use of any intervention is associated with "opportunity loss": the benefit forgone by not using alternative interventions. Take the example of biologicals for severe asthma (*e.g.* mepolizumab) or lung cancer (*e.g.* nivolumab), with annual costs of around EUR 15 000 and >EUR 100 000 per patient, respectively. The concept of opportunity loss applies whenever decisions are made, either by physicians in clinical practice who have to decide which treatment patients receive, or by health policymakers during the approval process of new interventions for market entrance. If resources are spent on these medications, it means that there will be less budget available for other interventions. In respiratory medicine, interventions could involve pharmacological treatments, but also new bronchoscopic procedures, biomarker tests, diagnostics or other health technologies [1–4].

Nowadays, once a new technology has been shown to be clinically beneficial, it is usually not automatically integrated into daily practice before an economic evaluation has been performed. Although not the only criterion for reimbursement, evidence on cost-effectiveness of the technology is often an important consideration in health technology adoption. To assess whether new technologies offer better value for money compared to existing technologies, we can make use of cost-effectiveness analyses (CEAs).

CEA refers to a set of concepts, methods and standards for comparing competing technologies in terms of both their costs and health effects. A common misconception is that the aim of a CEA is to lower total healthcare expenses. However, given that governmental healthcare budgets are often part of countries' national annual budgets, the amount of money that can be spent is relatively fixed. CEAs are used to ensure that available resources are optimally allocated, *i.e.* in such a way that health effects are maximised for the entire population.

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Most care providers acknowledge the added value of incorporating cost-effectiveness considerations in selecting the optimal treatments, but in-depth understanding of the analysis itself is often lacking. This article provides a practical overview for non-health economists, aimed at helping them to make sense of CEAs. Given the readership of the *European Respiratory Journal*, methodological issues are illustrated by respiratory examples.

## How does it work?

### *The basic concept of cost-effectiveness analysis*

CEA is a joint analysis of both the costs and health outcomes associated with the use of a (new) technology *versus* usual care. CEAs can be either model-based or performed directly alongside a randomised clinical trial (RCT). CEAs can be performed alongside RCTs if sufficient data are collected during the trial (*e.g.* healthcare resource use and quality of life of patients in each arm), with usual care as the comparator. However, most trials lack sufficient length, do not compare against usual care, do not measure hard clinical end-points and do not collect cost data. In addition, the external validity of RCTs is often relatively low [5]. Modelling, by contrast, enables incorporating evidence from multiple sources, extrapolating beyond the follow-up time of individual studies and converting treatment effects on surrogate outcomes to more relevant outcomes, such as costs and life-years. Among the most used modelling frameworks are decision trees and Markov models that basically simulate the disease under study in the target population, and the impact of adopting each of the competing health technologies on costs and health outcomes [6]. The parameters of such models (*e.g.* rate of disease progression, risk of events, treatment effect and their costs) are often elicited from the literature. For example, Zafari *et al.* [7] created a Markov model of severe asthma in which hypothetical patients at any given time could be in one of the following mutually exclusive states: exacerbation free, exacerbation requiring oral steroids, exacerbation requiring emergency room visits, exacerbation requiring inpatient care, and death. Patients could transition to other states once every week, and the transition rates were estimated from different clinical trials. Each state was associated with weekly costs and changes in quality of life. This model was used to compare the cost-effectiveness of bronchial thermoplasty, omalizumab or standard inhaler therapy for patients with moderate-to-severe allergic asthma.

The main output of a CEA is the incremental cost-effectiveness ratio (ICER). The ICER represents the average incremental cost associated with one additional unit of effect and is calculated by dividing the difference in costs (ΔC) between the intervention and comparator, over the difference in effects (ΔE). For example, Zafari *et al.* [7], using the aforementioned model, reported that over 5 years the use of bronchial thermoplasty compared with usual care is associated with excess costs of USD 12 700 (in 2013 US dollars) and an increase in quality-adjusted life-years (QALYs) of 0.16. As such, the ICER for bronchial thermoplasty compared with standard of care would be USD 78 700 per QALY. Of note, a QALY is a generic measure that includes both the quality and the quantity of life lived. One QALY represents one year in perfect health.

In addition to reporting the number, the ICER is often presented graphically as a point on the cost-effectiveness plane. In a cost-effectiveness plane, the *x*-axis is the difference in health outcomes and the *y*-axis is the difference in costs (figure 1, number 1). The main purpose of the cost-effectiveness plane is to show the distribution/uncertainty of outcomes over the quadrants (see also the sections entitled "Uncertainty in CEA" and "When is an intervention cost-effective?").

### *Choice of health outcome*

The health outcome evaluated in the CEA can vary per disease or analysis and is usually dependent on the data that are available (often based on the end-point of a clinical trial). Health outcomes can be disease-specific or generic. A disadvantage of some CEAs that use disease-specific effect measures is that their outcomes are difficult to compare. For example, some studies may express the ICER in incremental costs per chronic obstructive pulmonary disease (COPD) exacerbation avoided [8], while others may present the incremental costs per point increase on the Clinical COPD Questionnaire (CCQ). How should decision makers compare these outcomes? It is for this reason that decision makers often require the use QALYs as the preferred effect measure in CEAs. Using QALYs allows for a direct comparison of cost-effectiveness estimates within and between different disease areas. When QALYs are used as the outcome in a CEA, it is also commonly called a cost-utility analysis (CUA). In most countries, CUA is the preferred technique, but a CEA with a disease-specific outcome can still be presented alongside the CUA [9–11]. While being widely accepted, a criticism of the QALY is that it is not very sensitive to patient-relevant changes in health status (such as cough or dyspnoea), and therefore, maps poorly to clinical respiratory questionnaires such as the CCQ [12].

### *Choice of comparator, population, time horizon and discounting*

One characteristic of CEA is that the new intervention assessed should always be compared to usual care in a patient population that is representative for the target population. In this way, decision makers can

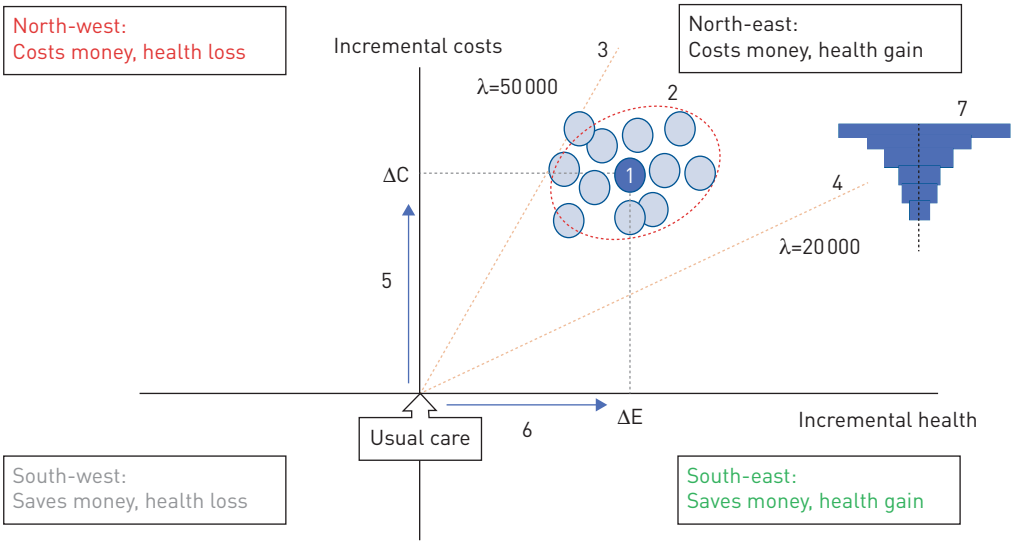


FIGURE 1 Cost-effectiveness plane. 1) Base-case scenario (incremental cost-effectiveness ratio=difference in costs (ΔC)/difference in effects (ΔE)); 2) 95% confidence interval (dots indicate individual iterations of the probabilistic sensitivity analysis); 3) maximum threshold (λ) for a willingness to pay of 50 000 per quality-adjusted life-year (QALY); 4) maximum threshold (λ) for a willingness to pay of 20 000 per QALY; 5) incremental costs; 6) incremental health; 7) tornado diagram (univariate sensitivity analysis).

assess whether or not the new intervention has added benefit over existing interventions. An important decision that has to be made upfront is the time horizon of the analysis, *i.e.* the time we look ahead to calculate future costs and effectiveness outcomes. Country guidelines provide recommendations, but generally, a time horizon should be sufficiently long to capture all relevant costs and effects resulting from the intervention assessed. In some cases (*e.g.* lung cancer screening), costs are made upfront, but benefits could be lifelong and therefore lifetime horizons are often applied in these analyses [13]. In other cases (*e.g.* antibiotics for acute exacerbations of COPD), time horizons of 4 weeks may be sufficient [14]. Note that in cases where clinical and/or economic gains are achieved in the future (>1 year ahead), "discounting" should be applied. The underlying idea of discounting is that humans have a preference for current compared to future gains, and thus future costs and effects should be adjusted to their present value. In the field, but also across countries, different views exist on the exact percentage (discount rate) and whether equal or differential discounting rates for effects and costs should be applied. This results in between-country differences in the discount rates that need to be used, commonly ranging between 1% and 5% [10]. The longer the time horizon, the stronger the effect of discounting on final costs and health gains.

### *Perspective*

Another factor that should be considered before designing a CEA is finding out who is responsible for paying for the intervention and who is going to gain from the intervention. This is called the "perspective" of the analysis. Importantly, the choice of the perspective determines which costs and effects should be taken into account. The two perspectives most often applied are the healthcare payer perspective and the societal perspective. In the former, only direct medical costs (*e.g.* doctor visits, medication and hospitalisations) are taken into account. In the latter, beside direct medical costs, direct non-medical costs (*e.g.* travel costs, caretaker's time), indirect non-medical costs (*e.g.* work productivity losses) and indirect medical costs (medical cost in life-years gained, not related to the intervention) are also included. As with the discount rate, country guidelines differ in their recommendations on which perspective should be adopted (*e.g.* the societal perspective in the Netherlands, but the healthcare payer perspective in the UK) [10]. Due to these country-specific recommendations, but also due to differences in local practice, disease prevalence, clinical guidelines, financial systems and price-levels, cost-effectiveness results cannot simply be transferred between countries or settings [15]. For example, screening for tuberculosis may be cost-effective in high-risk groups in endemic settings, but may not be cost-effective in low-risk groups or non-endemic settings [16]. Lastly, note that in countries like the Netherlands and the USA, it is mandatory to use the societal perspective and thus include all types of costs, but in practice, only direct medical costs and productivity loss are included in the majority of analyses from the societal perspective.

### *Uncertainty in CEA*

Calculating the ICER using the best available data and assumed model structure results in the "base-case" ICER. However, these best data are usually still surrounded by some degree of uncertainty that can impact

our confidence in the outcomes of the CEA. Therefore, assessment of uncertainty is an important aspect of all CEAs [9]. It tells us, for example, about cost drivers, how potential future scenarios (*e.g.* a drug's patent expires) could affect the ICER or how we could further enhance our certainty in the ICER. Uncertainty is assessed by the means of sensitivity analyses where we can apply univariate, multivariate and probabilistic sensitivity analysis. In univariate sensitivity analyses (also called one-way or deterministic analyses), the impact of uncertainty around individual parameters (*e.g.* intervention effect size) on the ICER is assessed by changing one parameter at a time. This could either be done using a fixed percentage (*e.g.* a 25% increase or decrease of the parameter) or by using the upper and lower boundaries of the 95% confidence interval of the individual parameter. A popular visual presentation of the univariate analysis is using a tornado diagram, where the parameter with the highest impact of its variation on the ICER is depicted on the top of the diagram (figure 1, number 7). In multivariate analyses (also called two-way analyses), two parameters are varied at the same time. In probabilistic sensitivity analyses, all parameters are varied simultaneously within their parametric distribution in an iterative process resulting in a cloud of likely alternative scenarios, representing different, but still plausible values of the ICER (figure 1, number 2). Given the ICER is calculated as a ratio, 95% confidence intervals are not often used. Instead, the uncertainty around the ICER is often visually presented in a cost-effectiveness plane (figure 1). In addition, a cost-effectiveness acceptability curve (CEAC) is commonly constructed. A CEAC visually illustrates the probability that an intervention is cost-effective given a certain threshold. The CEAC is made by applying different cost-effectiveness thresholds ($x$-axis) and presents the proportion of iterations below that threshold on the $y$-axis [6]. In our example, at a threshold of 50 000 per QALY (figure 1, number 4) the intervention seems cost-effective ("acceptable") with almost 100% certainty, while at 20 000 per QALY (figure 1, number 3) this probability seems 0%. Using the CEAC, decision makers can decide for themselves which threshold and uncertainty they find acceptable.

#### *When is an intervention cost-effective?*

In cases where the ICER falls in the north-west quadrant of the cost-effectiveness plane (costs money, health losses, figure 1), the balance is clearly negative and the intervention is considered not cost-effective. In the south-west quadrant, by contrast, the technology is associated with saving money, but patient outcomes are worse, making this option not ideal from a health point of view. It could still be considered cost-effective when the health loss is minimal and the cost savings are large. In the south-east quadrant, the balance is clearly positive (saving money, improving health). The north-east quadrant is the most interesting. Here the decision to consider an intervention "cost-effective" depends on the threshold that is accepted (*i.e.* the "willingness to pay" for one QALY). As with the methodological considerations, this threshold differs per country and sometimes even per disease. For example, in the UK a fixed threshold of GBP 30 000 per QALY is used, in the Netherlands the non-fixed threshold usually varies between EUR 20 000 and EUR 80 000 per QALY (depending on disease severity), and the World Health Organization promotes a threshold of three times a country's gross domestic product per capita.

## What is the current state of the art in respiratory medicine using this technology/method?

Initial health economic guidelines and methods were mostly developed to support decisions on reimbursement of new (respiratory) drugs, but are increasingly used for other respiratory technologies and interventions such as case finding, screening/monitoring, adherence interventions or integrated care programmes[17–22]. Health economics is a relatively young, but fast evolving field. Besides better integration of real-world data [23], especially in the modelling space, efforts are currently being made to optimise validation of models and prepare them for personalised medicine assessment [24–26]. This would include taking into account the impact of comorbidities on respiratory outcomes as well as identification of specific subgroups (*e.g.* based on biomarkers such as eosinophils, exhaled nitric oxide fraction or interleukin-5) where expensive therapies, such as biological treatments, can be cost-effective [27].

## How is CEA likely to be used in the future?

With ever increasing healthcare costs it is likely that CEA will become more popular and play more fundamental roles in resource allocation. According to the International Society of Pharmacoeconomics and Outcomes Research (ISPOR), around 45 countries have general health economic (submission) guidelines or recommendations in place [10], but in the majority of countries no guidelines exist or are not (fully) adhered to. To standardise the general reporting of CEAs, ISPOR has developed the CHEERS reporting checklist [28]. In our view, the way forward is to further standardise CEAs in the respiratory field regarding the agreed analytical approach (*e.g.* time horizon or cost units) per specific respiratory disease. For some common respiratory diseases, such as asthma, recommendations are in place [29], but this is still limited to outcomes and does not provide any methodological recommendations [30]. Furthermore, although the majority of CEAs in respiratory medicine focus on drugs, the concept may also

be more frequently applied to other types of emerging interventions such as nasal high-flow therapy or bronchial thermoplasty. Finally, CEAs have value beyond use as decision tools for policy making only and may be increasingly integrated into the care decisions of practising healthcare professionals.

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