Cost-Effectiveness in Goal-Directed Therapy: Are the Dollars Spent Worth the Value?

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HEALTHCARE FINANCING has become a fixed agenda of international discussions on health policy. An aging population coupled with an insatiable demand for new and costly medical technology pose an unpredictable challenge for future healthcare funding.[1–3] Under such economic pressure, policy-makers are expected to deliver cost-containment solutions for efficient and sustainable healthcare provision. On first sight, this idea seems to conflict with the clinicians' main concern of delivering comprehensive care to the patients, who then often dismiss the positive effect of careful resource allocation on long-term care provision and, consequently, on the overall good to society.[4] Cost-effectiveness analysis combines both principles by pooling clinical and economic benefit before suggesting sustainable strategies of effective resource allocation.[5–7] In this paper, the authors review the available literature on cost-effectiveness analysis and goal-directed therapy (GDT).

UNDERSTANDING COST-EFFECTIVENESS

Cost-effectiveness analyses now are used widely to appraise the value of new interventions and aim to inform decision makers on how to best allocate scarce resources to achieve the maximum clinical benefit for the patients within a given budget.[8–12]

Introduced decades ago, the concept of cost-effectiveness analysis is best described in terms of a cost-effectiveness ratio and quality-adjusted life years (QALY).[13–15] QALYs are a measurement of disease burden, combining the quality and quantity of the remaining years of life. A patient who experiences the long-term consequences of a severe complication might consider this state as a reduced utility of life when compared to someone in full health. This then can be described numerically (on a scale from 0-1 where 0 equates to death and 1 to full health). For example, someone undergoing hip replacement with a value of quality of life is 0.77, after partial recovery of physical functioning this value rises to 0.8 for the subsequent 2 years and then in the 3rd to 5th year to 0.9. Multiplying those qualitative numbers with the quantitative numbers of total observation year yields a QALY of 4.1 ($0.7 \times 1 + 0.8 \times 2 + 0.9 \times 2$) compared with 5 ($5 \times 1$) in a healthy individual and 3.85 if no surgery was performed.

The incremental cost-effectiveness ratio (ICER) considers the marginal value of a new intervention and the results are expressed numerically as a ratio (costs/QALY). In summary, it tells how much more money would be spent by introducing a new intervention to increase the value of life. These numbers are then related to a threshold, below which an intervention is deemed to be cost-effective; eg, if an intervention causes incremental costs of $20,000 USD and leads to an increase in QALY of 2 years compared to standard treatment, then the ratio is $10,000 USD/QALY. The commonly accepted threshold of reimbursing a new intervention varies among countries; current ranges are between $25,000 and $100,000 USD, meaning that interventions that fall below the given threshold in a country can be recommended to be financed, reimbursed, and implemented.[16–20]

In general, if an intervention is associated with financial gain and clinical benefit, it can be considered cost-saving. If clinical benefits are achieved, despite additional costs, then a cost-effectiveness analysis is performed, and if the ICER is below the threshold, the intervention is deemed cost-effective (Fig 1).

Predicting future costs is associated with a high degree of uncertainty and unpredictability and, therefore, a thorough sensitivity analysis is essential.[20] Estimating costs and outcomes are complicated for a number of reasons. The data do not fit a Gaussian distribution, thereby invalidating standard statistical approaches to describing future events. Input parameters often are derived from different sources with different practice patterns and costs. It is difficult to get homogenous data. It seems feasible to make certain assumptions and test the effect in a sensitivity analysis. In a one-way sensitivity analysis, one input parameter is varied each time, and the effect on the outcome is observed. Usually, hospital morbidity, mortality, length of stay, QALY, and discount rates are tested. If one parameter is found to affect the results, the further step of

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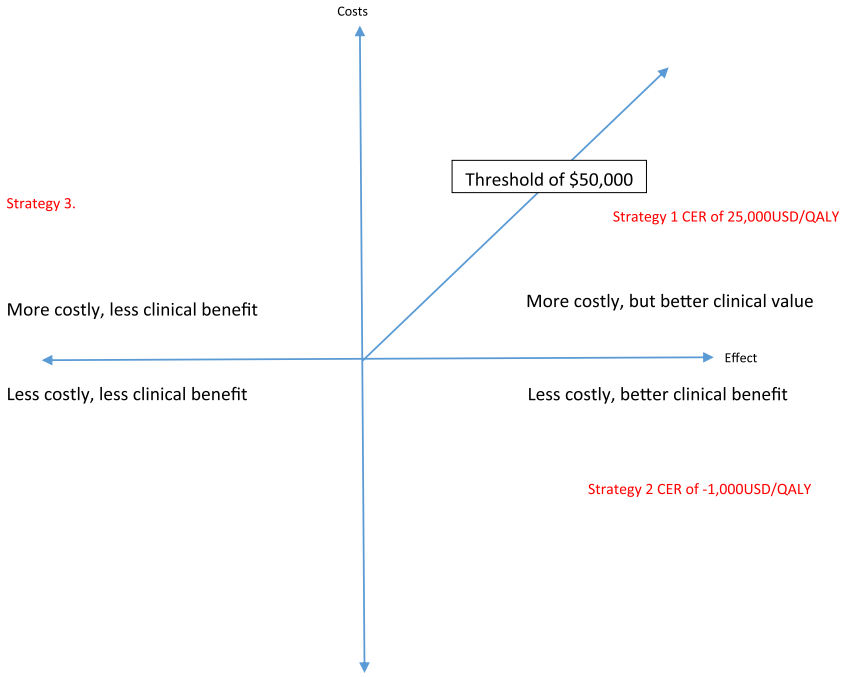

Fig 1. Cost-effectiveness plane. Difference in effects and costs. An intervention that falls in quadrant 4 (Strategy 2) can be considered cost-saving because clinical benefits can be achieved at lower costs. It can be adopted. If an intervention produces higher costs, with a reduction in benefit, it should be rejected (Strategy 3). In quadrant 2, the intervention provides better clinical value at higher costs. In such cases, a threshold of 30,000 can be applied. An intervention that falls below this threshold is deemed cost effective (Strategy 1), and can be adopted because there is a willingness to pay extra for the additional clinical value.

a multi-way sensitivity analysis can be performed to assess the joint effect of parameters, which allows variation of more than 1 parameter at a time. In addition to those deterministic sensitivity analyses (one- and multi-way), probabilistic analysis are now frequently used. Such mathematical techniques rely on random sampling to compute future outcomes. Rather than providing the optimal number, it answers "what if" questions and explains the best- and worst-case scenarios. A parameter range has to be specified a priori. In the subsequent analysis, a cohort of 10,000 patients, each with its own "in-range" parameter values, is run through the constructed pathway to the derived outcomes. The main advantage of such an analysis is not only the description of the absolute and relative costs associated with a certain treatment, but also the probability that this conclusion will hold up under varying circumstances. This then can be described illustratively in a cost-effectiveness acceptability curve that shows the probability that an intervention is cost-effective under different willingness-to-pay values (Fig 1).

GOAL-DIRECTED THERAPY

GDT is a concept of proactively manipulating hemodynamics by using flow- and perfusion-related measurements. It is based on the idea that optimal hemodynamic management increases oxygen delivery to optimize tissue perfusion. Previous studies have shown that this approach not only reduces complication rates but also length of inpatient hospital stay in septic patients and high-risk surgical patients.[21–24] Within a recent meta-analysis, Hamilton et al[25] were able to demonstrate that the use of GDT significantly reduced mortality (OR 0.48 [0.33-0.78], $p = 0.0002$) and complications (OR 0.43 [0.34-0.53] $p < 0.0001$) in high-risk surgical patients. A subsequent review[26] focused on the effect of GDT on different risk groups and showed a mortality benefit for high-risk surgical patients (OR = 0.20, 95% CI 0.09-0.41; $p < 0.0001$) as well as reduced complication rates (OR = 0.45, 95% CI 0.34-0.60; $p < 0.00001$), which were independent of the perioperative risk classification. Because hospital costs are the main driver of increasing expenses, GDT reduces morbidity and mortality and has the potential to achieve clinical and economic benefits. In septic patients, GDT showed similar outcomes. Rivers et al[27] were able to confirm a mortality benefit (46.5% *v* 30.5%; $p = 0.009$) for septic patients assigned to this targeted approach. Because of the significance of the positive outcome studies, GDT subsequently was included as part of the Surviving Sepsis Guidelines.[28] Recently, the PROCESS trial showed no differences between early goal-directed therapy when compared to the control group's usual care.[29]

METHODOLOGY

Major electronic databases (EMBASE, Medline) were searched using the terms "cost-effectiveness", "goal-directed therapy", "haemodynamic management", "perioperative management", "septic patients". The authors also searched the clinical trials registry of the Cochrane Library (Oxford, UK) to ensure completeness of preliminary or follow-up observational studies that are not included in Medline. The authors performed extensive searches using cross-references from original articles and reviews. Studies observing the effect of GDT on economic outcome in septic and perioperative patients were included.