JOURNAL OF HEALTH CARE FINANCE

Winter 2023

# Economic Evaluation Impact on Patient Access to Medicines and Biotechnology Sector

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**Abstract**

Economic evaluation has been shaping the healthcare industry in recent years and gaining more attention by professionals in the healthcare industry. One of the areas which has been significantly impacted is the pharmaceutical and biotechnology sector. As a result, patients access to innovative and repurposed drugs has also been impacted to the same extent.
This article serves to raise awareness and knowledge about the importance of economic evaluation and health technology assessment involved in drug approval process. It uncovers the economic aspect overlooked by many professionals in the healthcare industry.
It is also intended for healthcare financial professionals and investment analysts to offer them an insight while drafting equity research and due diligence acquisition reports.

## Introduction

In the realm of scarce resources, the need for adopting value for money strategies to achieve efficiency has been overemphasized by academic, governmental and healthcare institutions worldwide. Although there is no single universal definition, framework or strategy for the principle of value for money, economic evaluation in healthcare has been spreading in many high-income countries including North America and Europe. When taken in broader context, economic evaluation is referred to as Health Technology Assessment (HTA)[1].

Economic evaluation is used by healthcare organizations as part of their decision-making process for the approval of purchasing new medical technologies such as drugs, therapeutic devices, diagnostic devices and medical procedures[2]. Several forms of economic evaluation are performed by healthcare decision makers and these includes cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-minimization analysis (CMA), cost-consequences analysis (CCA), cost-benefit analysis (CBA) and budget impact analysis (BIA)[3]. Among the aforementioned forms, the most commonly used are CEA and CUA[4].

Healthcare finance professionals and investment analysts while being aware of the regulatory and approval requirements of the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) which reflect the clinical perspective[5], only handful of them are aware of the second line of approval which reflects the economic perspective. Nowadays, the need for both clinical and economic approvals must be met before purchasing new technology. Clearly, a government decision to acquire a new technology such as a drug or device may not only affects its own budget but also significantly impacts the revenue and value of the company which owns and sell the technology. This is why it is crucially important for healthcare financial professionals and investment analysts to be aware and knowledgeable about this aspect in particular.

## Overview of economic evaluation

We aim to explain CEA and CUA in a succinct manner because it is the most widely used form of economic evaluation by healthcare organizations. In order to conduct a proper economic study, it must be done alongside clinical trials or through decision analytical modelling. The latter is a framework which consists of a model, health outcomes, costs and a cost-effectiveness threshold. Models that are used most commonly are decision trees, Markov models, partitioned survival models and to lesser degree microsimulation, discrete event simulation and dynamic models[6].

[1] https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/new-definition-of-health-technology-assessment-a-milestone-in-international-collaboration/8A3BA65D279F3FDAA83ADB3D08CF8C17

[2] https://emj.bmj.com/content/19/3/198

[3] https://www.frontiersin.org/articles/10.3389/fpubh.2021.722927/full

[4] https://onlinelibrary.wiley.com/doi/full/10.1111/jcpt.12043

[5] https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.1565

[6] https://www.bmj.com/content/342/bmj.d1766

Health outcomes can be expressed in a variety of ways such as life-saved, disease averted, case-detected, disability-adjusted life year or Quality-adjusted life-year (QALY). QALY is the most commonly used health outcome. CUA is a form of CEA, where QALY is used as a health outcome. QALY has two dimensions, one is quantity of life or longevity and the other one is quality of life. One QALY is equivalent to one year of life lived in perfect health. Normally, the costs include those incurred from the consumption of healthcare resources such as inpatient care, outpatient care, drugs, tests, procedures and so on, in addition to the cost of the new technology. Cost-effectiveness threshold is used as a benchmark around which the new technology is considered either cost-effective or not, and is expressed in terms of cost per one unit of health outcome produced. Moreover, the new technology in question must be compared in terms of associated costs and health outcomes to the existing standard care in the current healthcare setting. The model must capture life-long health outcomes or benefits as well as costs[7]. Once these data are available, an incremental cost-effectiveness ratio (ICER) can be estimated as the ratio of cost difference (incremental cost) to health outcome difference (incremental effectiveness or incremental QALY):

$ICER = \Delta C / \Delta E = (C2-C1) / (E2-E1)$
Or
$ICER = \Delta C / \Delta Q = (C2-C1) / (Q2-Q1)$

C2: Costs incurred from new technology
C1: Costs incurred from current standard care

E2: Effectiveness of new technology
E1: Effectiveness of current standard care

Q2: QALY gained from new technology
Q1: QALY gained from current standard care

Figure-1 and 2 shows the cost-effectiveness plane and six regions where ICER can fall in. In region 1, the result is not cost-effective because the new technology while being cheaper, the loss of health outcomes is large and far more than acceptable by the threshold level. In region 2, the result is not cost-effective, because the new technology is more expensive than the standard care and leads to more loss of health outcome. In region 3, the result is not cost-effective, because the new technology creates more health benefits but at a cost higher than accepted by the threshold level. In region 4, the result is cost-effective, because the new technology creates more health benefits at a cost accepted by the threshold level. In region 5, the result is cost-effective and cost saving, because the new technology creates more health benefits and the associated costs are less than the standard care. In region 6, the result is cost-effective, because the new technology cost much less than standard care, while the loss in health outcomes is small and within acceptable range by the threshold level[8]. The methods of CEA and CUA have their own flaws, limitations, inconsistencies and challenges, however we will not cover these issues here because it is out of the context of this article.

[7] https://www.eunethta.eu/wp-content/uploads/2018/03/Methods_for_health_economic_evaluations.pdf
[8] https://www.eunethta.eu/wp-content/uploads/2018/03/Methods_for_health_economic_evaluations.pdf

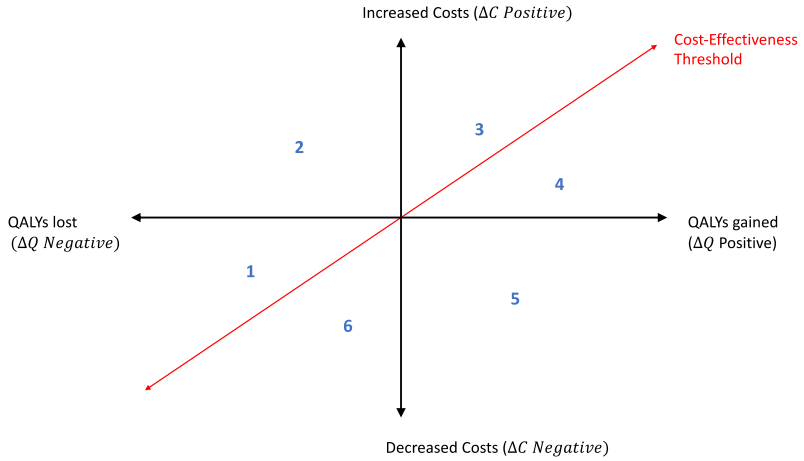


Fig-1: Cost-effectiveness plane of CUA

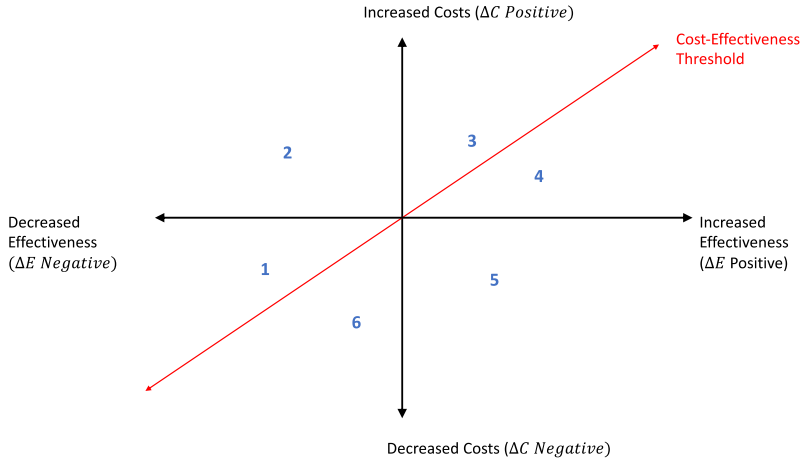


Fig-2: Cost-effectiveness plane of CEA

In many high-income countries, economic evaluation has been directly or indirectly guiding healthcare organizations, insurance agencies and even managed care organization in the acquisition of new technologies and patients access to them[9]. The European Network for Health Technology Assessment lists all the HTA bodies in Europe. To name few examples, National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK), The Institute for Quality and Efficiency in Health Care (IQWIG) in Germany, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) which is also one of the oldest HTA organization in the world[10].

[9] https://www.chcf.org/wp-content/uploads/2017/12/PDF-CostEffectivenessAnalysis.pdf
[10] https://www.eunethta.eu/about-eunethta/eunethtanetwork/

Other HTA bodies includes the Institute of Clinical and Economic Review in the United States (US), which is a nongovernmental HTA body attempting to provide solutions to problems related to fair access and fair pricing of drugs[11]. Canada's Drug and Health Technology (CADTH), advises the Canadian healthcare system on the cost-effectiveness of drugs, diagnostic tests, medical, dental, and surgical devices and procedures[12]. Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC) play as the main HTA bodies in Australia[13].

**Selected cases of impact on patients access to medicines and biotechnology sector**

For decades the British NICE has established a cost-effectiveness threshold from £ 20K to 30K per QALY. At such level many new or repurposed oncological drugs have been designated as not cost-effective, therefore rejected by the National Health Service of England and patients had no access to them. The resulting political and public pressure led the British government to introduce a separate funding entity, the Cancer Drugs Fund (CDF) in 2010 to funds and provides oncology drugs which were not cost-effective or have not yet been appraised by NICE[14]. In one of these cases, the British Institute of Cancer Research (ICR) expressed disappointment when NICE rejected "Lynparza" for treatment of BRCA-positive prostate cancer, which was previously approved for treatment of BRCA-positive ovarian cancer through the CDF[15]. In another case, "POLIVY" was given conditional authorization by the EMA for treatment of refractory diffuse large B-cell lymphoma because it showed a promising result from an early small study[16], yet NICE rejected it because of uncertainties of long-term benefits of the treatment[17].

[11] https://icer.org/
[12] https://www.cadth.ca/about-cadth
[13] https://www.health.gov.au/health-topics/health-technologies-and-digital-health/health-technology-assessments/for-subsidy#principal-hta-committees
[14] https://www.valueinhealthjournal.com/article/S1098-3015(16)30018-3/pdf
[15] https://www.icr.ac.uk/news-archive/icr-responds-to-nice-decision-not-to-recommend-olaparib-for-advanced-prostate-cancer
[16] https://www.ema.europa.eu/en/medicines/human/EPAR/polivy
[17] https://www.fiercepharma.com/pharma/roche-s-new-cancer-med-polivy-lacks-long-term-evidence-nice-says-rejection

In recent years, NICE developed a second cost-effectiveness threshold of 100k to 300k per QALY for highly specialized technologies such as gene therapies[18]. After the approval of an orphan drug "zolgensma" by FDA in 2019 for the treatment of less than 2-year-old infants with spinal muscular atrophy[19], and its approval by the EMA in 2020[20], NICE started to conduct an economic evaluation over a year and designated "zolgensma" as cost-effective in March 2021[21]. Earlier to that, the Institute of Clinical and Economic Review in the US announced that any price above $1.5 million would not be cost-effective[22] and soon after that Novartis announced a list price of $2.1 million for this one-time treatment orphan drug[23]. Another HTA report from Netherland showed that "zolgensma" was not cost-effective unless the price is lowered to $680,000[24].

In 2019, the EMA approved Bluebird bio's orphan drug "zynteglo" which is one-time treatment indicated for transfusion-dependent beta thalassaemia disease under conditional authorization[25]. NICE has rejected the drug because of uncertainties of clinical benefits and cost-effectiveness at the current list price which was set by Bluebird bio at $1.8 million[26]. This was followed by a dispute in Germany over pricing and reimbursement of the drug which led Bluebird bio to withdraw from the German market[27]. After a series of challenges with HTA bodies in Europe Bluebird bio eventually announced its complete withdrawal from the European market[28]. This meant the withdrawal of "Skysona" another approved gene therapy from Bluebird bio indicated for an inherited neurological disorder called cerebral adrenoleukodystrophy[29]. Eventually European patients were deprived access to these innovative drugs while Bluebird bio suffered a drawback on its revenue and share price[30].

[18] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-highly-specialised-technologies-guidance
[19] https://www.fda.gov/media/126109/download
[20] https://www.reuters.com/article/us-novartis-zolgensma-idUSKBN22V0JH
[21] https://www.genomicseducation.hee.nhs.uk/blog/nice-approves-new-sma-gene-therapy/
[22] https://www.fiercepharma.com/pharma/novartis-sma-gene-therapy-would-not-be-cost-effective-if-priced-over-1-5m-icer
[23] https://www.fiercepharma.com/pharma/novartis-slaps-2m-plus-pricetag-newly-approved-gene-therapy-zolgensma
[24] https://www.sciencedirect.com/science/article/pii/S109830152100053X
[25] https://www.ema.europa.eu/en/documents/overview/zynteglo-epar-medicine-overview_en.pdf
[26] https://www.nice.org.uk/guidance/GID-TA10334/documents/129
[27] https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-reports-first-quarter-financial-results-and
[28] https://www.fiercepharma.com/pharma/situation-untenable-bluebird-will-wind-down-its-operations-broken-europe
[29] https://www.biopharmadive.com/news/bluebird-withdraw-gene-therapy-europe-skysona/608666/
[30] https://www.genengnews.com/topics/genome-editing/gene-therapy/bluebird-bio-shares-plunge-as-cfo-resigns-company-raises-going-concern-doubts/

## Discussion and conclusion

The expectations of analysts in Wall Street were met with disappointments twice when the sales of "zolgensma" were 20% less than what they have projected earlier[31] and when the sales and revenue of "zynteglo" were less than they anticipated[32]. These imprecise projections result from overlooking HTA process and healthcare financing mechanisms in the global market.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) provides one of the most comprehensive guidelines for economic evaluation which is consistent with the observed fact that overwhelming economic evaluations are mainly targeting the pharmaceutical and biotechnology sectors rather than other parts of the healthcare system[33]. Furthermore, leading experts in HTA and economic evaluation in the UK have developed a pricing model for orphan drugs which accounts for several factors such as average returns from non-orphan drugs, the cost of research and development, the prevalence of orphan disease as well as the cost-effectiveness of the orphan drug[34]. This could potentially modify the valuation and acquisition model used by Novartis to acquire AveXis biotechnology company for $8.7 billion to claim "zolgensma"[35]. Other HTA experts in the UK are making an argument backed by research to lower current NICE's threshold down to £13k per QALY instead of the current £20k-30k per QALY in order to reduce the wasted opportunity costs associated with the current threshold, which could lead to further less approved drugs and could impact immunotherapies and antivirals therapies[36]. The same experts claimed that the CDF does more harm than benefit[37].

The accumulated experiences and interactions of pharmaceutical and biotechnology companies with HTA bodies in the US and International markets will definitely reshape future innovations. This course can take several possible scenarios such as a decline in expensive orphan or gene therapy innovations, a significant reduction in the prices of future gene therapies, a shifting of business strategies to focus on other profitable sectors such as pandemic vaccines and epidemic drugs, redesigning bench research and clinical trials to reduce costs, confining innovation within the US market and withdrawing from international markets, HTA bodies getting seats at venture capital firms, advances in precision medicine directing more personalized therapies and rejecting HTA agencies or the development of innovative financial and payment schemes and agreements.

Approvals by FDA and EMA reflects the efficacy and safety of the approved drugs or devices. However, HTA bodies have been casting doubts on the clinical effectiveness and utility of these approved technologies. Will HTA agencies be replacing the current FDA, EMA and other clinical regulatory bodies in the future? Are they going to merge? Only time will tell.

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[31] https://www.fiercepharma.com/pharma/novartis-ceo-pins-zolgensma-decline-market-expansion-slowdown-unrelated-death-reports

[32] https://www.reuters.com/article/us-bluebird-bio-gene-therapy-price-idUSKCN1TF1HP

[33] https://www.ispor.org/heor-resources/good-practices/economic-evaluation

[34] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7472708/

[35] https://www.reuters.com/article/us-novartis-avexis-idUSKBN1HG0FT

[36] https://www.journalslibrary.nihr.ac.uk/hta/hta19140/#/abstract

[37] https://www.york.ac.uk/che/news/2015/cancer-drugs-fund/