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Cost-effectiveness analysis: should it be required for drug registration and beyond?

Renée J. Goldberg Arnold

Arnold Consultancy & Technology LLC, 1 Penn Plaza – 36th floor, New York, NY 10119, United States

Cost-effectiveness analysis (CEA) is applied in situations where trade-offs exist, typically, greater benefit for an increased cost over an alternative therapy or strategic option versus usual care. CEA is useful where a new strategy is more costly but expected to be more effective or where a new strategy is less costly but less effective. A good example for the relevance of CEA is the unanimous recommendation of a US federal vaccine advisory panel to vaccinate 11-year-old girls against cervical cancer. This recommendation was at least partly because of data showing the relative cost-effectiveness of HPV vaccine. In this era of finite budgets, CEA may facilitate drug development, drug approval, patient segmentation and pricing model development throughout the drug lifecycle continuum.

A recent US government study indicated that speedier drug approval by the US Food and Drug Administration has saved more than 300,000 'life-years' [1]. Although faster drug approvals, in and of themselves, may save lives, is it worthwhile or is it 'efficient' to approve these drugs at all? Can the health system support the additional cost for each life saved if the new drug is both more costly and more effective than previous therapies? Conversely, if the new drug is less costly and less effective, as compared with existing therapies, how much of a diminution in efficacy can society/payers/patients withstand in order to save money? Further, how much money must be saved in order to make it 'cost-effective' to accept a reduction in efficacy over existing strategies? Currently, in most countries, safety and efficacy are the only criteria required for drug approval. Cost is considered primarily in terms of rationing, such as the Australian Pharmaceutical Benefits Advisory Committee's or PBAC's role in listing a drug for coverage (e.g. who should be allowed to receive these new drugs?) and reimbursement (such as in Canada, where the price of the new drug is set by the government based primarily on cost-effectiveness analyses (CEAs). CEAs are used to assess the benefit of drugs and other therapeutic strategies. CEA is applied in situations where trade-offs exist, typically, greater benefit for an increased cost over an existing therapy or strategic option versus usual care. An effective CEA answers certain questions, such as: is the treatment effective? What will it cost? and how do the gains compare with the costs? By combining answers to all of these questions, CEA helps decision makers to weigh the factors, compare alternative treatments and decide which treatments are most appropriate for specific situations.

Corresponding author: Arnold, R.J.G. (rarnold@arnoldllc.com) .

CEA

CEA is a systematic and quantitative method for summarizing health benefits and health resources of various treatment options into single numbers or ratios so that policy makers can choose among them. CEA compares the costs and consequences of treatment alternatives or programs where cost is measured in monetary terms and consequences are measured in natural units (e.g. mmHg) [2]. Typically, the preferable result is considered to be the option with the least cost per unit of measure gained; the results of the CEA are represented by the ratio of cost, a summation of *costs* of all resources surrounding a therapeutic option to *effectiveness*, the health benefit. With this type of analysis, various disease end points that are affected by therapy (risk markers, disease severity, death) can be assessed by corresponding indices of therapeutic outcome [mmHg blood pressure reduction, hospitalizations averted, life-years saved or quality-adjusted life-years (QALYs), respectively]. There are two ways of performing or representing CEAs – average cost-effectiveness and incremental cost-effectiveness. 'Average' cost-effectiveness is the result of dividing mean total costs by outcomes and is typically represented as a per

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patient value. It is calculated, as follows, for each therapeutic option:

$$\frac{X\,Cost}{X\,E\,f\;fectiveness}$$

The average cost-effectiveness of each therapy is then compared and the one with the lowest cost per unit of effectiveness is preferred. Although this type of analysis allows one to view the actual numbers involved in the calculation, *average* cost-effectiveness does not illustrate differences between alternative strategies [3,4]. Thus, many researchers prefer to use or further explain the results of a CEA in terms of an 'incremental' cost-effectiveness ratio, that is, additional cost for additional benefit, which may be calculated as follows:

$$\frac{\Delta C}{\Delta E} = \frac{\text{Cost}_1 - \text{Cost}_2}{\text{Effectiveness}_1 - \text{Effectiveness}_2}$$

where $\text{Effectiveness}_1 > \text{Effectiveness}_2$.

The term 'incremental' is commonly used interchangeably with the term 'marginal' to denote the additional cost and outcome of one intervention in comparison with another [3]. As an example, consider the model of the cost-effectiveness of a vaccine for human papillomavirus (HPV) [5]. Over a lifetime (see Table 1), providing HPV vaccination for a patient costs, on an average, USD310 (i.e. $\text{Cost}_1 - \text{Cost}_2$), more than screening for HPV infection and results in an average gain of 0.0092 QALYs, i.e., $\text{Effectiveness}_1 - \text{Effectiveness}_2$, a marginal cost-effectiveness ratio of USD310/0.0092 or USD33,700/QALY. A marginal or incremental CEA is useful in the following two instances: firstly, where the new strategy is more costly, but expected to be more effective or secondly where the new strategy is less costly, but less effective [6,7].

Factors affecting timing of CEA

CEA may be undertaken once, but at different times, or multiple times during the drug discovery and development process, depending upon numerous factors. These factors include funding sources, perceived value of drug success, degree of cooperation between clinical and marketing groups, ability of the company outcomes research team to convey the value of CEA to the company marketing team, perceived importance of outcomes research within the developer's organization, regulatory requirements, clinical trial advancement [8] and others. Each of these factors will be elaborated furthering the following. Funding sources for drug/device development may dictate where and if a CEA is performed in the drug's life cycle. For example, if venture capitalists are funding the development of a novel compound by a biotechnology company, the venture capitalists may be more focused on showing efficacy for drug registration, even though the clinical and marketing departments are in favor of early use of CEA for pricing and reimbursement purposes, particularly if the compound is expected to be expensive. In addition, the perceived need for CEA to assure the drug's entry or sustained profitability in the marketplace, the presence of a dedicated health outcomes group and the perception by upper management of the role of such an organization may dictate where CEA fits in.

Regulatory requirements can also affect if and when CEAs are undertaken. Apparently, no country requires CEA for drug registration, though the US, Belgium, Australia, Israel, England, France, The Netherlands, Finland, Canada and Germany have implemented guidelines for economic technology assessment [9–11]. Australia is one of the few countries that require CEA for a drug's inclusion on the National Formulary [11]. However, many countries strongly recommend that these analyses can be undertaken to help in determining formulary inclusion and pricing. In Canada, CEAs are used to 'inform programatic decision-making in regard to the appropriateness of health care interventions' [10]. Moreover, Canada and the US require portability of results, meaning that the results must be generalizable to countries and situations other than those specifically reported in the CEA, while England requires a National Health Service perspective. In the UK, the National Institute for Health and Clinical Excellence (NICE) initiates and conducts its own evaluations and the NHS is required to fund drugs recommended by NICE [11]. Lastly, Belgium, Canada, England and the US require that any CEA that is submitted to a health authority, whether in support of a new indication or reimbursement, be conducted to allow for capture of long-term cost and effect outcomes. That is, simple presentation of short-term CEA results are unacceptable and results of long-term evaluations must be presented or short-term studies must be extrapolated using transparent computational models (further explained below).

It depends on the stage during the development of a drug whether a CEA will be performed. For example, it is often cost-effective to perform CEA alongside pivotal clinical trials to have this information available upon drug launch [8]. Recent examples of CEA in the published literature show it being used for place in therapy/market advancement/characterization [12–15], market

TABLE 1

Health and economic outcomes of HPV vaccination [5]

Outcome	Cost (USD) per patient	Incremental cost (USD) per patient	Life expectancy (QALY[a])	Incremental life expectancy (QALY[a])	Cost-effectiveness (Cost/QALY)
No vaccination (current screening program)	1111		25.9815		
HPV vaccination at 70% efficacy	1421	310[b] (1421–1111)	25.9907	.0092[c] (25.9907–25.9815)	33,700 (rounded) 310/.0092

[a] QALY = quality-adjusted life-year.

[b] Total Cost was derived by aggregating the costs of cervical cancer screening (i.e., cytology, HPV DNA test, office visit, patient time), diagnosis and treatment and vaccination (vaccination series and patient time); incremental cost is the difference between 'No Vaccination' and 'HPV Vaccination at 70% Efficacy' to determine the life expectancy of a hypothetical cohort.

[c] Total Effectiveness was derived by aggregating the probabilities of the incidence and clearance of HPV infection, natural history of CIN, natural history of invasive cervical cancer (probability of progression, developing symptoms, survival at five years to determine the life expectancy of a hypothetical cohort; the results were calibrated to the lifetime risk of cervical cancer reported in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program [56].

segmentation [14,16–20], post-marketing surveillance [21–25], guideline development [5,26–30], break-even analyses [31], and policy decisions [32–37] among others. In no way are these uses of CEA exclusive or all-inclusive. Indeed, CEAs should not be static analyses that are performed once only and are never re-examined. Instead, CEA should be redone and adjusted as soon as more real-world experience and data are available.

Cervical cancer and HPV vaccine

A relevant example of the use of and need for CEA before their requirement for country-wide registration would be the various CEAs that have been performed in the evaluation of HPV vaccine as a prevention against the development of cervical cancer [5,29,30]. Owing to ethical and cost concerns, a prospective trial comparing different strategies for prevention of cervical cancer in women will never be performed. That is, long-term models, rather than prospective, randomized, double-blind, controlled trials, where one group receives the active vaccine and the other does not (or receives a placebo), during the patient's lifetime, would be too costly and may not be considered ethical. However, computer simulation/modeling of the natural course of the disease as well as the comparative cost-effectiveness of different strategies, is feasible and, indeed, was undertaken [5,29,30].

As mentioned previously, for a CEA to be useful, trade-offs and treatment alternatives need to be available; cervical cancer and HPV certainly present multiple opportunities for decision-making dilemmas. It is first necessary to understand some facts about cervical cancer and coverage of HPV strains by the vaccine that is currently available in the US for these dilemmas to become apparent. Persistent infection with cancer-associated HPV (termed oncogenic or high-risk HPV) causes the majority of squamous cell cervical cancer, the most common type of cervical cancer, and its histologic precursor lesions, the low-grade cervical dysplasia Cervical Intraepithelial Neoplasia-1 (CIN1) and the moderate-to-high-grade dysplasia CIN 2/3. Multiple HPV strains cause varying degrees of invasive cervical cancer (ICC) and its CIN precursors. HPV strains 16 and 18 cause approximately 70% of all cervical cancers [29,38] and CIN3, specifically, and 50% of CIN2 cases. In addition, HPV 16 and 18 cause approximately 35–50% of all CIN1. Low-oncogenic HPV risk types 6 and 11 account for 90% of genital wart cases [39]. Unfortunately, cytological and histological examinations cannot reliably distinguish between those patients who will progress from cervical dysplasia to ICC from those whose dysplasias will regress spontaneously, the latter being the vast majority of cases [40]. This inability to definitely ascertain the natural history of HPV infection is one of the primary reasons for the dilemma with HPV vaccination.

To argue for vaccination is the fact that although cervical cancer screening programs have substantially reduced the incidence and mortality of ICC in developed countries over the past 50 years [39,41], there has been a slowing of these declines in recent years because of poor sensitivity of cervical cytology, anxiety and morbidity of screening investigations, poor access to and attendance of screening programs, falling screening coverage and poor predictive value for adenocarcinoma, an increasingly common cause of ICC [41]. Other factors to be considered on the 'pro' side of the vaccination dilemma include the facts that HPV is the most common sexually transmitted disease in the US, that virtually 100% of cervical cancer is because of HPV, that treatment of cervical cancer is very expensive (USD1.7 billion/year using US Medicare dollars), and that HPV is also linked to head and neck cancer in men. On the 'con' side is the presence of >100 HPV strains (thereby potentially reducing vaccine efficacy for oncogenic strains not covered by the vaccine) and the facts that HPV infection is often self-limited, routine screening is still necessary, and the vaccine is expensive (in the US, it is priced at USD120/dose and given as three doses over six months). A mitigating factor for the argument against using the vaccine is the fact that the cost-effectiveness of screening with Pap smears is reduced (improves) from USD1 million/QALY if patients continue to be screened annually, as is the common current recommendation, to USD150,000/QALY if patients are screened every three years, the latter a likely scenario if the vaccine is used [5,29,30,42].

Worldwide, the incidence of cervical cancer is 470,000 new cases and 233,000 deaths per year; it is the second leading cause of cancer deaths [43], with 80% of these cases observed in developing countries [44]. Women in developing countries are especially vulnerable as they lack access to both cervical cancer screening and treatment. The demographics of cervical cancer in the US show that 9710 new cases of ICC were expected to be diagnosed in 2006 and about 3700 deaths in women were expected from ICC. Quadrivalent Human Papillomavirus (HPV) Vaccine recombinant (Gardasil®), the vaccine recently approved for use in the US and Europe, covers the two major oncogenic HPV strains (16 and 18) for cervical cancer. In addition, it covers HPV strains 6 and 11, the primary causes of genital warts. Therefore, the vaccine does not offer full protection against cervical cancer, since it does not protect against HPV strains 31 and 45, which are also implicated in ICC and cervical dysplasia. In order to significantly reduce the rate of cervical cancer in the population as a whole, 70% of girls need to be vaccinated to achieve what is called 'herd immunity' – when the vaccine's impact goes beyond just the people who are inoculated. So far, it is unknown if HPV strains will mutate as the vaccine is introduced, though this is not very likely, considering that HPV is a DNA-based virus [40].

HPV vaccine model CEAs

In addition to the model already previously used as an example of an incremental cost-effectiveness ratio [5] two other cohort or Markov analyses of the potential cost-effectiveness of HPV vaccines [29,30] have been published. These models are relatively similar in structure to each other [45] and simulate the progression and regression of cervical cancer and dysplasia in a theoretical cohort of women at risk for cervical cancer. Figure 1 depicts a health state transition or influence diagram, which is a simple schematic of the CEA model that simulates the natural history of HPV infection and cervical carcinogenesis. It is a depiction of the various stages of health (health states) of cervical dysplasia (CIN1 or CIN2/3), cervical cancer, and regression that are modeled in the CEAs. It demonstrates how women may be in any number of 'health states', including various stages of cervical intraepithelial neoplasia (CIN1 or CIN2/3) and may then progress to cervical cancer, regress or stay the same. At any point, they may die of cervical cancer or of unrelated causes. The probabilities of these events occurring follow the natural history of the disease and are

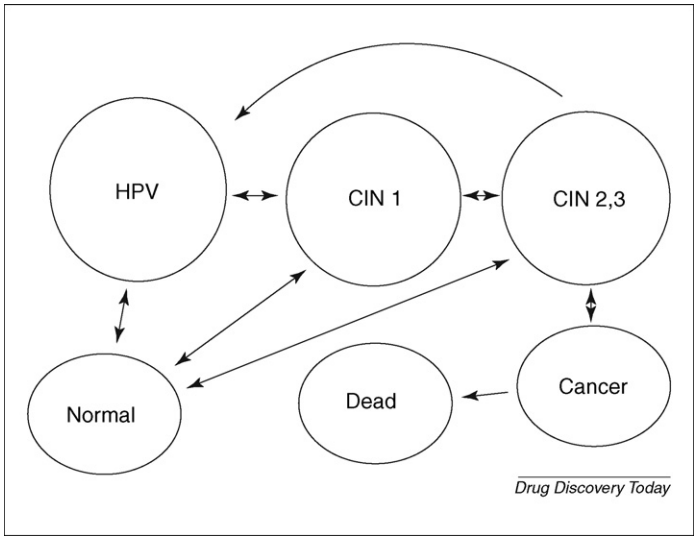

FIGURE 1

Health State Transition Diagram of HPV. The health state transition or influence diagram is a simple schematic of the CEA model that simulates the natural history of HPV infection and cervical carcinogenesis. It is a depiction of the various stages of health ('health states') of cervical dysplasia (CIN1 or CIN2/3), cervical cancer, and regression that are modeled for the CEA. CIN = cervical intraepithelial neoplasia.

taken from the published literature. Cost data are extracted from national databases such as MEDSTAT MarketScan databases, a paid US database (http://www.medstat.com), National Ambulatory Medical Care Survey or NAMCS (a US government survey source, http://www.cdc.gov/nchs), Medicare claims data, etc.

If one takes into consideration the nature of the transmission probability of HPV, in which there is an ever-changing population, transmission probabilities of HPV infection per partnership, and prevalence of HPV infection in the population over time, an alternate to the cohort model, known as a dynamic model, may more accurately reflect the natural history of HPV (Fig. 2). In a cohort model, the rate (*P*) at which susceptible individuals become infected over a small period of time (e.g. 1 day) is fixed and the model does not account for the reduction in the prevalence of HPV infection in the population over time after HPV vaccination is introduced. To account for this, the dynamic model takes into

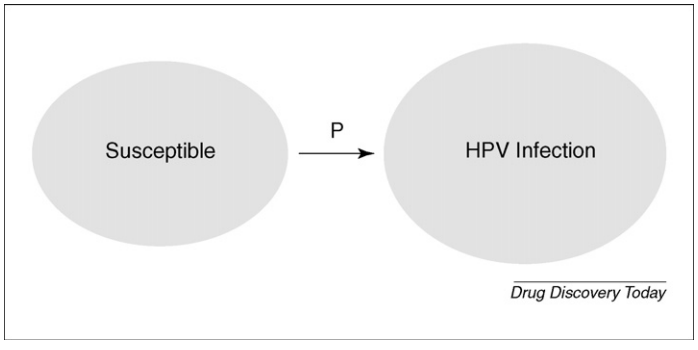

FIGURE 2

Dynamic Model. Unlike a cohort model, a dynamic model accounts for the changing prevalence of HPV infection in the population by taking into consideration the rate (*P*) at which susceptible individuals become infected over time.

TABLE 2

Comparison of HPV vaccine CEA

Study	Model type	ICER per QALY[a] gained
Sanders and Taira [30]	Cohort	22,755–52,398
Kulasingam and Myers [29]	Cohort	44,889–236,250 (LYG)[b]
Taira *et al.* [42]	Hybrid	14,500–442,039
Goldie [5]	Cohort	12,300–4,863,000

[a] Incremental Cost-effectiveness Ratio (ICER) per quality-adjusted life-years (QALY).
[b] Life-year gained (LYG).

consideration: time, age, the number of sexually active persons in the population who are infected and not infected, the way they form sexual partnerships, and the transmission probability of HPV infection per partnership. Also, with dynamic models, individuals can enter the model at any point and exit at death. There is no natural stopping point as long as people are being born. Reducing the prevalence of HPV infection over time means that susceptible individuals are less likely to become infected because there are fewer persons in the population to infect them with HPV. As mentioned previously, this indirect benefit of vaccination is referred to as herd immunity.

The fourth cost-effectiveness analysis [42] uses a dynamic model in conjunction with a cohort model to create a hybrid model [45]. Thus, the hybrid model incorporates the transmission dynamics of HPV infection over time. The analysis using the hybrid model showed a reduced incremental cost-effectiveness ratio by approximately USD8000/QALY (see Table 2). Yet a fifth, preliminary, Merck model suggests that catch-up vaccination of 12–24-year-old females is more cost-effective than vaccinating 12-year-old females only and that the addition of catch-up vaccination is cost-saving [46]. At its conclusion, the model calculates life expectancy and cost/cost-effectiveness by following each pathway and including various screening scenarios (primarily screening interval), assumptions about age at onset of vaccination, proportion of the population vaccinated, duration of vaccine efficacy, whether or not HPV types interact, duration of model follow-up, and transmission of infection. Although the robustness of the data influence the validity of the results, the effects of all of these assumptions can be modeled in sensitivity analyses, where the stability of a conclusion is evaluated over a wide range of parameter estimates and structural assumptions, to determine their impact on the cost-effectiveness of vaccination.

There are pros and cons to Markov (cohort) models versus dynamic models. Although Markov models reflect the natural history of HPV infection, they do not include transmission and herd immunity, which may understate the benefits of vaccination. By contrast, dynamic models or models with a dynamic component model transmission of HPV and are potentially more realistic but may introduce additional uncertainty [46].

Although all three models have shown the vaccine to be cost-effective if one uses a threshold of USD75,000/QALY, their results vary quantitatively (see Table 2). Therefore, it is valuable to use the model results as a relative, rather than absolute, benchmark for the comparative CEA of these various scenarios. Moreover, as mentioned previously, the type of model, implicit assumptions, data sources and degree of parameter uncertainty may have a large

effect on the model results [47]. However, the current HPV vaccine models are reasonably robust to variations in these data points. All of the models predicted that HPV vaccination would result in a reduction in HPV infection and/or a reduction in cervical pre-cancers and cancer. The magnitudes of these reductions were most influenced by the duration of protection conferred by the vaccine, the effectiveness of vaccination, the effectiveness of screening, whether or not HPV types interacted, and the duration of follow-up examined by the model.

Impact of HPV vaccine CEA models

Interestingly, these models were published in 2003–2004, more than two years before the approval of Gardasil® in the US. Lest funders, clinicians and marketing personnel should think that production of CEA is an esoteric undertaking, it was at least partially because of the availability of these data showing the relative cost-effectiveness of HPV vaccine that a US federal vaccine advisory panel [48], the Advisory Committee on Immunization Practices (ACIP), which advises the US Centers for Disease Control and Prevention (CDC) on vaccination matters, unanimously recommended that 11- and 12-year-old girls receive a new vaccine designed to protect against cervical cancer (Gardasil®, Merck) and that Gardasil should be added to the routine vaccination schedule for children and adolescents. It is assumed that such a unanimous vote will make it highly likely that the vaccine will be covered by private insurers and that it will probably be added to a US federal program that offers price-reduced or free vaccines to children (Vaccines for Children program).

The ACIP also recommended that doctors could vaccinate girls as young as nine and that girls and women of between ages 13 and 26 years also receive the vaccine, even if they are already sexually active, the so-called 'catch-up' period. Since then, the vaccine has achieved varying degrees of acceptance and marketing success. The controversial nature and potentially great cost of vaccinating 11-year-old girls have at least partially overshadowed the relative cost-effectiveness of this vaccine as shown by CEA. ACIP has conducted many CEAs of other vaccines that are cost-effective, such as pneumococcal conjugate [49] (USD80,000 per life-year saved at $58 per dose) and meningococcal conjugate [50] (USD121,000 per life-year saved). Although many new agents are more costly as they are incrementally more effective, ACIP has also completed multiple CEAs showing immunizations that are cost-*saving* including diphtheria, tetanus and pertussis (DTaP) [51], hepatitis B [52] and varicella [53]. CEAs are routinely carried out by ACIP and presented to the CDC before CDC's decision about implementation of federal vaccination programs.

CEA as basis for decision-making

Should cost-effectiveness be used as the sole or definitive data on which to base drug pricing, reimbursement coverage, policy decisions, market segmentation (i.e. who should or should not be vaccinated, covered, etc.), and guideline development? Most probably not, because of the quantitative uncertainty previously mentioned. Nonetheless, decision makers need these types of data to make informed, if not deterministic, decisions [54,55]. That is, as stated by Glassman and colleagues, 'decision rules [based on medical necessity or cost-effectiveness] are useful when they make assumptions explicit and specify trade-offs so that clinicians, patients and payers can make better decisions' [55].

Conclusion

This brings us full-circle to the question of whether CEA should be required for drug registration and beyond. The pharmaceutical industry is often at odds about how best to use CEAs as evidence for drug pricing, government reimbursement, formulary inclusion and compound novelty. Using examples from immunization CEAs, it can be seen that these analyses can greatly influence and inform governments and other policy makers on appropriate usage of therapeutic options for the common good. Indeed, it is ACIP's charter that 'Committee deliberations… should include consideration of population-based studies such as efficacy, cost-benefit, and risk-benefit analysis.'

Unfortunately, CEA is not yet required in any country for registration, though it is an integral part of many applications for formulary listing and reimbursement. As has been demonstrated throughout this review, in this era of finite budgets, consequent healthcare rationing, shortages of medications, global aging and burgeoning of populations, CEA, correctly applied, may facilitate drug development, drug approval, rationing, patient segmentation, disease management and pricing model development throughout the lifecycle continuum, starting with development alongside Phase II/III clinical trials through long-term post-marketing surveillance. Conversely, incorrect application of such analyses may result in far-reaching and devastating consequences to global populations, the pharmaceutical industry, health authorities and individual patients.

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