

When Is a Cost-Effectiveness Claim Valid? How Much Should the FDA Care?

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Abstract

Federal law requires the Food and Drug Administration (FDA) to regulate the promotional claims of prescription drugs and certain devices. Standards of evidence for claims of safety and therapeutic efficacy are rigorous because inappropriate product use may place human life at risk. However, equally demanding criteria for claims of cost effectiveness of marketed technologies seem to be unnecessary because the consequence of error is principally a bad buy rather than patient harm. Concern exists about the validity of cost-effectiveness studies, the potential for bias, standards for the conduct of cost-effectiveness research, and the needs of managed care. The FDA should moderate its role in regulating cost-effectiveness claims of drugs and devices. This would foster information flow to healthcare providers and insurers and protect the FDA concern regarding false or misleading claims of effectiveness. Although the issues are applicable to both devices and drugs, we draw mainly from the field of pharmacoeconomics because this is where most of the policy has developed.

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Federal law requires the Food and Drug Administration (FDA) to regulate the promotional claims of prescription drugs and certain devices.¹ In 1995, the FDA Division of Drug Marketing, Advertising and Communications circulated the draft document "Principles for the Review of Pharmacoeconomic Promotions."² Since then, the FDA has held a conference³ and a hearing⁴ about the issue. The principles rely on traditional FDA measures of evidence of effectiveness ("adequate and

well-controlled studies including placebo, active, and historical controlled studies"), full disclosure of methods and costs, and the requirement that claims not extend beyond clinical labeling. After two years, the FDA is still debating internally exactly what would be appropriate guidelines to accomplish the following aims: (1) to have guidelines apply to both drugs and devices, (2) to be helpful to managed care (possibly by permitting direct exchange of information, including the use of models, between manufacturers and managed care organizations), and (3) to continue to enforce strict standards for conventional promotion.⁵

In spite of millions of dollars of cost-effectiveness research spent annually by industry, there are almost no formal claims of cost effectiveness of medical products in the United States. We attribute this lack of cost-effectiveness claims to the unrealistically high hurdles posed by the FDA regulatory standards. We argue herein that the FDA can and should relax its stringent regulatory requirements of cost-effectiveness claims for drugs and devices without unduly jeopardizing public safety and that managed care would welcome such a change.

Validity Concerns

In past years, the cost effectiveness of medical technologies has not been central to healthcare decision making, so the validity of cost-effectiveness claims has not been challenged. However, around the world, those responsible for pricing, reimbursement, and formulary decisions are increasingly using cost-effectiveness analysis (CEA) either formally or informally.⁶ The US marketplace has changed rapidly. The price sensitivity and increasing market power of managed care have prompted manufacturers to sponsor cost-effectiveness analyses at an increasing rate⁷ for the purpose of promotion, causing the FDA to question the validity of such claims. One journal editorial expressed concern that journals may be unwitting vehicles of biased promotional

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reports.⁸ Partly because of criticisms that the CEA methods used were neither valid nor necessarily fair, Oregon ran into a political firestorm when it tried to ration care on the basis of CEA criteria.^{9,10}

Questions about validity of cost-effectiveness claims stem in large part from the need to extend analyses beyond empirical data. Table 1 summarizes the differences between safety and efficacy research and cost-effectiveness research. Clinical trials typically are derived from narrowly constructed protocols that seek to maximize internal validity. The end points are often intermediate outcome measures (eg, blood pressure). Estimation of the overall health and economic impact in CEA often requires additional data and modeling, sometimes including estimates of the effect of community practice settings and long-term health and economic consequences. These models and estimates introduce additional uncertainty and subjectively derived assumptions. This calls into question the validity of findings. However, the validity of rigorous clinical trials also may be questioned because the clinical and economic outcomes generated in such studies are not neces-

sarily reproducible in routine clinical practice. The effect of uncertainty, often present in CEA, is tested through sensitivity analysis, which is different from and may be less rigorous than traditional statistical methods.^{11,12}

Systematic Bias

There is concern about the unstandardized nature of CEA because of the wide variety of methodologic choices: What perspective should be taken? What are appropriate comparisons? What costs should be included? How should costs be valued? Does patient time count? If so, how is it valued? What measures of health outcomes or effectiveness should be used? How should outcomes be valued? Which discount rate should be used? Which sensitivity analyses are needed? Should data be taken from prospective clinical trials (containing "piggy backed" economic analyses), specially designed naturalistic cost-effectiveness clinical trials, retrospective claims analyses, or decision models?

The wide discretion available to the analyst, the complexity of many models, and the difficulty in

Table 1. Safety and Efficacy Research Versus Cost-Effectiveness Analysis

	Clinical Research	Cost-Effectiveness Analysis
Purpose	Evaluate safety and efficacy end points for market approval	Determine value for money spent as a basis for assisting decisions about healthcare resource allocation
Question Addressed	What are the health consequences of the use of the product when it is used as approved?	What are the health and economic benefits foregone by the decision to use the product in actual clinical practice?
Setting	Ideal controlled conditions	Estimated average community care conditions*
Design	Experimental design; analysis with classic statistical techniques and a testing of null hypothesis (probability that a difference exists)	Use of data from multiple sources; requires sensitivity analysis to test ranges of values and assumptions†
Outcomes	Intermediate outcomes (eg, change in blood pressure)	Estimates of final health and economic outcomes, such as change in net total cost per quality-adjusted life year saved‡
Validity	Designed to maximize internal validity	Designed to maximize external validity
Uncertainty	Managed with traditional tests of statistical significance such as confidence intervals	Managed with sensitivity analysis, elaboration of best- and worst-case scenarios, and a search for decision thresholds

*When traditional clinical trials are used to collect resource utilization data (to estimate costs), additional assumptions and modeling are often required to eliminate protocol-induced costs and to simulate community practice patterns

†Models and sensitivity analysis are necessary to analyze uncertainty

‡Models often are required to estimate final outcomes. Outcomes may include preference-based measures and opportunity costs.

verifying models may allow exercise of systematic bias by sponsors or analysts, especially if there is potential conflict of interest (eg, when CEA is used to promote a product).¹³ To compound matters, many readers, even reviewers, do not understand the methods used and can easily misinterpret (or be misled by) findings. Finally, the poor quality of some CEA literature¹⁴ tarnishes good work.

Minimizing Bias and Increasing Validity

Although bias is possible and may even be intentional, appropriate safeguards can minimize bias and improve validity of CEA as a useful means of estimating the value of healthcare products. First, good methodologic principles and guidelines are available and should be followed.¹⁵⁻²⁰ Most guidelines recommend full disclosure, justification of methods and assumptions, and full discussion of the validity of findings and the degree to which they can be generalized. Although CEA is commonly characterized as unstandardized,²¹ which has led to multiple efforts around the world to develop methodologic guidelines, all of these efforts are roughly in agreement with one another. Most guidelines are generally in accord with similar efforts by methodologists dating back to the mid 1970s.²²⁻²⁴ Much of the unstandardized nature of CEA is the result of both poor application of accepted principles or guidelines and the use of unstandardized data (clinical trials, claims files, medical records, expert opinion) required by different applications. In general, CEA experts tend to agree on basic principles of analysis and on the appropriateness of a methodologic approach and its application even though the method chosen may not be the only valid approach.²⁵

Second, good peer review is essential. Peer reviewers must be expert in the methods used and the clinical condition under study. Because CEA tends to require multidisciplinary teams, peer review must mirror those disciplines, requiring several reviewers. These reviewers often need extensive technical appendices, especially if sophisticated models are used (currently these are rarely made available to reviewers). More intensive reviews may necessitate special funding to induce busy researchers to undertake them. Good peer review helps ensure that the study is unbiased and the findings valid. Good peer review will not inappropriately devalue the findings of analytical approaches such as modeling. Cost-effectiveness manuscripts are commonly assigned to well-intentioned reviewers who lack the necessary knowledge and expertise to conduct a valid review. Consequently, some manu-

scripts are accepted when they should be rejected, and some are dismissed as invalid when they should be accepted.

Third, researchers and sponsors should adhere to the recommendations of the Task Force on Principles for Economic Analysis of Health Care Technology.²⁶ Rather than methodologic guidelines, these principles are essentially rules of conduct designed to minimize the potential for bias. The Task Force makes many recommendations including the need to maintain investigator independence, especially freedom to publish findings regardless of the outcome. However, adhering to any guidelines does not guarantee validity or freedom from bias.²⁷

Fourth, claims of cost effectiveness have to be limited in time, circumstance, and scope. At any given time, the cost effectiveness of a product relates to a specific comparator, to a specific pricing schedule, and within a particular setting. Once any of these factors change, cost effectiveness is likely to change. The implications of this time constraint seem to be that claims might have to be either time-limited or recertified in some way, perhaps annually or biannually. Entirely new studies cannot be automatically imposed, but updating analyses by use of new prices or including known change in practice patterns should be possible and may be an important requirement.

Thresholds for Acceptance of Uncertainty

Given the uncertainty surrounding CEA, at what point are we confident in passing on a claim of cost effectiveness? Society's tolerance of uncertainty depends on the consequences of error (Fig. 1). There is a very low tolerance of uncertainty for safety issues, but as we move from safety to efficacy to effectiveness to cost effectiveness, the purpose changes, as does the nature of the decision, and so society's threshold for uncertainty relaxes. Decisions about price, formulary inclusion, or purchase are less important to society, we believe, than FDA approval to market a drug or device. A final reason for less concern is that CEA should be a *decision-assisting*, not a decision-making, tool for resource allocation.²⁰

How Much Does Managed Care Need Protecting?

To what extent do managed care and other healthcare decision makers need protection from false and misleading cost-effectiveness claims? To date, except for a few isolated examples such as the pneumococcal vaccine described later, there is little evidence that CEA has had substantial influence on

resource allocation decisions. Decision makers who are the main consumers of cost-effectiveness information include technology assessment and formulary committees, many within highly organized and sophisticated businesses (eg, managed care organizations and pharmacy benefit managers).^{28,29} These decision makers would not seem to be easily fooled by false or misleading claims, nor would the organizations for whom they work seem to need much protection by the FDA. And apparently they do not want it. A recent national survey of randomly selected managed care pharmacy directors found that 69% favored either no regulation or a simple rating system whereby claims and their scientific support are submitted to a peer-review panel.³⁰ Such claims would be rated as to the extent to which they were based on scientifically valid methods.

Effect of Cost-Effectiveness Studies on Policy

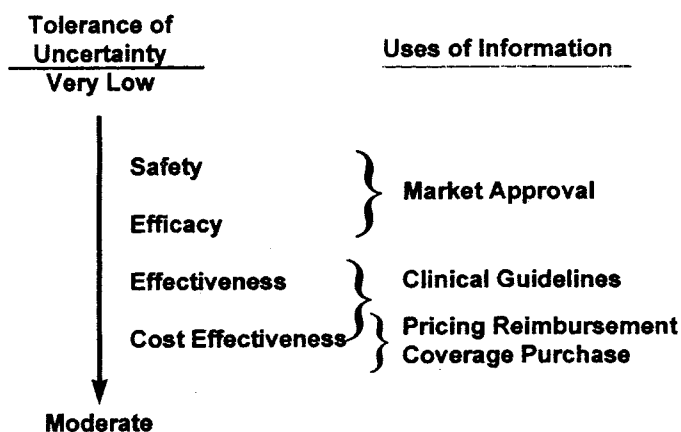
The pneumococcal vaccine provides a good case study to illustrate the risks and benefits of using CEA for assisting policy decision making.^{31,32} It is one of the few examples in which CEA appeared to make a direct impact on coverage policy. In the late 1970s, Congress requested its Office of Technology Assessment to study whether Medicare should provide the pneumococcal vaccine as a benefit. Because

the vaccine had just been approved by the FDA, there was little experience on which to base a coverage decision. The Office of Technology Assessment used an epidemiologic model to estimate cost effectiveness in which clinical trial data were used to estimate safety and efficacy. Claims databases and other sources were used to estimate costs for the pneumococcal vaccine, alternative vaccines, clinic or physician office visits. Expert opinion was used to estimate factors for which there was controversy or no data. The model results suggested that the vaccine was very cost effective for the elderly (\$1000 per year of life saved), but cost ineffective for the very young. There was extreme uncertainty in many key variables: estimates of efficacy varied 40% to 100%; duration of immunity ranged from 3 to 72 years; and vaccine costs ranged from \$3.50 to \$11.00 per dose. Nevertheless, the investigators' conclusions were not shaken even when extreme values of the key factors were tested in the sensitivity analysis.³¹

Largely as a result of the foregoing study, Congress passed legislation establishing pneumococcal vaccine as the first preventive benefit in Medicare.³³ Was this a good decision? At the time it was difficult to say. Was it an informed decision? Certainly it was more informed than it would have been in the absence of an analysis. Did the analysis meet the FDA criteria of two well-controlled studies? Not even close! Could two well-controlled studies have been conducted to produce the information required? No, but even if this were possible, these studies would have been very expensive and would have taken years to conduct, thus not meeting the needs of Medicare.

The Medicare coverage decision was quite different from the FDA decision to permit marketing of the vaccine. Both the methods and standards of evidence used by Medicare differed from the FDA two well-controlled studies standard. An important point is that consequences of a wrong coverage decision are quite different from those of an incorrect FDA approval decision. To approve an unsafe vaccine would be disastrous; to cover a safe but inefficacious vaccine would be, at minimum, a serious breach of faith with beneficiaries. To include a safe, efficacious, but cost-ineffective vaccine as a Medicare benefit would be less onerous—it would mainly be a bad buy.

Figure 1. Threshold Societal Standards for Acceptance of Uncertainty



Are There Other Risks of a False or Misleading Claim?

Making a bad buy is not a good outcome, but the important question for the FDA would seem to be whether there are health risks of a false or misleading cost-effectiveness claim. The FDA draft document differentiates the numerator and the denominator of a cost-effectiveness ratio.² The numerator consists only of costs, thus the FDA document expresses little concern, requiring simply that costs and prices be "fully disclosed." However the FDA regards the denominator as an expression of "effectiveness," and as such requires that burden of proof approach that of all claims of efficacy and effectiveness, that is, adequate and well-controlled studies. This requirement stems from the FDA concern that drug and device companies might take advantage of less stringently regulated cost-effectiveness claims to bypass highly regulated efficacy and safety claims.³⁴

Does it make sense for a cost-effectiveness claim to be held to such a burden of proof? We believe not. First, such a burden would cause most cost-effectiveness claims to be rejected because the requirement of adequate and well-controlled studies, as interpreted by the FDA, generally refers to randomized, controlled trials, and they are often an impractical or impossible standard for estimating cost effectiveness. Second, holding a numerator to a standard vastly different from that of a denominator makes no scientific sense (moreover, in CEA the numerator is in large part derived from the denominator because the effectiveness of a product highly influences cost). Third, a stringent burden of proof would in effect require companies to invest in expensive, time-consuming naturalistic cost-effectiveness trials,³⁵ which although impressive, may not always be the best use of research moneys. Fourth, we believe that decisions about resource allocation should not require the stringent standards of those for safety and efficacy. Finally, managed care neither needs nor wants such protection.

One potential concern of a more relaxed FDA regulatory policy could be direct-to-consumer advertising of cost effectiveness, although there is little evidence of this. Would this pose a problem? It may well increase consumer demand that managed care and other insurers cover what consumers believe to be cost-effective technologies. It is not clear, however, that such a response is contrary to public interest, certainly in light of widespread concern that managed care may be denying access to expensive new medical technology. In any case, coverage still

would depend on (presumably) informed institutional decision making.

A further concern of a more relaxed FDA regulatory policy of cost-effectiveness claims may be the possibility of multiple bad buys, resulting in a poor distribution of societal resources. Although theoretically a problem, it is directly counter to the main point of a policy to relax regulatory standards of cost-effectiveness claims. More information should help to better inform decision makers, leading to better decisions and optimal allocation of societal resources. Furthermore, a more relaxed FDA policy should stimulate even more cost-effectiveness research, ultimately raising not only the amount but also the quality of information about the value for money of expensive medical technologies. Therefore the few bad buying decisions would be more than compensated by many better buying decisions.

Possible Solutions for the FDA

Relying strictly on the market, with no regulation of cost-effectiveness claims, as some have suggested,^{36,37} leaves the FDA with legitimate concerns that cost-effectiveness claims may be used to subvert the tightly regulated claims of efficacy and effectiveness.³¹ Fortunately, there are realistic solutions. One is to require a disclaimer, for example: "This claim of cost effectiveness is based on assumptions and simulations that may not meet the FDA criteria for claims of efficacy and safety" or "This cost-effectiveness claim relates to resource allocation decision assisting and does not necessarily meet the standard for claims of comparative safety and efficacy. The package insert should be consulted for safety and efficacy information." A more appealing solution might be to do what journals do: submit each claim, with the respective scientific evidence supporting it, to peer review, after which the FDA would confer or withhold a label, such as: "This claim is based on research that conforms to generally accepted cost-effectiveness methods and principles." Depending on the volume of claims, the FDA could reach out to the extensive health economic and outcomes scientific community for the reviews.

... CONCLUSION ...

Healthcare decision makers today have increasingly powerful financial incentives to question whether drugs and devices are worth the high prices charged. In response, drug companies invest heavily in cost-effectiveness studies, and device companies are beginning to do so. These studies generally do

not, cannot, and should not meet the rigor of randomized clinical trials. They are designed to assist market-oriented, not clinically oriented, decision making. The consequence of an error in resource allocation is mainly a bad buy rather than harmful clinical misinformation. Cost-effectiveness studies are intended to assist the market to function more smoothly. As the managed care marketplace becomes ever more sophisticated, it is increasingly dominated by large institutionalized buyers, at whom cost-effectiveness studies are aimed. These decision makers are not easily influenced by cost-effectiveness claims and may even dismiss them. They do not need or want FDA protection.

Nevertheless, the FDA interprets its present legal mandate as a requirement to regulate cost-effectiveness claims. Rather than enforcing unreasonable standards, the FDA should require disclaimers that clearly state the degree to which the underlying cost-effectiveness research of drugs and devices meets acceptable scientific standards.

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