

**Good Research Practices for Measuring Drug Costs in Cost Effectiveness Analyses:
A Report of the ISPOR Drug Cost Task Force – Part I: Issues & Recommendations**

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Abstract

Objectives: The assignment of prices or costs to pharmaceuticals can be crucial to results and conclusions that are derived from pharmacoeconomic cost effectiveness analyses (CEAs). Although numerous pharmacoeconomic practice guidelines are available in the literature and have been promulgated in many countries, these guidelines are either vague or silent about how drug costs should be established or measured. This is particularly problematic in pharmacoeconomic studies done from the “societal” perspective, since typically the measured cost of a brand name pharmaceutical is not a true cost but also includes transfer payments from some members of society (patients and third party payers) to other members of society (pharmaceutical manufacturer stockholders) in large part as a reward for biomedical innovation. Moreover, there are numerous and complex institutional factors that influence how drug costs should be measured from other CEA perspectives, both internationally and within the domestic U.S. context. The objective of this report is to provide guidance and recommendations on how drug costs should be measured for CEAs done from a number of key analytic perspectives.

Methods: The Task Force was appointed with the advice and consent of the Board of Directors of ISPOR. Members were experienced developers or users of CEA models, worked in academia, industry, and as advisors to governments, and came from several countries. The Task Force met to develop core assumptions and an outline before preparing a draft report. They solicited comments on the outline and drafts from a core group of 174 external reviewers and more broadly from the membership of ISPOR at two ISPOR meetings and via the ISPOR web site.

Results: Drug cost measurements should be fully transparent and reflect the net payment value most relevant to the user’s perspective. The Task Force recommends that for CEAs of brand name drugs done from a societal perspective either i) CEA analysts use a cost that more accurately reflects true societal drug costs (e.g., 20%-60% of average sales price), or if that is too unrealistic to be meaningful for decision-makers, ii) refer to their analyses as from a “modified societal perspective”. CEAs done from a payer perspective should use drug prices actually paid by the relevant payer net of all rebates, co-pays or other adjustments. When such price adjustments are confidential, the analyst should apply a typical or average discount that preserves this confidentiality.

Conclusions: Drug transactions prices not only ration current use of medication but also ration future biomedical research and development. CEA researchers should tailor the appropriate measure of drug costs to the analytic perspective, maintain clarity and transparency on drug cost measurement and report the sensitivity of CEA results to reasonable drug cost measurement alternatives.

Introduction

The primary purpose of economic evaluation (specifically, cost effectiveness analysis) in health care is to provide valid and reliable information to health care policy- and decision-makers regarding the relative value of alternative health care interventions. The key rationale supporting these economic evaluations is that the market for health care interventions is so severely distorted by insurance coverage, third-party payments, information failure, taxes, subsidies, and numerous competition barriers that prices don't serve the normal economic function of guiding efficient resource allocation. Unlike a competitive market, in health care, Adam Smith's "invisible hand" of price signals is so severely withered and atrophied that it must be replaced by the virtual reality glove of the economic analyst to ensure that scarce resources are allocated appropriately.¹

While there are many areas of health care where prices are distorted, perhaps no area is subject to more complexity, confusion, imprecision, misunderstanding or conflicting methods than that of what price measurements to use for the cost of pharmaceuticals in economic evaluations.² The fundamental reason for this is that pharmaceuticals are launched into the market only after lengthy governmental review of safety and efficacy (e.g., the U.S. Food and Drug Administration—FDA, or the European Agency for the Evaluation of Medicinal Products--EMA). Drugs are only sold by licensed medical professionals under strict regulations regarding allowable usage indications, patient populations and appropriate marketing.

Pharmaceutical research, development and innovation is rewarded and encouraged primarily through patents, giving the innovative manufacturer (the patent holder) a time-limited monopoly over drug pricing for the patented drug. Because patents reward innovation by transferring brand-specific monopoly profits (the excess of drug price over drug marginal cost) from consumers to innovator pharmaceutical producers, they distort competitive drug prices with the specific intent of encouraging future drug R&D. Without patent protection, drug companies would quickly discontinue pharmaceutical R&D. But patent protection creates clear political, economic and social tensions, since certain drugs could be provided to some patients and/or payers at a price that would cover the marginal costs of production, but are not high enough to generate optimal profits to the innovative manufacturer. As has been the case of AIDS drugs in Africa, patients get sick and die without access to existing medications partly in order to protect the patent monopoly reward system to ensure pharmaceutical innovation for future generations.

It is often in the interest of both the pharmaceutical manufacturer and its consumers to allow price discrimination among different market segments. That is, the pharmaceutical manufacturer, particularly when holding patents on brand name drugs, can often make more profits and also make their products more accessible to more market segments by charging different prices to different consumers, based on the consumers different demand elasticities (willingness-to-pay). This strategy is most effective when such price

discrimination is secret or confidential, since confidential price rebating minimizes the potential for supply leakage between market segments.

Drug price discrimination is most obvious in comparing prices for the same brand name pharmaceuticals in different countries (e.g., the price of a hypertension drug in Canada, the United States, Mexico and China). While many health care providers can price discriminate across market segments, this strategy is often challenged politically, since consumers in the richer (higher priced) market segments usually resent having to pay more for the same pills as consumers in the poorer (lower priced) market segments. Unlike hospital or physician services, pharmaceuticals are generally available as tangible and tradable products, and when drug price discrepancies become too large between different market segments (or countries) there will be substantial arbitrage through legal, illegal or grey market re-importation activities.

Given this background, drug pricing (or costing) for economic evaluation is complicated. The complexity is compounded when one considers that each economic evaluation is done from a specific perspective (e.g., hospital, government payer (in a large or small country), managed care organization, patient, societal, etc.) and the various perspectives reflect tangibly different objectives, impacts, allocation priorities, market power and demand elasticities. At the societal perspective level, particularly in countries with large domestic innovative pharmaceutical industry, there is a clear tension between encouraging pharmaceutical innovation with brand name drug prices that are substantially higher than marginal drug production costs and encouraging less-expensive medications to reduce health care costs.

For managed care organizations, or for smaller countries without domestic innovative pharmaceutical industries, there is little incentive to encourage pharmaceutical innovation, since such innovation disproportionately benefits other consumers, payers or countries. In these organizations, it is preferable to take maximum advantage of one's local monopsony market power to drive drug prices as low as possible for both payment and evaluation purposes. Since such organizations or countries cannot impact R&D innovation substantially, it is in their interest to "free-ride" on larger payers and countries whose drug payments do have a significant impact on drug manufacturer profits and R&D incentives.

It is beneficial to both pharmaceutical producers and consumers to engage in market segmentation; but because it is difficult to prevent leakage from lower-priced markets to higher-priced markets, the pharmaceutical industry engages in extraordinarily complex and often secretive negotiations with different customers with the explicit purpose of preventing richer market segments from knowing the actual transaction prices in the more demand-elastic market segments. For example, in the United States the Medicaid program is required by law to receive the lowest possible transaction price for every purchased brand name pharmaceutical. However, this transaction price is fully disguised through secret volume rebates paid from the pharmaceutical manufacturers to the state Medicaid programs. Thus, even though they are all directly involved in the purchase and sales of Medicaid drugs, Medicaid patients, retail pharmacists, drug wholesalers and

other intermediaries have no idea what the real transaction prices are for the Medicaid drug purchases.

Similar secretive price discounting mechanisms, often triggered by volume targets and multi-drug purchasing from the same manufacturers, as well as rebates for formulary placement, make it extremely difficult to know what any given government or third-party payer actually pays for specific pharmaceutical products. Moreover, there is no requirement to make such information publicly known. Generally speaking, those organizations with the greatest market power (e.g., single-payer government healthcare systems) and those with the highest demand elasticity will capture greater discounts from publicly quoted or published prices, while those with the least market power and lowest demand elasticity will achieve smaller discounts and pay close to full price.

It should be kept in mind that the traditional method for rewarding pharmaceutical R&D through patent protection and monopoly prices for new drugs is the result of historical precedent and institutional inertia. It is an imperfect system for rewarding biomedical innovation; often allocating scarce resources towards “me-too” patentable new molecules rather than towards genuine innovations, while leaving critically important innovations (e.g., low-dose aspirin for heart disease or generic antibiotics for ulcers) to languish for years without being widely researched or adopted due to inability to obtain patent protection and to profit from valuable innovations.³

Moreover, it is vitally important to provide adequate incentives for biomedical research generally and pharmaceutical R&D in particular. There is consensus among health economists that the societal returns to biomedical R&D are on the order of 10-100 to 1.^{4,5} Cutler et al. (2006) have recently estimated that within the U.S. population, average life year gains from 1987-2000 were approximately 1-2 years and the average quality-adjusted life year (QALY) gains were 3-4 years.⁶ Valuing these QALY gains at a societal willingness to pay of \$150,000, and assuming that 2/3 of these gains are due to medical care improvements, mostly due to biomedical innovations,⁷ implies that medical care gains added \$90 trillion, or approximately \$2.7 trillion annually to the societal wealth of the U.S. population during this time period. The global value of biomedical innovation would be several times larger than these estimates.

Several alternatives to the patent system have been proposed to reward biomedical R&D.^{3,4,5} These include government patent buy-outs, rewards or tax-funded pharmaceutical R&D. If such alternative mechanisms can be implemented to incentivize pharmaceutical R&D without requiring a monopoly pricing structure for brand name pharmaceuticals, it would be feasible to use marginal cost (or generic) drug prices in economic evaluations of pharmaceutical interventions, particularly when done from a societal perspective. In fact, as argued below, given that the monopoly profits awarded to drug manufacturer patent-holders is not a true cost, but rather a transfer payment from one member of society to another, there is a strong argument to exclude these profits from drug costs when doing economic evaluations from a societal perspective.

Beyond these theoretical concerns, there are institutional complexities and opaque payment structures in every country and health care financing system that make drug cost measurement difficult even when the analytic perspective is straightforward and clear. For example, in the U.S. managed care environment, a particular medication could experience a dozen or more different transactions prices depending on where it is in the supply chain from manufacturer, to wholesaler, to retailer, to patient, and where it is in the payment/reimbursement chain from manufacturer to managed care organization, to pharmaceutical benefits manager, to patient, to rebate coupon. While this report is not an exhaustive compilation of all of the complexities and variations in drug transactions costs, it does give examples from many of the typical scenarios that CEA analysts will encounter around the globe. More importantly, it provides guidance and recommendations based on the authors and reviewers experience and understanding of what works best.

Task Force Process

The co-chairs of the ISPOR Task Force on Good Research Practices—Use of Drug Costs for CEA Modeling, Joel Hay and Jim Smeeding, were appointed in 2005 by the ISPOR Board of Directors after this Task Force topic was recommended to the Board by the ISPOR Health Sciences Policy Council. The members of the Task Force signed up on the basis of ISPOR website and newsletter publicity and self-designated into leadership, authorship and reviewer groups. Leaders were chosen for each of the key CEA modeling perspectives on the basis of their experience as developers or users of CEA models for that particular perspective. These individuals were recognized as scientific leaders in the field, who worked with that perspective in academia, industry, and as advisors to governments, and who came from a variety of countries and health care settings. This document reflects the authors' own experiences developing drug costs for use in CEA models and publications, but is not intended as a comprehensive review of the literature.

A reference group of ISPOR members from whom comments would be sought also was self-identified. The Task Force held its first meeting at the ISPOR 10th Annual International Meeting in Washington DC in 2005 and held open Forums at the ISPOR 8th Annual European Congress in Florence in 2005 and at the ISPOR 11th Annual International Meeting in Philadelphia in 2006. The Task Force reviewed other ISPOR guidance documents that were developed to inform good scientific conduct.^{8,9,10} The Task Force held teleconferences and used electronic mail to exchange outlines and ideas during the subsequent months. Sections of the report were prepared by Task Force members and a draft of the complete report was then prepared by the co-chairs, and circulated to the Task Force members for review. Several teleconferences of the Task Force leadership group were held to discuss the draft, incorporate feedback and make revisions. This draft report was then sent to a group of primary reviewers self-selected from broad range of perspectives. The reviewers are identified in the Acknowledgments section of the report. Following this review, a new draft was prepared by the Task Force members and made accessible for broader review by all ISPOR members. This final report reflects the input from all of these sources of comment.

Purposes of the Document:

The purposes of this document are: 1) to develop a coherent set of guidelines for those developing or reviewing drug cost measurements in CEAs; and 2) to develop a format for good research practices in drug cost measurement that is useful for decision-makers from various perspectives. The intended audience is research analysts who perform CEA analyses for health-care decision-makers as well as health care decision-makers who are responsible for local or national formularies. Others who may find this document useful include members of the press, patient advocacy groups, health care professionals, drug and other technology manufacturers, and those developing guidelines for their settings. The panel recognizes that the methods for measuring and reporting drug costs continue to develop. This report highlights areas of consensus as well as areas where continued methodological development is needed.

The report is divided into five main sections based on analytic perspective. In the next five sections we present the issues and recommendations for pharmaceutical pricing from the different perspectives, including 1) Societal, 2) Managed care, 3) Medicare, Medicaid, and other U.S. Government Payers, 4) Industry, 5) European countries and other international country perspectives. These perspective-specific analyses are presented to provide guidance and recommendations for how to obtain and use appropriate drug cost measurements when doing economic evaluations of health care interventions for different health care decision-maker audiences.

General Recommendations;

While most of the Task Force's recommendations are specific to each of the analytic perspectives that we focused on, there are some general recommendations that we believe apply to drug cost measurement in any cost effectiveness analysis setting or application.

- 1) More clarification of the "societal perspective" is needed. For CEAs of brand name drugs done from a societal perspective either CEA analysts i) use a cost that more accurately reflects true societal drug costs (e.g., 20%-60% of average sales price), or if that is unrealistic and not meaningful for decision-makers, ii) refer to their analyses as conducted from a "modified societal perspective".
- 2) Drug cost measurements should be transparent and made available to any reader or user of a CEA, with the data sources and rationale fully documented.
- 3) One-way and/or threshold CEA sensitivity analyses should demonstrate how much higher/lower drug costs would have to be to alter pharmacoeconomic model conclusions.
- 4) CEAs done from a payer perspective should use drug prices actually paid by the relevant payer net of all rebates, co-pays or other adjustments. When such price adjustments are confidential, the analyst should apply a generic average discount that preserves this confidentiality. As a corollary of this, when done from a government perspective, drug costs should be net of any sales tax, value-added tax (VAT) or other

taxes that are direct revenue offsets to the payer. Program eligibility and coverage issues should be clearly stated or referenced.

5) For drugs that are off-patent or likely to be off-patent in the near future, particularly when looking at treatments for chronic diseases, it is appropriate to consider multisource drug prices in either the base case or sensitivity analyses of pharmacoeconomic models. It is also appropriate to include longer term trends in applicable drug prices (net of general inflation) for chronic disease medications.

6) ISPOR should publish a website where current DCTF recommendations for drug costing are updated as important new information becomes available.

7) Population-based estimates of drug costs should incorporate predicted adherence and persistence with drug therapy.

8) When done from a patient/consumer perspective, the total net out-of-pocket payments for medications should be used as the drug cost measurement. Implications of extreme changes in marginal or average drug costs on patient drug utilization (e.g., completion of deductible expense limits, reaching maximum coverage benefits, Medicare-type coverage “doughnut holes”, etc.) should be fully evaluated and explained.

9) For international comparisons, drug units should be standardized in terms of volume/weight of active ingredient, regardless of package and dosing frequency or strength variations across countries.

10) Drug costs should be measured in local currency per unit of active ingredient and should be converted to other currencies using Purchasing Power Parity indexes (PPP).

11) When using drug prices from different years, the consumer price index for the local currency should be applied before the PPP conversion.

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