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 economic 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: ISPOR Task Force on Good Research Practices—Use of Drug Costs for Cost Effectiveness Analysis (DCTF) was appointed with the advice and consent of the ISPOR Board of Directors. Members were experienced developers or users of CEA models, worked in academia, industry, and as advisors to governments, and came from several countries. Since how drug costs should be measured for CEAs depend on the perspectives, five Task Force subgroups were created to develop drug costs standards from the societal, managed care, US government, industry, and international perspective. The ISPOR Task Force on Good Research Practices—Use of Drug Costs for Cost Effectiveness Analysis (DCTF) subgroups met to develop core assumptions and an outline before preparing six draft reports. 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 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.
Background to the Task Force

The ISPOR Task Force on Good Research Practices—Use of Drug Costs for Cost Effectiveness Analysis (DCTF) was recommended by the ISPOR Health Science Policy Council on December 13, 2004 and approved by the ISPOR Board of Directors May 15, 2005. Joel Hay and Jim Smeeding were appointed as Task Force leaders by the ISPOR Board. The core members of the Task Force who became the leaders of the Task Force subgroups were chosen based on the key CEA modeling perspectives and 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. Since how drug costs should be measured for CEAs depend on the perspectives, five Task Force subgroups were created to develop drug costs standards from the societal, managed care, US government, industry, and international perspective. Therefore, this Task Force Report is given in six parts. Part I: issues and recommendations; Part II: a societal perspective; Part III: a managed care perspective; Part IV: US government perspective; Part V: industry perspective; and Part VI: international perspective. The Task Force Report 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.

The Task Force held its first meeting at the ISPOR 10th Annual International Meeting in Washington DC in 2005 and held open forums and/or group leader breakfast meetings at the ISPOR 8th Annual European Congress in Florence in 2005, at the ISPOR 11th Annual International Meeting in Philadelphia in 2006 and at the 14th Annual International Meeting in Orlando in 2009. The Task Force reviewed other ISPOR guidance documents that were developed to inform good scientific conduct [1-3]. The Task Force subgroups held teleconferences and used electronic mail to exchange outlines and ideas during the subsequent months. The ISPOR Task Force on Good Research Practices—Use of Drug Costs for Cost
Effectiveness Analysis (DCTF) subgroups met to develop core assumptions and an outline before preparing draft subgroup reports. Several teleconferences of the Task Force subgroup leaders were held to discuss the draft reports, incorporate feedback and make revisions. Each part of the Task Force Report was prepared by Task Force subgroup co-chairs and members and circulated to 174 Task Force primary reviewers (who were self-identified from a broad range of perspectives). Following this review, new drafts was prepared by the Task Force subgroups and made accessible for broader review by all ISPOR members. Comments for these reports by Task Force primary reviewers and ISPOR membership are published at the ISPOR website. All opinions reflect those of the authors and not necessarily their affiliations.

Introduction

The primary purpose of economic evaluation (specifically, cost effectiveness analysis as recommended in numerous international payer guidelines [4]) 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 [5].

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 [6]. 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 Medicines Agency—EMA). Prescription 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 confidential or parallel imports are restricted, since this 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.

Measurement of drug costs depends firstly on the perspective of the analyst. Depending on the country or region, the drug cost burden is ultimately shared in varying degrees between government or other third party payers and patients. There are drug supply chain intermediaries (e.g., wholesalers, retailers, etc.) who receive payments for maintaining inventories, product distribution and dispensing. There can also be demand-side intermediaries (e.g., pharmaceutical benefits managers, group purchasing organizations, etc.) who receive payments for negotiating price discounts or rebates and managing drug product lists and formularies. At each step of these demand and supply chains, drug acquisition costs may vary in complex and non-transparent ways.

Given this background, drug valuation (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 direct 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.

Frank Ramsey showed in 1927 that a monopolist facing segmented markets (e.g., consumers with high income/high insurance coverage versus low income/low insurance coverage) would achieve both higher profits and higher social welfare by setting prices in each market segment inversely proportional to the market segment elasticity of demand [7, 8]. It is beneficial to both pharmaceutical producers and many 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 manufacturer price available to private and certain public purchasers for single source drugs. 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, formulary placement 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 health care 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 [9].

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 [10, 11]. 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 [12]. 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 [13] 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 [6-8, 14]. These include user licenses, 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, 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 [15], there is a strong argument to exclude these profits from drug costs when conducting economic evaluations from a societal perspective.

In fact, one can demonstrate that government buy-outs of drug patents with all drugs being sold at generic pricing levels could achieve a much better outcome for government programs, private consumers and third party payers without damaging the incentives for pharmaceutical R&D. Currently, the brand name pharmaceutical spending on R&D is about $60 billion [16]. U.S. federal drug spending is $81 billion [17]. Each year, the U.S. federal government could buy out all drug patents (by fully subsidizing the private costs of pharmaceutical R&D) and still save money since it would be able to purchase all drugs at generic prices. US consumers would additionally benefit by more than $100 billion per year if all drugs were generic.

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.

**Purposes of the Report**

The purposes of this Task Force Report 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 Good Research Practices for Measuring Drug Costs in Cost Effectiveness Analyses Report is published in six parts based on analytic perspective. The next five papers in this issue of *Value in Health* report the issues and recommendations for pharmaceutical pricing from the different perspectives, including 1) Societal [18], 2) Managed care [19], 3) Medicare, Medicaid, and other U.S. Government Payers [20], 4) Industry [21], 5) European countries and other international country perspectives [22]. These perspective-specific analyses are presented to provide guidance and recommendations for how to obtain and use appropriate drug cost measurements when conducting economic evaluations of health care interventions for different health care decision-maker audiences.
We recognize that this initial task force report is over-represented by topics relating to U.S. payment and reimbursement issues. This happened despite strong efforts by the task force to recruit ISPOR members from all countries and regions and is not meant to give offense to anyone. The task force members serve as volunteers, and because of a large number of drug payment policy issues coming forward in the U.S. context recently, there were more people motivated to address these topics. We certainly hope and expect that this is just the first chapter of an ongoing effort to assess drug cost evaluation issues globally and that future reports of the DCTF will be comprehensively representative of global drug evaluation concerns, whether they be different countries, regions, stakeholder perspectives, methodological approaches or other issues. We certainly encourage any reader who sees gaps that need to be addressed to join the DCTF and add their perspective in future reports.

**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 values and 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 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) or a currency exchange rate relevant to the decision-maker.

11) When using drug prices from different years, the consumer price index (preferably the medical care component price index or the pharmaceutical component price index) for the local currency should be applied before the currency conversion.

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References


