perspective

Pharmacoeconomic Analysis in Saudi Arabia: An Overdue Agenda Item for Action

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Pharmacoeconomics is a branch of health economics related to the most economical and efficient use of pharmaceuticals. Pharmacoeconomic research identifies, measures and compares the costs and outcomes (clinical, economic and humanistic) of pharmaceutical products and services. Pharmacoeconomic evaluation can play a significant role in the efficient allocation of resources in healthcare systems with constrained budgets. Countries are trying to control the rising costs of health care in their aging population. They are all asking the same question: Is the new drug good value for money; and if so, what is the society willing to pay for it? This article reviews the importance of, and the need for, adaptation of pharmacoeconomic analysis to the conditions in Saudi Arabia. It will shed some light on the important steps for converting the concept into practice, including the need for identifying the willing-to-pay (WTP) or the threshold cutoff, the existence of a real cost for each utility, the nonexistence of an pharmacoeconomic advisory forum, pharmaceutical budget allocation, and the impact of pharmaceutical marketing. It will also provide recommendations for easing any challenges that might jeopardize the conduct of such analysis in Saudi Arabia.

Pharmacoeconomics is a branch of health economics that deals with the economical and efficient use of pharmaceuticals.[1] The discipline of health economics has generated one of the most active and fast-growing applied body of literature in economics. Economic evaluation can play a significant role in the efficient allocation of resources in healthcare systems with constrained budgets.[2] The pharmacoeconomics concept is applied to guide the use of limited resources to yield maximum value to patients, healthcare payers and society.[1] Pharmacoeconomics as a term did not appear in the literature until 1986, when Ray Townsend, from the Upjohn Company, published a two-part presentation describing the need to develop research activities in this evolving discipline.[3] Townsend defined pharmacoeconomics at that time as "the description and analysis of the costs of drug therapy to healthcare systems and society."[4] Later this definition was modified to include "the costs and quality-of-life consequences associated with the use of a new drug therapy."[3] Since 1986, many methodological advances have been added to the definition to better measure the outcomes that describe the consequences of the use of a new drug.

Several countries have introduced economic evidence as a requirement for resource-allocation decisions, with some success. For instance, Australia formed the Pharmaceutical Benefits Advisory Committee (PBAC) and Medicare Services Advisory Committee; England and Wales established the National Institute for Health and Clinical Excellence (NICE); and New Zealand established the Pharmaceutical Management Agency.[5] Just recently, Germany founded the Institute for Quality and Efficiency in Health Care (IQWiG) to support national decision-making related to health care and, most of all, drug usage. Almost all European countries have established some kind of a committee or institute in which the main task is the economic evaluation of drugs.

In Saudi Arabia, the provision of health care is dominated by public-sector providers, primarily the Ministry of Health (MOH). The government plays a central role in providing healthcare services, accounting

for about 75% of the total healthcare spending in the country.[6] The pharmaceutical market remains reliant on pharmaceutical imports, particularly for high-tech patented drugs.[6]

In addition, the market is highly regulated, given that the MOH, previously did not, and currently, the Saudi Food and Drug Authority (Saudi FDA) does not allow the sale of any pharmaceutical product that has not met the country's licensing requirement. In addition, the Saudi FDA has strict price control policies in place to limit both public and private spending on branded, generic and over-the-counter (OTC) pharmaceuticals.

The forecast is that total pharmaceutical spending in Saudi Arabia will increase from $2.65 billion in 2008 to $3.68 billion by 2013, representing a compound annual growth rate of 6.8% in US dollar terms.[7] The main driver for such growth is thought to be the increasing burden of respiratory diseases in the country, along with diabetes, hypertension and cancer.[7] Furthermore, the Saudi Arabian government has recognized that the population is projected to increase to 27.6 million people by 2013, and has admitted that it is challenging to finance a sustainable healthcare sector.[8] It has therefore proposed to restructure the management of all existing 218 governmental hospitals into private enterprises and to introduce mandatory health insurance throughout the Kingdom.[8] The aim of the Saudi Arabian government is to reduce public sector spending on health care, along with improving the quality and standard of care at its local hospitals.

These healthcare reforms should increase access to healthcare services and pharmaceuticals as the penetration of health insurance increases across the country. Accordingly, a significant increase in overall expenditure on drugs is likely, with a greater shift towards the use of generics.[7] As competition increases, insurers will attempt to increase profits by implementing cost-containment measures such as pharmacoeconomic drug evaluations, generic substitution and formulary lists. At the regional level, the Gulf Cooperation Council (GCC) has established a 'group' purchasing program as an attempt at cost minimization. A total of $33 million was saved by five of the GCC states, and more than $11 million was saved by 3 GCC states in 2001.[8]

Rationale for Conducting Pharmacoeconomic Analyses in Saudi Arabia

Saudi Arabia is considered the largest consuming market affiliated with the GCC.[9] The gross domestic product (GDP) per capita in Saudi Arabia is $14 486 to 19 022, and 4.3% of the GDP is spent on health care.[10] Despite a high GDP and a wealthy population, Saudi Arabia's healthcare spending is challenged by different factors: Drug prices have increased over the years because the development cost of drug manufacturers has risen due to an increase in regulatory requirements to protect the public from ineffective and unsafe use of drugs following the thalidomide tragedy;[11] new techniques for drug design and new types of drugs engineered using the techniques of biotechnology have meant that cost of manufacturing drugs is also likely to rise; both of these increases in drug costs have resulted in multinational drug companies charging more for their drugs that successfully made it to the market, in order to obtain an acceptable return on their high investment.[5]

Unlike countries that prefer generics, patients in the GCC have chosen branded medications over generics. One study estimates the market share of generic medicines in Saudi Arabia is 5.8% compared to many European countries, where the market share of generic medicines was about 50% in 2009.[12] Additionally, in Saudi Arabia, because most medicines can be purchased from a pharmacy without a prescription, consumers can easily exercise their preference for branded medicines.

Finally, the fact that new therapies and technologies are being introduced makes the need for economic evaluation and pharmacoeconomic analyses vital. The performance of randomized controlled trials used to assess drug efficacy, as well as the results thereof, is not enough to guide the choices among different alternatives. All countries are facing the same questions: How can I best spend my money? Is the new drug good value for money; and if so, what is society willing to pay for it?

Types of Pharmacoeconomic Analyses

Pharmacoeconomic research identifies, measures and compares the costs and outcomes (clinical, economic and ethical) of various pharmaceutical products. It uses different methods and tools for examining the impact of alternative drug therapies and other medical interventions. Research methods such as cost-effectiveness, cost-utility, quality-of-life evaluations are drawn from many areas: economic, medical epidemiology, pharmacy and social sciences.[12,13] **Table 1** is a description of the different types of pharmacoeconomic methodologies.

Cost-benefit analysis (CBA) consists of identifying all of the benefits that occur from the program or intervention and representing them in dollar terms in the year in which they occur. This flow of benefit in dollars is then discounted to its equivalent present value at the selected interest rate. At the same time and on the other side of the equation, all program costs are identified and

allocated for a specific year and the costs are discounted to their present value. If all pertinent factors remain constant, the program with the largest present value of benefits with the least cost is the best in terms of its economic value. Basically, cost-benefit analysis can be used when comparing the value of different programs where the outcomes are in different units. For example, a given hospital or organization can measure the cost benefit of having a neonatal program versus cardiac rehabilitation program, taking into consideration the availability and distribution of other programs in the same geographical region.

Cost-effectiveness analysis (CEA) is defined as a series of analytical and mathematical procedures that aid in the selection of course of action from among various alternative approaches. This technique can be applied only when the program's output can be readily measured in dollars, but the outputs are more appropriately stated in terms of health improvement created [e.g., life-years gained (LYG), time to event, higher survival rates, or faster clinical cure). In cost-benefit or cost-effectiveness analysis, a program or intervention providing a high benefit (effectiveness)-to-cost ratio in terms of value to society may not be valued in the same way by all members of the society.

Cost-utility analysis (CUA) measures the consequence of intervention in terms of "quantity and quality of life." The results are often expressed as cost per quality-adjusted life-year (QALY) gained or changes in quality-of-life measurement for a given cost of intervention.

Finally, cost-minimization analysis (CMA) is used when two or more interventions that are demonstrated or assumed to be equivalent in terms of a given outcome or consequence, are evaluated. The Cost associated with each intervention may be evaluated and compared with that associated with another intervention.

Table 1. Description of the different types of pharmacoeconomic methodologies.

Methodology: Definition	Unit of cost measurement	Unit of outcome
Cost-benefit analysis (CBA): consists of identifying all of the benefits that occur from the program or intervention and converting them into dollars in the year in which they occur.	Dollars	Dollars
Cost-effectiveness analysis (CEA): a series of analytical and mathematical procedures that aid in the selection of course of action from among various alternative approaches.	Dollars	Natural units [life-years gained, blood glucose (mg/dL), blood pressure (mm Hg)]
Cost-minimization analysis (CMA): used when two or more interventions that are demonstrated or assumed to be equivalent in terms of a given outcome or consequence, are evaluated. The cost associated with each intervention may be evaluated and compared with that associated with another intervention.	Dollars	Assumed to be equivalent in the groups compared
Cost utility analysis (CUA): a tool that measures the intervention consequence in terms of "quantity and quality of life."	Dollars	Quality-adjusted life-years (QALYs), or other benefit

Practical Examples of the Usefulness of Pharmacoeconomic Analyses in Decision Making

The application of pharmacoeconomics is a challenge for many pharmacists today.[14] Several barriers exist when using CEA for decision making. One important barrier is that clinically relevant, unbiased, published cost-effectiveness studies are generally not available at the time a new drug is considered for addition to the formulary.[15] The studies that are available are mainly industry-funded, published in abstract form or are described in non-peer-reviewed journals, and/or are often lacking measurable outcomes. Currently, insurers, for reimbursement purposes, are increasingly making use of CEA to assess the financial "value" of new technologies, especially pharmaceutical or biopharmaceutical products.

Aspinall and colleagues, in a review published in 2005,[15] assessed the approval of gefitinib by the FDA. The drug was granted accelerated approval in 2003 for the treatment of non-small cell lung cancer (NSLC) based on evidence that 10% of patients treated experienced shrinkage in their tumor, but there were no CEAs ever published for this drug at that time. A subsequent clinical trial failed to show a mortality benefit,[16] and the manufacturer no longer recommended starting this drug for treatment of lung cancer. Before the publication of that study, sales in the United States approached $113 million during the third quarter of 2004. Spending of these 'healthcare' dollars would have been avoided had there been a CEA performed immediately following drug approval. Another example given by the authors was treprostinil for the treatment of pulmonary hypertension. It was approved by the FDA in 2001 based on one study and two abstracts published in the literature, with no CEA ever available following the approval of the drug. The one study that was published was funded by the industry, and the authors did not discuss the primary endpoints. A trend toward reduced mortality or a reduced need for lung transplantation after treatment with treprostinil was discussed in the report of the FDA given by the advisory committee reviewing the drug. Another problem with the study was the fact that

the comparison group was on a placebo rather than on standard drug therapy. This drug was never added to the Veterans Health Administration (VHA) formulary due to the paucity of data and the lack of evidence supporting improved survival or measurable improvement in quality of life. A subsequent analysis showed that the drug was less cost-effective than other available agents.[17]

Recombinant human DNase (dornase-alfa) is another drug where limited evidence is available concerning cost-effectiveness. It is considered an effective mucolytic and is indicated in conjunction with standard therapies for cystic fibrosis (CF). Clinical trials have indicated a small improvement in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), but whether quality of life is affected in a meaningful and measurable way is yet to be clarified.[18-20] When dornase-alfa was compared to hypertonic saline, it was found to result in a mean improvement in FEV1 of 8% at a mean additional cost of £1 409 over a 12-week period. In addition, using alternate-day dornase-alfa was not a cost-effective alternative in comparison with daily treatment for the same period.[20] In general, clinical trials in CF have shown improvements in lung function.[21] However, the drug is considered an expensive treatment, costing £7 442 per patient per year, and not all patients benefit from it.[22,23] The main evidence on the relative cost-effectiveness of dornase-alfa therapy comes from a study by Oster et al,[19] using data from a US phase III clinical trial.[24] The authors compared the effectiveness of dornase-alfa with that of placebo in adults with CF. They excluded the cost of dornase-alfa and only evaluated health costs related to respiratory tract infection. Nebulized hypertonic saline (HS) is an alternative treatment for CF and appears to have beneficial effects on lung function, mucociliary clearance and sputum expectoration in the short term that are comparable to those of dornase-alfa.[24] The intervention cost is substantially less than that with dornase-alfa, but the relative total cost of care has not been assessed, leaving the question of cost-effectiveness unanswered.[25]

Another example is sorafenib—an orally active biaryl urea, small molecule inhibitor of various tyrosine kinase receptors—used for patients with advanced hepatocellular carcinoma who are not suitable for surgery. It is found to increase survival by about 3 months. The British NICE, however, ruled that sorafenib should not be made available on the National Health Service (NHS)[26] because, although it is clinically efficacious, with tolerable side effects, it is not cost effective. It is believed to be too expensive even when NICE took into account a patient access scheme, offered by the drug's manufacturer, to provide every fourth pack of treatment for free. NICE calculated that the cost of sorafenib per QALY was about £52 000, well above its usual £30 000 threshold for approving drugs.[27,28] The cost-effectiveness has also been estimated for second-line treatment of advanced renal cell carcinoma from the perspective of the UK National Health Service. However, compared to the best supportive care, it offered additional health benefits, but with a cost per QALY in excess of £70 000.[28]

The MOH was the responsible authority for registering all pharmaceutical companies until the establishment of Saudi FDA in March 2003. The Saudi FDA took over this function in July 2009 and is now responsible for licensing pharmaceutical products. Because pharmacoeconomic data are becoming vital to practitioners involved in formulary decisions, it is important to have these data as soon as possible after Saudi FDA approval.

Global Continuous Challenges to Pharmacoeconomic Studies

Despite the potential value of pharmacoeconomic evaluations, one should not assume that decision making is immediately improved by using one of the above-mentioned tools for guidance. It has to be taken into account that these tools can only be as good as the data that are used for their creation; therefore, these analyses are best used as one tool alongside others for assessing the consequence of medical interventions.[29] Moreover, in cost-benefit analysis, all benefits are estimated in monetary terms related to the individual's maximum 'willingness to pay' (WTP). The term WTP is the maximum amount a person would be willing to pay, sacrifice or exchange for a good. Projects are considered valuable when the net benefits outweigh the cost. As a threshold, either the cutoff implied by the maximum budget or the maximum WTP per unit of health gained can be used.[28] Evidently, this leads to methodological inconsistency, since using the societal perspective entails including all costs (inclusive of indirect costs as productivity losses and patient-born costs) and not only those that fall in the specific healthcare budget. Therefore, as Johannesson and O'Connor emphasized, pharmacoeconomic analysis based on a fixed budget will not be consistent with using a social perspective.[30] Alternatively, the maximum WTP per unit of health gained could be defined as having a role in decision making. It is unlikely, however, that a single value for the WTP per LYG or QALY as the decision-making basis that is scientifically and thoroughly evaluated will be elicited soon. As an alternative, policy makers could define values of WTP per unit of health gained for

groups of interventions.[30]

One of the biggest challenges for pharmacoeconomic research is the fact that there is no agreement on what should be the benchmark value (threshold) for a cost-effectiveness ratio and how to restrict delivery of health care that has a cost-effectiveness ratio above the threshold value. Furthermore, there is no agreement on how to incorporate uncertainty of the results into the decision-making process and how to make a decision when only poor-quality data is available.[5] Finally, there are controversies about who should fund the studies and whether publication bias results in inefficient use of healthcare resources. For all these reasons, it is critical that healthcare decision-makers are trained and educated in pharmacoeconomics; and in its tools, methodologies and valid interpretation of the results.

Specific Challenges for the Saudi Arabian Adaptation of the Pharmacoeconomic Concept

Despite all challenges associated with the application of the concept, the healthcare system in Saudi Arabia is not only required to overcome such challenges, but is also required to establish basic elements of pharmacoeconomic analyses. This involves first identifying the WTP or the threshold cutoff. The World Health Organization (WHO) defines the threshold for cost-effectiveness as being less than three times the gross domestic product per capita (GDP/capita).[30] Current thresholds for cost-effectiveness are established or implicitly used by a number of countries worldwide (**Table 2**).[31-34] The GDP per capita for Saudi Arabia is estimated to be $14 486-$19 022.[34,35] Therefore, based on the definition provided by the WHO, the estimated threshold for cost-effectiveness is about US$57 000.[35] However, a threshold has to be discussed and agreed upon by MOH, Ministry of Finance (MOF) and the society.

Second, considering the fact that most of the health care is proivded by governmental hospitals, MOH, military, National Guard, Security, and specialist hospitals, the real cost for each utility, such as bed cost, x-ray, and lab tests, remains unknown. Therefore, a practical approach to assessment needs to be adopted in order to estimate the cost of these utilities in Saudi Arabia, based on the cost in private hospitals. A recommendation is to average the cost incurred at three or five private hospitals from among different categories of hospitals.

Third, there is no pharmacoeconomic advisory forum, resembling NICE, for example. This forum should be an independent, non-profit organization that can provide evidence-based recommendations on the cost-effectiveness of a given medication. Creating a full forum from scratch would be a tedious and resource-depleting approach; however, having an agreement or affiliation with such a forum so as to be able to use the modules developed by it would be a reasonable start. At present, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), an international educational and scientific organization fosters excellence in the core disciplines of pharmacoeconomics. The Saudi Arabian chapter of ISPOR [ISPOR-Saudi Arabia] maintains affiliation as a component chapter of ISPOR.[36]

Table 2. Currently used thresholds for cost-effectiveness in different countries.*[28]

Australia	Aus $42 000-76 000
Canada	Can $20 000-100 000
The Netherlands	€20 000
New Zealand	NZ $20 000
United Kingdom	GB £30 000
US	US $50 000-100 000
Sweden	SEK 500 000

*None of these thresholds is a fixed (legally binding) threshold.

Fourth, a pharmaceutical budget allocation in most of the hospitals is fixed and does not communicate with other counterpart budgets (i.e., admission, transplant program, cancer center, and others). For instance, if we were to introduce a new cutting-edge high-cost medication for kidney transplant patients that has been shown to reduce rejection, as well as hospital admission; then, although the medication budget has reached its ceiling already, the institution should still be able to offer this therapy by subtracting the cost from the kidney transplant program. Without this communicating 'budget compartment' module, the pharmaceutical budget continues to be in serious deficit.

Fifth, additional long-term challenges include the need for expertise, the lack of understanding of economic evaluation methodology among healthcare practitioners; the lack of quality data for outcome measurement in the Saudi population; and the inapplicability of the available pharmacoeconomic evidence due to the differences in healthcare provisions. One option would be that a clear national strategic plan be put in place to overcome these challenges. Healthcare providers, in particular physicians, need a better understanding of the relationship between cost and benefits ("Do I get value for money?") to become more cost-conscious in the future. Health-related economic assessment should be a part of their curriculum in the schools of medicine, internship and residency training. On top of this, physi-

cians need to assume responsibility for the increasing costs associated with their prescribing habits. This will become obvious as health insurance companies begin to mandate specific formulary items for specific disease states. In the meantime, pharmacists should assume a leading role in the adoption of the pharmacoeconomic concept in Saudi Arabia and push for its use in the decision-making process for formulary addition. None of this will materialize if budget decision makers are not aware of the concept or the advantages gained by the adoption of the concept.

Finally, the pharmaceutical industry must also be included in an overall health-related economic strategy, e.g., their marketing approaches must be evaluated and pressure has to be put on them to ensure the quality of their data and publication.

In conclusion, the application of pharmacoeconomic principles is pivotal in controlling the increasing costs of medications and supports rational decision-making in the healthcare sector. Pharmacoeconomic analyses can be used as additional tools for assessing the consequences of medical interventions. In Saudi Arabia, we propose that a WTP or threshold cutoff be agreed upon nationally. Other challenges require good strategic planning, and building the infrastructure (e.g., teachers of health economics in medical and pharmacy schools) that is crucial to creating sustainable outcomes from these types of analyses.

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