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PHARMACOECONOMIC COMPONENT OF A CLINICAL TRIAL CONDUCTED IN LATIN AMERICA

Conceptual and Empirical Considerations

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Abstract

Background: Although pharmacoeconomic studies constitute a valuable tool for better managing drug consumption, the conditions under which such studies would be performed in Latin American countries have not been explored.
Objectives: The aim of this paper is to evaluate the potential advantages of and pitfalls in doing pharmacoeconomic research in Latin America and to propose avenues to facilitate the development of this field in the region.
Methods: The Canadian guidelines for the economic evaluation of pharmaceuticals served as a structured framework to assess, both prospectively and retrospectively, the conditions under which the pharmacoeconomic component of a clinical trial held in Mexico and Brazil would be and actually was conducted.
Results: The conditions under which pharmacoeconomic evaluations are conducted must be improved if studies are to contribute to the better management of scarce resources across the entire health care system.
Conclusions: The creation of a public funding agency, the reappraisal of administrative data as a management tool in both the public and the private sectors, and the establishment of national guidelines should be considered within the framework of reforms aimed at allowing healthcare systems to meet their objectives of efficiency and equity.

Keywords: Pharmacoeconomics, Latin America

Under the impetus of structural adjustment programs, the healthcare sector in most Latin American countries is undergoing dramatic changes that affect the conceptual basis of service delivery (7). One characteristic of the new foundations on which healthcare organization is being erected is the emphasis placed on sound management of scarce resources. Concentrating in the hands of a few decision makers the responsibility of determining what the system should provide and how funds should be allocated has become the cornerstone of the new paradigm underpinning the transformation of these healthcare systems (10;11).

In this shifting landscape, one of the most daunting challenges facing healthcare managers in both the public and private sectors is keeping drug expenditures under control. Medication already constitutes a major strain on health budgets and continues to grow faster than any other single item of care. More and more, difficult and critical decisions have to be made as to which drugs should be made available and under what conditions (9).

Pharmacoeconomic (PE) studies aim to provide the two bits of information required to reach rational and therefore justifiable decisions regarding the provision of drugs: their cost (investment) and their expected benefits. These studies have become essential analytical tools for healthcare managers.

The field of pharmacoeconomics has witnessed tremendous change over the past decade. Most importantly, it has attained a fairly advanced level of formality and standardization. Highly instrumental guidelines have been laid down to provide investigators with useful tools and approaches for conducting PE studies (2). Moreover, economic evaluation training has become readily accessible nearly everywhere in the world (8).

This notwithstanding, very few PE studies have been performed to date in Latin America, and no literature exists regarding the factors and conditions that could have an impact on how such studies are conducted in the region. Consequently, anyone wishing to carry out a PE study in Latin America must do so without the benefit of specific data indispensable for planning purposes and for predicting how the endeavor might contribute to improve management in the healthcare sector. At a more macrolevel, planners lack information necessary to reconsider the administrative data structure with a view to promoting a more rational management of resources. Finally, pharmaceutical companies interested in conducting clinical trials in developing countries—an emerging trend in the pharmaceutical sector (6)—are devoid of information on the expected returns of investing in such ventures.

The aim of this paper is to evaluate the potential advantages of and "pitfalls" in doing PE research in Latin America and to propose avenues to facilitate the development of this field in the region. It is based on the experience gained from a multicenter clinical trial with a secondary economic component that took place in Mexico and Brazil.

METHODS

The Canadian guidelines regarding PE research (4) were used as a structured framework to evaluate, prospectively and retrospectively, the conditions under which an economic evaluation of pharmaceuticals was to and actually did take place in Mexico and Brazil. As the Canadian document is one of the very few of its kind, it has become a widely consulted reference in many countries. The specificity of each guideline with respect to the particular context of Mexico and Brazil was first assessed conceptually as a tool to prepare the PE component of the multicenter trial, which was funded and directed by a pharmaceutical company. The guidelines were then compared against the empirical evidence obtained during the implementation of the economic arm of the trial. The consensus of all the investigators was sought on each guideline.

RESULTS

Conceptual and empirical considerations regarding the PE study in question are presented in Table 1. Each guideline was evaluated in turn. Cells were left blank if there was no apparent discrepancy between a guideline and the situation prevailing in the two countries.

No major differences emerged between the two Latin American countries. In both cases, patients were covered by a combination of systems: private and public in Brazil, and private and social security in Mexico. The choice of participating hospitals where patients were identified was essentially a matter of practicality and convenience driven by the desire to constitute a sample with statistical power as rapidly as possible.

No discrepancy between conceptual consideration and empirical findings was noted. A blank cell in the empirical column essentially indicates that the situation was not relevant to the study.

Nevertheless, PE studies conducted in the two countries risk presenting a series of limitations. These could have a direct impact on a study's potential to meet the basic objective of contributing to improve management of the healthcare system as a whole.

The first and perhaps most serious limitation stems from the difficulty of drawing a representative sample of the population. The limited means of communication with certain subgroups, particularly the poorest people and those living in rural areas, may impede their enrollment in studies. Moreover, as financial resources may derive mainly from the private sector, the less economically rewarding groups of the population, at least according to the funding agency, risk being excluded.

A second major limitation arises from the poor quality and accessibility of data. The estimation of service utilization and unit prices may be biased by an empirical imperative—the need to access whatever data, provided they are usable—instead of being driven by an overriding concern with providing useful information to the key interested stakeholders.

As a result, the external validity of the PE study conducted in Brazil and Mexico cannot be ascertained with any confidence. We have reason to question whether the conditions necessary for PE results to contribute toward better management, particularly of the public system (the one most in need of improving its efficiency), were met.

Moreover, certain methodologic approaches may not be very pertinent. The use of utility scores based on a nonrepresentative population is hardly acceptable. Contingent valuation in countries marked by severe economic inequity even runs counter to the fundamental objective of promoting equity in care provision.

DISCUSSION

Conceptual and empirical considerations raised a number of interesting questions regarding the feasibility of conducting proper PE evaluations in Latin American countries. Difficulties emerged or loomed that should provide food for thought on how to integrate regional specificities in the design and conduct of PE studies.

A first major concern relates to the difficulty in promoting studies with a fairly acceptable external validity. Several factors converge to undermine the extrapolation of results, even to settings within the same insurance system. The healthcare systems in Latin America are, generally speaking, highly fragmented. They present numerous and very diverse coverage plans that are not accessible to everyone. No information exists that would make it possible to determine which institution or coverage plan is most representative. Patient samples may not be sufficiently representative. There is a risk of seeing certain groups excluded from studies, particularly those that live in rural areas and that might present very particular epidemiologic and consumption profiles.

Table 1. Conceptual and Empirical Considerations for Conducting a Pharmacoeconomic Study in Brazil and Mexico

	Conceptual considerations	Empirical considerations
Guideline		
1. Target audience must be identified		Funding body gave no thought to who would be interested in receiving study's results. Completing the clinical trial took precedence over the economic evaluation. Target audience was defined after the fact.
2. Timing of studies: at any point in product's life cycle		
3. Management of studies: no restriction on who can do studies	Scarcity of resources means pharmaceutical companies are primary funding agencies. Independence of researchers may be difficult to ascertain.	Scarcity of resources locally trained in economic evaluation limits the capacity to conduct peer-acceptable studies independently.
4. Incremental analysis: costs and effects must be reported as increments		
5. Analytic technique	Approaches other than cost-effectiveness analysis may be ill suited to poorly industrialized countries (see 12, 13, and 14).	
Criteria		
6. Indications: drug's target population must be clearly identified	Because of a highly fragmented system, lack of public funding for research, and poor accessibility to valid data, target population may be either reduced to a subgroup or poorly defined. Most at risk of being excluded are those covered by the public system.	Absence of centralized and accessible source of information on financial and operational issues for each type of system under study made it impossible even to extrapolate results to sites similar to the ones participating in the study.
7. Treatment comparator: existing practice and minimum practice should be used		
8. Perspective: all studies should report from a comprehensive societal perspective; perspective should be broken down into those of other relevant viewpoints	Accessibility to valid data varies according to insurance systems and centers. Some perspectives may be very difficult to assess and integrate in studies.	Poor quality and/or accessibility of data impeded the production of convincing results from a societal perspective. Certain perspectives were assessed by proxy based on parallel sources of information, such as another coverage plan. Consequently, the real costs borne by certain payers were evaluated rather approximately.

(*Continued*)

Table 1. (*Continued*)

	Conceptual considerations	Empirical considerations
9. Analytic horizon: should be extended to capture all relevant outcomes	Postdischarge events may be difficult to capture owing in part to limited means of communication (i.e., not everyone is hooked up by telephone).	The horizon was limited to the clinical trial's follow-up period. Getting into contact with the poorest patients was deemed unrealistic.
10. Assumptions: should be clearly stated		
11. Efficacy vs. effectiveness	Limited means of communication and highly decentralized and poorly accessible data seriously undermine feasibility of effectiveness studies.	
12. Health-related quality of life: when possible, one instrument from each of the following 3 types should be used: specific measures, generic profiles, and preference-based measures	Validating scores provided by tables may be difficult because of the difficulty of drawing a representative sample from a population that may be hard to reach. Devising relevant tables for each system concerned may not be feasible.	
13. Outcomes for cost-utility analysis	See 12.	
14. Outcomes for cost-benefit analysis: use contingent valuation	Besides the concern expressed in 12, sharp income disparities within developing countries make cost-benefit analysis inconsistent with the concern for the provision of equitable care. Also, monetary value may not mean much for the poorest, who may not be able to evaluate the opportunity costs of an intervention in monetary terms.	
15. Source of preferences	Preference scores must be based on a representative sample (see 12). Otherwise, the use of instruments such as QWB, HUI, or EQ-5D should be questioned.	
16. Equity	Because of the potential difficulty of generalizing results, particularly to the most disadvantaged groups of the population, PE findings could ill-serve the principle of equity.	
17. Discounting future outcomes: at same rate as costs		
18. Cost identification		

(*Continued*)

Table 1. (*Continued*)

	Conceptual considerations	Empirical considerations
19. Cost measurement (resources used)	Two potential problems were foreseen: 1) variable quality of administrative data across centers would limit value of administrative records; and 2) local research assistant would have little or no experience.	Both potential problems appeared as a real difficulty.
20. Cost valuation (unit prices)	Unit price identification may be extremely difficult in some settings. Unsuitable management data may not provide much information on cost and production, which would make unit price calculations rather difficult. Moreover, whether suitable or not, data are not always easily accessible, even when supposedly in the public domain.	Different insurance systems yielded data of different quality. Expedients such as reference price tables had to be used, although it was impossible to ascertain their validity. Very crude approximations had to be made, as general costs could not always be broken down into manageable components. Because of data quality and accessibility problems, prices had to be calculated from data (e.g., from a more accessible hospital) from which representativeness could not be ascertained.
21. Discounting future costs: at 0%, 3%, and 5%	Countries with different life expectancies may differ in terms of the most appropriate discounting rate. The most appropriate rate should be validated in different epidemiologic settings and in different groups of the population concerned.	
22. Dealing with uncertainty: should be addressed in studies		
23. Reporting results: in disaggregated detail first, with aggregations and value judgments later		
24. Portability of economic evaluations	The generalizability of results may be impossible to validate without first knowing how representative each source of information is. Too many payers and huge price variations across the numerous contracting parties involved may make it very difficult to arrive at a representative sample. A real societal perspective on the value to all the care providers of a country might be impossible to provide.	The absence of centralized and accessible sources of information by system concerned (public/private) made it impossible to ascertain the representativeness of the data collected. Results could not be extrapolated even to similar sites belonging to the same system.
25. Disclosure of relationships	No mention is made in the Canadian guidelines of the freedom to publish results. If the pharmaceutical sector is the main source of funding, unfavorable results risk being censored.	

Moreover, the lack of public funding for PE studies may limit financial sources to commercial groups such as the pharmaceutical industry. Because of their natural and overriding economic objectives, pharmaceutical companies may have little concern for the information needs of sectors outside their main market targets. Consequently, the results obtained may not apply to sectors, especially the public sector, where efficiency is in sore need of improvement.

Voices have also been raised in the industrialized countries (1;3) over the fact that the pharmaceutical industry is the major source of PE funding and that this may place its short-term profit motives above broader population concerns. The risk of this happening is even greater in the rest of the world. The public sector there might be inclined to consider the only data available, although they may be ill suited to its own needs. As a result, decisions regarding the allocation of scarce resources would be made on the basis of information shaped by purely economic interests, thereby depriving of needed funding those domains that are neglected by the commercial system and that fall within the public purview. These include poverty-stricken groups of the population and less economically rewarding fields of intervention, such as health prevention and promotion (5). By relying on privately funded studies, the public sector is at risk of deviating, albeit unwittingly, from its fundamental mission.

Moreover, records are often not suitable for evaluation purposes. When accessible and of acceptable quality, administrative data often cannot serve to measure service utilization or to place unit prices on different items consumed. As the quality of the data varies across sites, there is the risk that only those where the needed information appears most manageable will be selected for PE purposes. This would introduce a selection bias that could have considerable repercussions on the scope of a study and the generalizability of its results.

Another major concern is the scarcity of investigators trained locally to perform economic evaluations. Universities and public agencies have little experience in the matter. Conducting an economic study under such conditions is time- and resource-consuming. Moreover, this shortage of investigators is likely to rob the public sector of experienced professionals drawn to greener pastures where, however, the right to publish their results may be circumscribed.

One last major concern relates to whether the type of PE information that theoretically would be most relevant to planners can actually be produced. The validity of some approaches may be difficult to establish. For example, in countries where limited means of communication represent a real barrier to constituting a representative sample of the general population, tables of preference scores may not be practicable. Moreover, certain approaches are ethically questionable in very inequitable countries. This is obviously the case for contingent valuation, which would dwarf the contribution of the neediest segments of the population who, incidentally, might not be able to place a monetary value on an intervention.

These difficulties raise certain questions about the current feasibility of conducting PE evaluations in Latin American countries. Above all, they draw attention to the necessity of promoting certain realizable changes in order to better prepare the terrain for economic studies.

An interesting and rather obvious measure would be to set up an attractive, independent, and publicly owned agency to promote PE studies and disseminate their results. This would provide investigators with the necessary conditions to work more independently with a view toward providing information of interest to the entire healthcare sector.

Another useful step would be to reconsider the type of administrative, financial, and operational data systematically collected in order to make them more suitable for research purposes. Efforts should be made to render them accessible to investigators. Efforts should also be made to produce unit price tables that have some meaning (i.e., that incorporate

different perspectives while being more representative of the situation prevailing in the healthcare sector) for those who have to make crucial decisions regarding what should be offered in the healthcare sector.

Painting a broad picture of the diversity of prices is definitely challenging, but its expected benefits are invaluable. It would not only help but also promote the undertaking of PE studies. Decisions in the healthcare sector would become more rational. Efficiency would be increased, which would free valuable resources to meet more of the important needs of the population.

Finally, specific economic evaluation guidelines relevant to local conditions should be developed. The focus on certain approaches, such as cost-benefit analysis and cost-utility analysis, or on setting the most appropriate discount rate raises concern about the risks of using guidelines established in highly industrialized countries to ascertain the quality of a study performed elsewhere.

The production of national guidelines would certainly give impetus to the advancement of the PE field. These would also benefit the highly industrialized countries by providing fresh fodder for epistemologic rumination. Rationality should be promoted in different healthcare systems for the good of not only the Latin American population, but also the populations living in countries where guidelines have helped planners enormously to better manage health care.

POLICY IMPLICATIONS

The development of an independent and publicly funded agency of economic evaluation should be considered in order to establish economic guidelines specific to the context prevailing in each country and foster conditions conducive to the conduct of economic studies and the dissemination of results.

The architecture and accessibility of existing administrative data in the private, public, and semi-public systems should be reconsidered in order to promote economic evaluation as a tool for a more efficient and equitable provision of care in Latin America.

REFERENCES

1. Angell M. Is academic medicine for sale? *N Engl J Med.* 2000;342:1516-1518.
2. Baladi J, Menon D, Otten N. Use of economic evaluation guidelines: 2 years' experience in Canada. *Health Econ.* 1998;7:221-227.
3. Bodenheimer T. Uneasy alliance: Clinical investigators and the pharmaceutical industry. *N Engl J Med.* 2000;342:1539-1544.
4. Canadian Coordinating Office for Health Technology Assessment. *Guidelines for economic evaluation of pharmaceuticals: Canada*. 2nd ed. Ottawa: CCOHTA; 1997.
5. France G. Centralised versus decentralised funding of evaluative research: Impact on medical technology policy in Italy. *Soc Sci Med.* 1994;38:1635-1641.
6. India promises to become a world centre for testing new medicines. *The Economist.* January 29, 2000.
7. Ingraham PW. The reform agenda for national civil service systems: External stress and internal strains. In Bekke AGM, Perry JL, Toonen TH, eds. *Civil service systems in comparative perspective*. Bloomington: Indiana University Press; 1996.
8. James S, Waddington C. Capacity building in health economics: Opportunities for training in developing countries. *Health Econ.* 1996;5:473-478.
9. Pan American Health Organization. *Health in the Americas.* Washington, DC: PAHO; 1998:295-302.
10. Pérez-Stable EJ. Managed care arrives in Latin America. *N Engl J Med.* 1999;340:1110-1112.
11. Stocker K, Waitzkin H, Iriat C. The exportation of managed care to Latin America. *N Engl J Med.* 1999;340:1131-1136.