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REVIEW

The use of pharmacoeconomic evidence to support formulary decision making in Saudi Arabia: Methodological recommendations

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Abstract In pharmacoeconomics the costs and consequences of alternative medications are compared. Many countries have begun to use pharmacoeconomic evidence to support decisions on licensing, pricing, reimbursement, or addition to the formulary. In Saudi Arabia, it is not mandatory to submit cost effectiveness evidence to support licensing or addition to the formulary decisions however, data will be considered if submitted. Previous evidence suggests that the use of pharmacoeconomic evidence by Saudi Pharmacy and Therapeutic (P&T) committee members in formulary decisions making process is limited mainly because of lack of expertise and lack of resources. This paper intended to provide Saudi P&T decision makers with a clear set of best practice methodological recommendations to help in increasing the utilisation of pharmacoeconomic evidence in the formulary decisions making process.

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Contents

1. Introduction

Given the increasing demand for health care interventions and limited resources, there is a growing interest in evidence on value for money. Economic evaluation serves to demonstrate the value for money of health care interventions. It addresses the question of whether a new health intervention is worth funding when compared with other possible uses of the same resources, to ensure that efficiency has been attained. Efficiency implies that we make choices that maximize benefits (health gains) from limited resources (Palmer and Torgerson, 1999). In economic evaluation the costs and consequences of alternative interventions are compared (Drummond et al., 2005). Pharmacoeconomics is the economic evaluation of pharmaceuticals.

According to the American Society of Hospital Pharmacists (ASHP) a formulary system should be developed and implemented in hospital settings to promote the rational, evidence-based, clinically appropriate, safe, and cost-effective use of medications in order to optimize patient care (ASHP, 2008). The ASHP also recommends that the pharmacy and therapeutics (P&T) committee is responsible for administering the formulary system.

Many countries have begun to use economic evidence to support decisions on licensing, pricing, reimbursement, or addition to the formulary (Taylor et al., 2004). Formal and informal guidelines for the submission of pharmacoeconomics data to support reimbursement or pricing decisions were issued in many countries (Hjelmgren et al., 2001). Guidelines for the submission of pharmacoeconomics data to help P&T committees make informed decisions about which products to include on health plan formularies have been proposed (Marshall et al., 2008; Sullivan et al., 2001).

In Saudi Arabia, it is not mandatory to submit cost effectiveness evidence to support licensing or addition to the formulary decisions, however, data will be considered if submitted. A survey of P&T committee members in Riyadh, Saudi Arabia indicated the reason for the limited use of pharmacoeconomic evidence when making formulary decisions is lack of expertise and lack of resources (Alsultan, 2011). There is no publication yet that aims to guide Saudi decision makers when need arises to use pharmacoeconomic evidence. This paper intended to provide Saudi decision makers with a clear set of best practice methodological recommendations to help in increasing the use of pharmacoeconomic evidence in the formulary decision making process. The intended audience for the guidelines are decision makers at the P&T committees of Saudi hospitals, the paper, however, is still relevant to decision makers at the Ministry of Health (MoH) and Saudi Food and Drug Authority. As the target audience may not necessarily be an expert in the area of pharmacoeconomics, the recommendations were deliberately kept brief and written in non-technical language.

If pharmacoeconomics evidence is required to support formulary decision making process in Saudi Arabia, two situations can be identified: conduct a new pharmacoeconomic evaluation or use the results of existing pharmacoeconomic evaluation. The best practice recommendations for both situations are described below.

2. Conduct a new pharmacoeconomic evaluation

Approaches to conduct a full economic evaluation can be categorized as (i) either trial-based studies using patient-level data or (ii) decision analytic modelling based on secondary data or institution specific data. In both cases, the initiator of the study has to consider a few important aspects of the evaluation design. This section will focus on three of these: the research question, outcome and costs measurement and valuation, and presentation of results and analysis.

2.1. Define the evaluation question

The evaluation question could be structured around three items: perspective, choice of alternative medications, and choice of analysis technique. The analysis perspective dictates which costs and benefits are collected and assessed (Drummond et al., 2005). Possible viewpoints include those of the hospital, the insurance company, the patient, and society itself. The use of societal perspective is encouraged because it is wide enough to ensure that all costs and outcomes are included. Ignoring important costs and benefits in an economic analysis will lead to an inefficient allocation of resources (Jönsson, 2009). In Saudi Arabia, health care services are provided primarily by the MoH and other government agencies such as the Ministry of Defence and Aviation, the National Guard, and the Ministry of Interior. Services offered by these hospitals

Table 1 Perspectives of economic evaluations and their related costs.

		Social services Disability benefits	Society
Central Provider (e.g Ministry of Health)	Hospital	Medications, medical devices Diagnostic, investigational, screening procedures Health care providers and other staff Outpatient clinic visits, readmission	
		Primary care center visits, Rehabilitation in a facility or at home Community-based services, such as home care or health promotion	
	Patient	Cost of travel of transportation for treatment Paid caregivers Lost workdays lower productivity (being at work but not feeling well)	

are free of charge for all eligible citizens. In addition, large private companies are obliged to buy health cover for their employees. If adapting a social perspective proves difficult, the adaptation of central health service provider such as MoH is advisable more than adapting the narrow perspective of one governmental hospital for instance. This means costs and outcomes not relevant to the MoH such as costs incurred by reduced productivity of patients and their family as a result of illness, death or treatment would be excluded (Table 1). However, an indication of the nature and likely magnitude of any excluded benefits and costs from the patients' perspective is also advisable.

Pharmacoeconomic analysis involves a comparison between at least two alternative medications (Drummond et al., 2005). The new drug should be compared with the most commonly prescribed treatments used for the same indication in the institution including non-drug therapies and no-treatment. If the most prescribed treatment is not the most efficacious, then the treatment with the best proven efficacy for the same indication should also be included.

Cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost benefit analysis (CBA) represent the main pharmacoeconomic evaluation techniques. All analyses identify and quantify costs in the same manner but measure and value health outcome, benefits, or outputs differently. Table 2 illustrates the differences between types of pharmacoeconomic evaluation and gives examples on each type.

In cost minimisation analysis, outcomes of the two [or more] comparators are assumed to be equal, based on evidence to that effect, thereby resulting in an assessment based solely on comparative cost. When two medications are different in their effects on patient outcomes, the authors recommend the use CUA, CEA, and/or CBA. CBA is grounded in economic welfare theory, however, there are many controversies associated with monetary valuation of clinical and non-clinical outcomes (Drummond et al., 2005; Johannesson et al., 1996) which explain why it is less commonly used than CEA and CUA. The use of CUA or CBA has the advantage that they facilitate the comparison of interventions and the allocation of resources across different medical conditions. On the other hand, the results from CEA facilitate the comparison only between interventions that produce the same (or very similar) clinical outcomes (Oliver et al., 2002). Another technique which is complementary not as a variant or replacement to pharmacoeconomic techniques is budget impact analysis (BIA) (Mauskopf et al., 2007). Whereas, pharmacoeconomic evaluation measures the costs and outcomes of alternative technologies to estimate their economic efficiency, BIA addresses the financial consequences related to the uptake and diffusion of interventions to assess their affordability (Table 2). Readers can find more details on this technique elsewhere (Mauskopf et al., 2007).

2.2. Outcomes measurement and valuation

In CEA outcomes are measured in natural health effectiveness units, such as life years gained, symptom-free days, or bad clinical events avoided. A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign (a reduction in blood cholesterol level, for example) used as a substitute for a clinically meaningful endpoint such as life saved, death avoided (Drummond et al., 2005). As effects of new medications on surrogate end points often do not predict the true clinical effects of interventions (Fleming and Demets, 1996; Moynihan, 2011), it is advisable to use final and patient oriented outcomes rather than intermediate disease oriented outcomes. When this is not possible and there is a requirement to use a surrogate outcome, assessment of whether surrogate variables actually measure what they are supposed to measure (i.e. their validity) is required. Evidence on effectiveness should be derived from high quality, up-to-date systematic reviews or adequately powered randomised controlled trials identified through a comprehensive literature review. The generalizability of the collected evidence and its applicability to local context should be assessed. This should include at least the estimation of Saudi baseline risk, case–mix, life expectancy, and progress rate.

In CUA outcomes of alternative interventions would be expressed in terms of a single, ''utility based'' unit of measurement. In a healthcare context, utility is a value that is attached by an individual to a particular health state on the utility scale, which generally ranges from 0, indicating death, to 1, indicating perfect health (Brazier, 2008; Johannesson et al., 1996). Three methods are used for direct measurement of preference: standard gamble, time trade-off, and visual analogue scale (Brazier, 2008). Instruments such as the health utilities index (HUI) and the EQ-5D are available for obtaining utilities without undertaking direct measurement (Brazier, 2008; Arnold et al., 2009). The most widely used utility-based measure is the quality-adjusted life year (QALYS) which is calculated by multiplying the number of life-years gained from an intervention by a standard weight (utilities) that reflects the health related quality of life during that time. Although, there are now a Saudi validated version of EQ-5D which can be utilised locally, a P&T committee might not have the resources (financial and expertises) to take locally generated utility results for the study. In such a case transferability of published utility evidence can be considered (see Section 3 below).

Table 2 Types of pharmacoeconomics evaluation.

Type	Measure		Outcomes measure	Example from literature
	Outcome	Costs		
CEA	Yes	Yes	Natural unit e.g. death, life years gained, reduction in rate of infection, stroke prevented, disease free days	De Cock et al. (2009) compared linezolid vs vancomycin in suspected methicillin-resistant staphylococcus aureus nosocomial pneumonia. Outcomes included patient cured, death avoided, and life-year gained
CUA	Yes	Yes	Utility e.g. quality adjusted life years (QALY)	Punekar et al. (2010) compared standard care with scheduled maintenance treatment with infliximab in children suffering from severe active Chron's Disease (CD) over 5 years. The QALY estimated using the EurQol (EQ-5D) from a European CD population
CBA	Yes	Yes	Monetary e.g. financial value of the benefits	Sullivan et al. (2004) quantified the total costs and benefits of first-generation antihistamines (FGA). The benefit associated with FGA use was estimated using the willingness-to-pay method. The costs of FGA-associated sedation included lost productivity and the direct and indirect cost of unintentional injuries
BIA	No	Yes	–	Simoens (2011) computed the budget impact of lacosamide, a new anti-epileptic drug. The BIA calculated how a change in the mix of anti-epileptic drugs used to treat uncontrolled epilepsy would impact drug spending from 2008 to 2013. Data on the number of patients and on the market shares of anti-epileptic drugs and unit costs of anti-epileptic drugs were taken from Belgian sources
Cost analysis	No	Yes	–	Suh et al. (2010) estimated the total costs of fluorouracil when administered with leucovorin, by intravenous infusion or bolus. The costs comprised drug costs, dispensing costs, and administration costs (i.e. pharmacy staff time spent handling admixture, and dispensing of fluorouracil)

Cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), budget impact analysis (BIA).

While monetary valuation of some clinical outcomes such as hospitalisation is available, some benefits can be measured using the willingness to pay of individuals who benefit from the intervention. In the contingent valuation method, for example, respondents are presented with hypothetical scenarios about the interventions under evaluation and they are required to think about the contingency of an actual market existing for these interventions and to reveal the maximum they are willing to pay for such an intervention under evaluation (O'Brien and Gafni, 1996). The net monetary gain or loss by each alternative is then calculated and high value interventions are considered to be those preferred by patients.

2.3. Costs measurement and valuation

All resources consumed in the process of providing treatment such as drugs, equipment, disposables, medical and nursing time, hospitalisation days, and outpatient visits should be collected and estimated. The data on resources used may be gathered as part of a trial, from medical records, hospital databases, national registries or expert opinion. A word of caution when collecting data alongside clinical trials as it is possible that the procedures followed in the trial are not typical of care provided in every day practice (Shi et al., 2010; Miners, 2008). Similarly, if the analysis used experts' opinion to estimate resources quantities, there is a risk that resources estimated are for ideal care, rather than that actually provided in practice. If a need arises to use foreign data to estimate resources use then it must be checked and validated by local health care providers. To attach costs to resources used, market prices, that are the prices actually paid for particular goods or services, can be used. Prices or unit costs can be obtained from the finance departments of particular institutions or from national statistics, but charges (or fees) usually differ from real costs should not to be used (Shi et al., 2010; Miners, 2008). This requires conducting a cost analysis study (see Table 2) to identify and measure all resources relevant to the perspective. All costs should be expressed in values for the current year and are reported in Saudi riyals. Costs occurring beyond one year should be discounted to present values when they occur in the future in order to reflect society's rate of time preference (Shi et al., 2010; Miners, 2008). The Saudi Arabian Monetary Agency, the central bank for the country, suggested discount rate can be used. Alternatively the World Health Organisation suggested discount rate of 3% can be used (WHO, 2003).

2.4. Calculate and present results

For both the treatment and its comparator(s), the total costs and total benefits arising from their use should be presented with their statistical distribution (mean, median, confidence

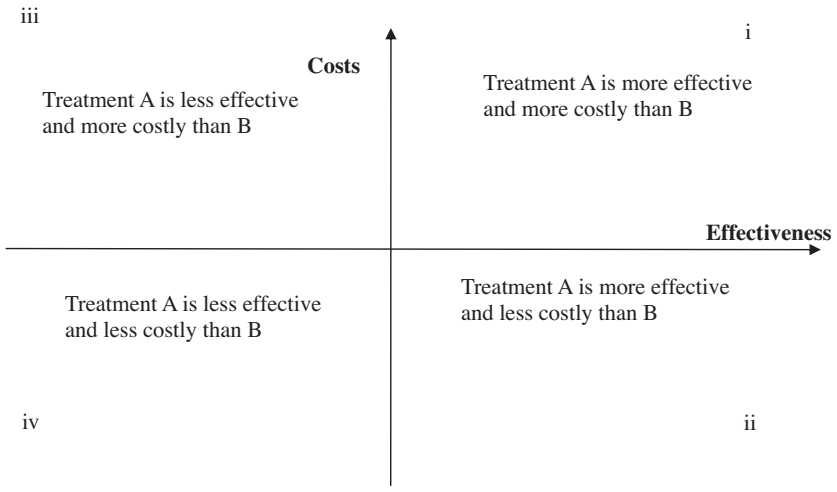

Figure 1 Incremental cost-effectiveness plane for treatment A versus B.

interval, etc.). The calculation of the average cost-effectiveness ratio, which is defined as the mean value of the costs divided by the mean value of the effect, can be useful in considering the overall affordability of a medication. However, when making a trade-off decision between two exclusive treatments, the incremental cost-effectiveness (utility) ratios (ICERs) should be calculated. In ICERs the difference in costs between two treatments is divided by the difference in outcomes produced by the same treatments. For example, a study compared the use of everolimus versus sorafenib in renal cell carcinoma and found that the use of everolimus resulted in life-years gained (LYG) of 1.273 over sorafenib (Casciano et al., 2001), however, everolimus was more costly by $81,64. The deterministic analysis resulted in ICER of $64,155/LYG (81,64 ÷ 1.273). That is it costs $64,155 to gain one additional life year. The ICER can be placed on a cost-effectiveness plane, as shown in Fig. 1 (O'Brien and Briggs, 2002). The choice between medications with ICERSs in quadrants ii and iii is straightforward as one therapy dominates the other in each case (has superior effectiveness and lower cost). Medications with ICERs in quadrant i improve health but cost more than the alternative. The decision whether or not to choose them should be based on the level of additional resources available and whether the additional costs of the new therapy justify the additional benefits to gain.

The results of pharmacoeconomic evaluation should be subjected to sensitivity analysis to verify the robustness of the conclusions and handle uncertainty (Claxton, 2008; O'Brien and Briggs, 2002). In sensitivity analyses, key parameters are varied within a range in order to explore the impact of uncertainty on the evaluation conclusions. A plausible range can be determined by reviewing the literature, consulting expert opinion, and using a specified confidence interval around the mean (for stochastic data). Types of sensitivity analysis include one-way and multi-way analysis, threshold (or break-even) analysis, analysis of extremes (i.e., best and worst case scenarios), or probabilistic sensitivity analysis. The use of probabilistic sensitivity analysis has the advantage over other types that it can quantify the effect of uncertainty around two or more parameters simultaneously. It is therefore, recommended to be used. Sensitivity analysis results can be presented using cost effectiveness threshold and tornado analysis. More advanced options such as confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves can also be used (O'Brien and Briggs, 2002). Within a probabilistic sensitivity analysis it is also helpful to present the contribution of the uncertainty in each parameter to overall decision uncertainty. This can be achieved using expected-value-of-information methods.

3. Transferring the results of existing pharmacoeconomic evaluation

One could argue that this option is more suited for the Saudi decision makers for a number of reasons. Currently there is no nationally recognised body responsible for commissioning and funding of pharmacoeconomic evaluation. Pharmacoeconomic evaluation is usually time-consuming, expensive, and demanding in terms of statistical sophistication and research expertises and such expertise is limited in Saudi Arabia. This argument is further supported by the fact that P&T committee face budget or time constraints in decision-making process, as a result, it is not possible to conduct a pharmacoeconomic evaluation on every medication. Indeed, in a recent survey involving 48 head of pharmacy departments of 11 different hospitals in Riyadh, Saudi Arabia, respondents were asked to indicate the data sources for pharmacoeconomic evidence utilised in formulary decision-making. Published literatures in peer-reviewed journals (30%), in-house expertise (5%), pharmaceutical company (5%), and combination of the three sources (50%) were the reported sources of evidence (Alsultan, 2011). However, the cost-effectiveness estimates of one medication might vary from place to place for a variety of reasons such as the incidence and severity of the disease in question, clinical practice patterns, resources utilisation, and relative prices (Drummond et al., 2009). A review of economic evaluations of medicines undertaken in Western Europe found that the extent of variation in the estimates of the incremental cost-effectiveness ratios between the countries to be substantial (a twofold difference) (Barbieri et al., 2005). Therefore, according to recent recommendations simple extrapolation of international pharmacoeconomics results to the Saudi context is

Table 3 Pharmacoeconomic methodological and reporting recommendations.

The chosen perspective, time horizon, and analytical technique(s) should be clearly stated and justified
The alternatives being compared should be relevant and clearly described
Time horizon, and analytical technique(s) should be clearly stated and justified
The primary outcome measure(s) should be stated and justified in relation to the primary aim of the health intervention
The methods used to identify and select evidence should be described together with the main characteristics of selected evidence
The method used to estimate utility measures should be explained clearly
The methods for the estimation of resources quantities and unit costs described
Outcome measures should be presented with the relevant statistical measures of dispersion (mean, median, confidence interval, etc.)
Significant outcomes should be reported in aggregated and disaggregated forms.
Resource use data should be reported in physical units such as hours of staff time, hospital days, number of consultations, and volume of drugs
Quantities of resources should be presented separately from the prices of those resources
The choice of discount rate, if performed, should be given and justified
For both the treatment and its comparator(s), the total costs and total benefits arising from their use should be reported with their statistical distribution
Incremental analysis is reported

Source Drummond et al., 2005.

not acceptable (Drummond et al., 2009; Welte et al., 2004). Saudi decision makers need to assess whether, and to what extent, the pharmacoeconomic results from other settings applies to the Saudi setting.

To guide the reader through this section, three critical issues are outlined: Is there pharmacoeconomic evaluation available of sound methodology? Is the pharmacoeconomic evaluation likely to be of value to Saudi Arabia decision makers? How to adapt and transfer the pharmacoeconomic data? The first two questions will help the reader to decide if good quality data are available and transferable and the third will discuss issues to consider when transferring existing cost effectiveness information to the Saudi context.

3.1. Is there pharmacoeconomic evaluation available and of sound methodology?

If the literature search shows that published pharmacoeconomic study exists, then it is important to ensure that it is of good methodological quality, transparent, and adequately reports on methods, and results. Table 3 presents the most important methodological and reporting criteria. A useful tool for decision makers is online databases that systematically identify and describe economic evaluations, appraise their quality and highlight their relative strengths and weaknesses. One example is the economic evaluation database maintained by the Centre for Reviews and Dissemination in the UK.

3.2. Is the pharmacoeconomics data likely to be of value to Saudi decision makers?

Pharmacoeconomic evaluation might be of sound methodology but not relevant to the Saudi context. For instance, if either the new medication or the comparator(s) is (are) not relevant in the Saudi setting, the existing pharmacoeconomic evaluation results are irrelevant. This could be the case for example, if the licensed indications are different from the Saudi context, and this in turn affects the clinical applications of the new product or those of the comparators. Furthermore, if the patient population from existing pharmacoeconomic evaluation is different from the Saudi population, then the pharmacoeconomic evidence is not transferable.

3.3. How to address transferability issues of evaluations from other settings?

Where an evaluation already exists that is of good quality and relevant to the Saudi decision makers, consideration should be given to three main transferability issues: transferability of clinical data, health state valuations or utility estimates, and costs data.

As for the transferability of clinical data, the treatment effects (i.e., relative risk reduction) can be derived from a trial or meta-analysis of trials conducted outside the Saudi context. However, decision makers need to determine if the baseline risk of patients within their own setting is the same as the baseline risk of those patients considered within the existing evaluation. They also need to consider the impact of local epidemiological and demographic data on the baseline risk.

Some evidence indicates that the population health state valuations might vary among different settings and countries (Knies, 2009), therefore, the data used to generate utility measures, such as QALYS, should be collected from the Saudi population. However, in view of lack of this type of research in Saudi Arabia and if a decision needs to be made in a short time period, data from other countries can be used. In such a case sensitivity analysis should be used to test the sensitivity of the study conclusions to various health state valuations. Sources of feasible range to be used in sensitivity analysis are explained in Section 2.4.

It is important to evaluate whether there is evidence of heterogeneity in patterns of resource utilisation between published evidence and Saudi clinical practice. For instance, there could be laboratory tests or patients counselling sessions which are commonly applied in the published study setting but not in the Saudi setting. This mean that costs associated with the use of these extra resources should be excluded. This is only possible if published evidence was transparent in reporting quantity of resources used and prices of those resources. Other characteristics of existing pharmacoeconomic evaluation, for which adjustment may be required, concern the perspective used and the impact this has on the approach for estimating health care cost. For instance, if the analysis adapted the society perspective then transportation and productivity costs will be included, but from a hospital perspective

these costs are irrelevant. For this reason, exclusion of some cost or outcome data might be required. Furthermore, differences in unit costs between countries make recalculation using Saudi-specific cost data necessary. The discount rate should also be adjusted using the previously suggested rate of 3% and testing the sensitivity of results to a rate of 6% (WHO, 2003).

P&T decision makers can use decision-analytic models as vehicles of pharmacoeconomic evaluation to address transferability issues. A model is a decision aid that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources (Weinstein et al., 2003). Decision makers could substitute relevant Saudi-specific parameters, input the data into the model, and re-calculate new ICERs. If Saudi parameters are not available then the use of probabilistic or multivariate sensitivity analysis is useful for assessment of variability of non-substituted parameters. The most frequently encountered type of modelling techniques are decision trees, in particular the Markov models used for chronic diseases requiring long-term evaluation. The basic model structure, assumptions, and parameters should be subtended by a process of internal and external validation to ensure that they are reasonable and accurately reflect the condition, process, and the impact of the intervention and comparators in real life (Philips et al., 2006). Those interested might benefit from reading more in depth discussion of modelling techniques (Weinstein et al., 2003; Philips et al., 2006). A good example where modelling techniques have been used to combine Saudi data and non-Saudi data is a study by Ali et al. (2008) on the cost effectiveness of conversion to biphasic insulin aspart 30 from human insulin.

4. Conclusion

In the light of lack of formal Saudi guidelines on pharmacoeconomic evaluations, this paper should be the one of many resources to guide decision makers when utilising pharmacoeconomic evidence. The authors have recommendations to facilitate further the use of pharmacoeconomics. There is a need for establishment of a national agency responsible for commissioning and funding of pharmacoeconomic evaluation. We also recommend that investments are made in the collection of epidemiological and demographic data, plus data on clinical practice patterns, resource use, costs, and health state valuations. We also suggest that the Gulf countries with similar health-care systems and clinical practice patterns should develop partnerships to develop relevant regional databases and registries. When designing a pharmacoeconomic evaluation, cooperation with a researcher who has experience in performing such studies is recommended. Investment in education and training of pharmacists in pharmacoeconomics is also required.

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