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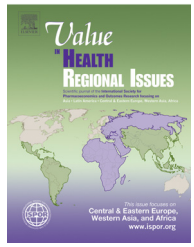

CONCEPTUAL PAPER

Recommendations for Reporting Pharmacoeconomic Evaluations in Egypt

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ABSTRACT

Objective: Introduction of economic evaluations for pharmaceuticals or other health technologies can help the optimization of outcomes from resource allocations. This article aims to provide recommendations for researchers in presenting pharmacoeconomic evaluations in Egypt with special focus on pricing and/or reimbursement applications of pharmaceuticals. **Methods:** The Minister of Health approved the initiative of establishing a focus group of decision makers that included academic and industry experts with experience in health economics, pharmacovigilance, and clinical pharmacy. The focus group has reviewed 17 economic evaluation guidelines available on the Web site of the International Society for Pharmacoeconomics and Outcomes Research for reporting health economic evaluations. To develop core assumptions before preparing a draft report, focus group meetings were held on a regular basis starting June 2012. The recommendations were developed by using the Quasi-Delphi method, taking into account current practices and capacities for conducting pharmacoeconomic evaluations in Egypt. **Conclusions:** Worldwide, health care decision makers are challenged to set priorities in an environment in which the demand for health care services outweighs the allocated resources. Effective pharmaceutical pricing and reimbursement systems, based on health technology assessment (HTA) that encompasses economic evaluations, are essential to an efficient sustainable health care system. The Egyptian Ministry of Health and Population was encouraged to establish a pharmacoeconomic unit, as an initial step, for the support of pricing and reimbursement decisions. We anticipate that standardization of reporting would lead to a progressive improvement in the quality of submissions over time and provide the Egyptian health care system with health economic evidence often unavailable in the past. Therefore, recommendations for pharmacoeconomic evaluations provide an essential tool for the support of a transparent and uniform process in the evaluation of the clinical benefit and costs of drugs that do not rely on the use of low acquisition cost as the primary basis for selection. These recommendations will help inform health care decisions in improving health care systems and achieving better health for the Egyptian population.

Keywords: economic evaluation, Egypt, recommendations, reporting.

Introduction

Egypt's general budget devotes limited amounts to the health sector. In the period 2008 to 2009, Egypt spent LE 61.4 billion (Egyptian pounds) on health, which represents 5.9% of the country's gross domestic product. Out of the total health care expenditure, pharmaceutical expenses constitute a large portion, 34%. [1]. In addition, over the past 16 years, the share of out-of-pocket spending in total health spending has increased dramatically from 51% to 72% [2]. These numbers suggest the increasing need for optimizing the limited resources available. With the growing public demand for improving health care services and reducing the out-of-pocket expenses, economic evaluations of pharmaceuticals and health technologies are critical for efficient allocation of the limited resources.

To better allocate resources and with the growing awareness of the importance of health technology assessment (HTA), the Ministry of Health and Population (MOHP) established a pharmacoeconomic unit to support and inform pricing and reimbursement decisions [3]. No economic evaluations guidelines or standards, however, have been set up yet.

This article provides recommendations based on reviewing other countries' national guidelines for economic evaluation as well as experts' opinions. Other factors influencing the feasibility of conducting such studies in Egypt, including the complexity of the health sector, the availability of data on health care outcomes

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and the costs data, and current capacities for conducting pharmacoeconomic evaluations, were put into consideration in developing these recommendations.

Objective

This article aims to provide recommendations for researchers to present pharmacoeconomic evaluations in Egypt with special focus on pricing and/or reimbursement applications of pharmaceuticals. Policymakers are encouraged to consider these recommendations in developing the national guidelines for the economic evaluation of pharmaceuticals.

Methods

As a self-initiated activity by government personnel, with the approval of the Ministry of Health at the time, a focus group was formed. The aim of the focus group was to develop a set of recommendations and standards for economic evaluation studies used in applying for reimbursement and coverage to 1) promote the concept of combining efficacy, safety, effectiveness, and economic evaluation in the decision-making process; 2) provide instructions for drug manufacturers: how to supply information directly to health care decision makers to support the use of their products; and 3) emphasize that simple assessment of acquisition cost is not a sufficient approach for the control of overall health care expenditures.

To develop the recommendations, two steps were undertaken. The first step was to review the available national economic guidelines. It included a review of 17 recently published national economic evaluation guidelines for conducting and reporting of economic evaluations (Table 1) that included an English version available on the Web site of the International Society for Pharmacoeconomics and Outcomes Research [4].

The second step was to solicit inputs and feedback from key leaders and stakeholders through focus groups. For a comprehensive representation of key stakeholders in health care, focus groups included decision makers experienced in health economics, pharmacovigilance, and clinical pharmacy, health providers as well as researchers and experts selected from both industry and academia, as shown in Table 2.

A consensus approach developed by using the Quasi-Delphi method consisted of an iterative series of meetings and interrogations. Anonymous responses were synthesized into a series of statements. Then, the synthesized statements were submitted to the focus group members for comment until convergence or stasis of opinion was identified in the third round.

Starting June 2012, focus group meetings were held on a regular basis to develop core assumptions before preparing a draft report. The discussions were recorded in written minutes. The recommendations were developed by consensus approach, taking into account current practices and capacities for conducting pharmacoeconomic evaluations in Egypt.

Developing Recommendations for Reporting Pharmacoeconomic Evaluations

Disease and Product Background

Economic evaluations should provide information about the epidemiology of the disease and treatment pathways according to most recent treatment guidelines. Data on the product should include pharmacological class, proposed dosing regimen, route of administration, and results of clinical studies performed to date [5].

Study Design

The study question should address the needs of the decision makers by clearly establishing the context of the study. It should provide details of the study perspective, the proposed product and its comparator(s), the target population, and the effect on specific subgroups where appropriate. Secondary questions that relate to the primary study question should be clearly stated [6].

Perspective should be relevant to the research question and adapted to benefits gained by the health care system. The perspective adopted should maximize the health gain for the population while representing the most efficient use of the finite resources available to the Ministry of Health [7]. It should include direct medical costs as well as additional costs, savings, or other benefits when data are available.

The proposed product should be used primarily in the approved indications with detailed information about its

Table 1 – Focus group members' information.

Member of Focus Group	Degree	Title	Organization	Government Employee
Gihan H. Elsisi	MSc	Head of Pharmacoeconomic Unit	Central Administration for Pharmaceutical Affairs, Cairo, Egypt	Yes
Randa Eldessouki	MSc, MD	Director, Scientific and Health Policy Initiatives/Lecturer	International Society for Pharmacoeconomics and Outcomes Research, NJ, USA/Faculty of Medicine, Fayoum University, Egypt	No
Mahmoud D. Elmahdawy	PharmD	Manager of Hospital Pharmacy Administration/Part Time Lecturer of clinical pharmacy	Central Administration for Pharmaceutical Affairs/Misr International University, Cairo, Egypt	Yes
Amr Saad	MSc, PhD	Head of Pharmacovigilance Center	Central Administration for Pharmaceutical Affairs, Cairo, Egypt	Yes
Samah Ragab	MPA	Director of the Technical Support Office	Central Administration for Pharmaceutical Affairs, Cairo, Egypt	Yes
Amr M. Elshalakani	MBBch, MSc, MBA	Head of Health Economics Unit	Ministry Of Health, Cairo, Egypt	Yes
Sherif Abaza	MBA	Market Access & Governmental Affairs Manager	Hoffmann-La Roche Ltd. Cairo, Egypt	No

Table 2 – The national health economic guidelines reviewed by the focus group members.

Title of the document	Source, Country	Published Year
Guidelines for the Economic Evaluation of Health Technologies: Canada	Canadian Agency for Drugs and Technologies in Health (CADTH), Canada	2006
Guidelines of Methodological Standards for Pharmacoeconomic Evaluations in Taiwan	Taiwan Society for Pharmacoeconomics and Outcomes Research, Taiwan	2006
Prescription for Pharmacoeconomic Analysis: Methods for Cost-utility Analysis	The Pharmaceutical Management Agency (PHARMAC), New Zealand	2007
Guidance to Manufacturers for Completion of New Product Assessment Form	Scottish Medicines Consortium, Scotland	2007
Guide to the Methods of Technology Appraisal	National Institute for Health and Clinical Excellence (NICE), England and Wales	2008
Guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee	Pharmaceutical Benefits Advisory Committee (PBAC), Australia	2008
Guidelines for Pharmacoeconomic Evaluations in Belgium	Belgian Health Care Knowledge Center (KCE), Belgium	2008
Health Technology Assessment Guideline	*Journal of the Medical Association of Thailand*, Thailand	2008
The Academy of Managed Care Pharmacy Format for Formulary Submissions	Academy Of Managed Care Pharmacy, United States	2009
General Methods for the Assessment of the Relation of Benefits to Costs	German national institute for quality and efficiency in health care (IQWiG), Germany	2009
Guidelines for conducting Health Technology Assessment	Poland Agency for Health Technology Assessment, Poland	2009
Decree of the Ministry of Social Affairs and Health on applications and price notifications made to the Pharmaceuticals Pricing Board–Appendix: Guidelines for Preparing a Health Economic Evaluation	Ministry of Social Affairs and Health, Finland	2009
Procedure for Clinical and Economic Evaluation of Drug Lists That Are Submitted for Reimbursement Coverage from Public Health Care Budget.	ISPOR Russia HTA Regional chapter, Russian State Medical University, Russian Federation	2010
The Guidelines for Pharmacoeconomic Evaluations of Medicines and Scheduled Substances	National Department of Health, South Africa	2010
Guidelines for the Submission of a Request to Include a Pharmaceutical Product in the National List of Health Services	Pharmaceutical Administration, Israel	2010
Guidelines for the Economic Evaluation of Health Technologies in Ireland	Health Information and Quality Authority, The National Centre for Pharmacoeconomics, Ireland	2010
Guidelines on How to conduct Pharmacoeconomic Analyses	Norwegian Medicines Agency, Norway	2012

technical characteristics (to differentiate it from its comparators), regulatory status, and the specific application.

The selection of the comparator has to be justified. Comparators should be policy relevant; therefore, widely used and reimbursed health care technology for a given patient group and indication is the preferred option. If no such technologies are reimbursed in the tender list at the time the assessment is conducted, the investigated product can be compared with the most frequently used technologies to treat the same patient groups. If a new product is used as first-line, second-line, or third-line therapy, it should be compared with first-, second-, or third-line therapies, respectively.

The targeted population should include both those who are insured by the Egyptian health system and those who are uninsured. Parameters to define the population include baseline demographic characteristics, disease characteristics, treatment setting, the context of past treatment, and any confounders adjusted [5].

Specific subgroups should be identified for those for whom clinical effectiveness and cost-effectiveness may be expected to differ from those of the overall population. Stratified analysis used to quantify the differences in cost-effectiveness that may exist in different subgroups is recommended because it may contribute important information to the final advice. The evidence supporting the clinical plausibility of the subgroup effect should be fully documented, including details of statistical analysis [8].

Appropriate Pharmacoeconomic Method

The choice of method of analysis depends on the research question and must be justified. If the compared health technologies result in equal health gain, cost minimization analysis is the preferred analytical approach.

If at least one of the compared health technologies is better than the other, and the clinical benefit can be aggregated and interpreted as naturalistic clinical outcomes, cost-effectiveness analysis (CEA) is the preferred method. CEA, where an intermediate marker is chosen, must have a validated, well-established link with an important hard end point (e.g., patient survival, heart attack, and bone fracture) [9]. Because the measure of primary clinical outcome may differ in different therapeutic areas, CEA cannot be used to compare or rank the cost-effectiveness of a broad set of products.

If the quality of life of patients is an important clinical outcome in the treatment course of patients, cost-utility analysis is the preferred analytical approach. In cost-utility analysis, the health gain is expressed in a combined single measure of life-years and health-related quality of life (HRQOL), for example, in quality-adjusted life-years (QALYs) [10]. Ignoring quality-of-life differences among products would provide less than complete data to decision makers to address the health care dilemma of where to allocate resources [11]. Adherence to the reference case

approach for estimating QALYs for inclusion in economic evaluations would facilitate comparability [12].

Time Horizon

In choosing the time horizon, it should be ensured that the chosen outcome and the resource consumption of the treatment alternatives are observable in this period to reflect the course of the disease and the effects of the interventions. The same time horizon should be applied to both costs and outcomes [9]. A decision to use a shorter time frame should be justified. When extrapolating data beyond the duration of the study, assumptions regarding future treatment effects and disease progression should be clearly outlined. Censoring might be used to account for the incomplete information [13].

Choice of Outcome Measure

The choice of outcome parameters depends both on the indication and on the research question. Primary outcome measures are the first choice whenever possible. When an intermediate end point is used, it must have a high degree of predictability of the final end point.

HRQOL is an appropriate outcome indicator for the evaluation of health status. HRQOL can be measured by using generic questionnaires, disease-specific questionnaires, or preference-based measures. If HRQOL is to be included in the study design, this variable must be measured by validated instruments. The direct use of the EuroQol five-dimensional questionnaire, six-dimensional health state short form (derived from short-form 36 health survey), or similar generic measures is recommended, because they are easy to use and interpret and are based on preferences of the general public. If the use of disease-specific HRQOL instruments increases the sensitivity of measurement, mapping of disease-specific HRQOL results with the EuroQol five-dimensional questionnaire or similar generic measures can be useful to translate the findings into QALYs.

Information on the changes in the health state should be reported directly by the patient or the caregiver. A valuation of these changes in the health state should then be reported for the general population. The outcome parameter chosen must be sensitive, valid, and consistent [14].

Synthesis of Clinical and Economic Evidence

Evidence synthesis has to be based on objective, systematic, and reproducible search criteria. Estimation of health gain must be based on scientific literature review and/or results of primary data collection, and the best available evidence should be considered. Meta-analysis based on large randomized controlled trials is the highest hierarchy of evidence with the heterogeneity of data accounted for. If compared drug therapies differ in adherence or persistence of patients, then these factors should be incorporated in calculating the relative effectiveness. In case of orphan drugs where randomized controlled clinical studies have not been conducted, the results of uncontrolled clinical studies can be accepted, including studies with small sample size. All product safety data need to be included whether from clinical studies or from national and foreign pharmacovigilance centers and patient registries with attention given to those that differ substantively among the products being compared [15]. Economic evidence should be synthesized from systematic review of the local data sources and the best available evidence.

Costs Determination

Resource use data should be obtained mainly from primary data collection (e.g. health care providers or non-interventional studies) from Egypt; if not available, secondary data sources such as local administration, accounting data, or patient chart review data can be used. Official sources of unit cost data for products (e.g., tender lists) are preferable. In the absence of a published tender list price, the price submitted by a manufacturer for a product may be used. The quality, validity, relevance, and generalizability of local data should be clearly described. Both estimated consumption of resources and their unit prices must reflect real-world settings in Egypt because relative and absolute price levels differ among countries [16].

Resource use and costs should be identified, measured in their natural units and values [17]. The primary perspective for these studies is the overall health care services. Therefore, the resources that should be considered are direct medical costs, which include drugs, medical devices, medical services including procedures, laboratory, or diagnostic tests, hospital services and emergency department visits, and primary care visits. Other direct nonmedical and indirect costs paid by patients, including lost productivity costs, might be included only in the sensitivity analysis. If indirect costs are included in the analysis, the rationality of the costs and how they are estimated should be explained. Current and future costs arising as a consequence of a product, and occurring during the specified time frame of the study, should also be included. Mean values should be used. Different costs or costs of the same resources that are used in different quantities should be included in the analysis [18].

Out of the two general approaches to determine costs, microcosting and macro-costing, macrocosting is preferred [19]. The source of cost data must be reported in detail. Data should be the most recently available, with the cost year specified. Retrospective input costs should be inflated to the most recent calendar year by using the Consumer Price Index for health [20]. The drug cost used should reflect the formulation and pack size that gives the lowest cost. For drugs available in the outpatient pharmacies, the full public price should be used for calculating costs. For hospital products, the wholesale price should be used for cost calculations. Future costs should be calculated at constant current costs; therefore, results are not subject to uncertainty in future inflation rates.

Modeling

Economic modeling based on prospectively collected data is the preferred method by decision makers in an increasing number of countries to aggregate the expected costs and health effects for all options relating to appropriate population and subpopulations, based on the full range of existing evidence [21]. The major aim of applying modeling techniques is to aggregate short- and long-term outcomes in the most appropriate time horizon.

The results of economic modeling studies presented should take into account the following requirements: 1) the model should be described in detail and should correspond to real practice of patient management; 2) the model should be as simple as possible, and easily understood; and 3) to facilitate assessment of the outputs of a model, full documentation of the structure, data elements, and validation of the model should be addressed in a clear manner, with justification provided for the options chosen and presented through diagrams (e.g., decision trees and Markov models) [22].

In addition, the model should be adapted to exclude clinical events not expected to differ among the comparator products [20]. For state transition models, such as Markov models, the cycle length should be sufficiently short to ensure that multiple changes in disease, treatment decisions, or costs do not occur within a single cycle. Heterogeneity in the population should be accounted by disaggregating the population into clinically plausible subgroups that require different structural assumptions. The internal validity of the model should be tested before using to ensure that the model is robust. The external validity should be tested by comparison of the results with those generated by other models and explaining differences if they exist.

Discounting

Discounting should be made according to the time horizon. Any costs or outcomes occurring beyond 1 year should be discounted by using standard methods [19]. For comparability of results across evaluations, it is important that a common discount rate is used. Because constant prices and outcomes are used in the economic evaluation, there is no need to take into account inflation in the discount rate. A real discount rate of 3.5% per year should be used for both costs and health gains. The discount rate should be varied from 2% to 6% in the sensitivity analysis.

Uncertainty

Data for a health economic analysis are derived from various sources, and this may be incomplete and affected by uncertainties. In a sensitivity analysis, critical component(s) in the calculation should be varied through a relevant range or from the worst case to the best case, and the results recalculated [13].

Probabilistic sensitivity analysis (PSA) is an appropriate method for exploring uncertainty around the true mean values of cost and efficacy inputs in decision-analytic modeling. In PSA, however, probability distributions are applied by using specified plausible ranges for the key parameters rather than the use of varied point estimates for each parameter. Its results are difficult to interpret for decision makers, while the stochastic approach, such as deterministic sensitivity analysis (DSA), examines how parameter variables (included as point estimates) affect the model output [23]. We propose, given the difficulty in interpreting the PSA, that DSA should be required, while PSA remains optional.

To avoid potential bias and uncertainty that arise from the modeling process, assumptions about the model structure should be clearly stated and justified and their impact on cost-effectiveness explored though a series of plausible scenario analyses so that whether the study results will be changed can be observed. All choices and the ranges of the parameters, and the method used in sensitivity analysis, should be clearly explained.

Present Study Results

Total costs and health outcomes must be reported separately, and the aggregated result be explained. All parameters used in the estimation of clinical effectiveness and cost-effectiveness should be itemized in a tabular form with data sources transparently. Negative results should be reported. Incremental cost-effectiveness ratio has to be calculated, unless one of the compared health technologies dominates the other one. In addition, the potential impact of the introduction of the new treatment on the society needs to be assessed [24].

Where more than two products are being compared, the results should be presented in the order of increasing costs and the incremental cost-effectiveness ratio calculated by comparing each product with the one above it, excluding those products that are dominated. Equity issues, affordability, and resource constraints should be considered in judging the cost-effectiveness of a product for reimbursement [20].

Tornado diagrams are useful tools to display DSA. If PSAs are performed, the probability that the intervention is cost-effective at a range of threshold values should be reported and the data should be displayed graphically to facilitate the uncertainty interpretation [9].

Equity and Generalizability Issues

To meet the needs of the decision makers, an attempt should be made to include equity considerations in the study report. The equity assumption of the basic case in economic evaluations means that all patients should have a fair participation opportunity and obtain the expected treatment outcomes.

To determine equity in economic evaluation, we propose that all lives, life-years, or QALYs should be valued equally, regardless of the age, gender, or socioeconomic status of individuals in the population [12]. The equity assumption should be included in every model and analytical method of economic evaluations and must be clearly stated.

Analysts must consider two specific areas of concern regarding the generalizability of clinical and economic data in the assessment of technologies. The first area of concern is the extent to which the clinical efficacy data are representative of the likely effectiveness and similarly the extent to which economic data are representative of the costs and resource utilization [8]. The second area of concern is the generalizability of the economic and clinical data across different patient ages and genders as well as regional differences in health care practice within Egypt. These areas of concern should be identified and discussed, and the likely effect on the results and conclusions of the report should be highlighted [25].

Discussion

There is an increasing need for justification of resource allocations and policy decisions, especially with the scarcity of public resources. Fig. 1 shows that among all middle-income countries in the region, Egypt invests a smaller proportion of its gross domestic product on health care [1]. Investments in economic evaluation studies and development of pharmacoecomic guidelines and expertise will help in allocating these limited resources in the most efficient way to improve health care services.

The current reimbursement decisions in Egypt are based on the lowest price after clinical review and approval of efficacy and safety of the medication by the Procurement Technical Committee. The Procurement Technical Committee reviews all MOHP hospitals and primary care units' needs of medications and applications submitted by drug manufacturers. It then decides whether this medication is to be listed or not, according to pharmacokinetics, pharmacodynamics, safety, and efficacy. Then, the applications go to the Committee for Financial Offers at the MOHP to review the financial issues and decide which drug manufacturer or wholesaler, the one that presents the lowest price for each active ingredient (medication), is to get reimbursement. Drug manufacturers or wholesalers who submitted identical price levels for the same active ingredient are given reimbursement by an equal process. Fig. 2 presents the decision makers and influencers in the Egyptian pricing and reimbursement decision-making processes [26].

There is a growing need to incorporate high-quality economic evaluation studies into the reimbursement decision-making process to adequately evaluate clinical and economic benefits of medications in addition to the assessment of their acquisition costs. These evaluations will improve decision making with prioritizing our resources, which results in reducing our huge expenditure on pharmaceuticals and save these resources to be allocated to other cost-effective health technologies. In Egypt, there is no limited budget that should be allocated for drug coverage only but is allocated to the whole health sector.

The submission of an economic evaluation is currently recommended in Egypt. And an economic evaluation guideline to standardize the process and provide a transparent and uniform approach was approved by the Ministry of Health. There is a big chance that these recommendations will be implemented in Egypt. Policymakers are encouraged to consider these

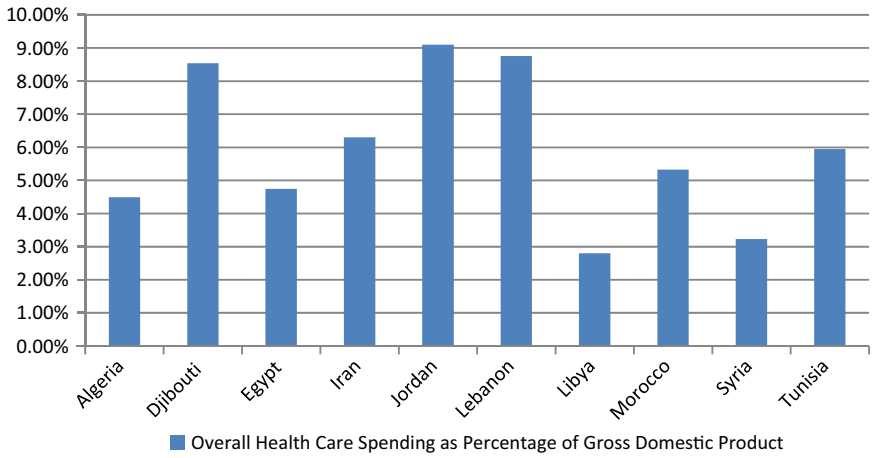

Fig. 1 – Egypt in comparison with other middle-income countries in overall health care spending as percentage of gross domestic product. Data from USAID [1].

recommendations in developing the national guidelines for the economic evaluation of pharmaceuticals.

The Canadian guidelines reported that by providing standards for conducting and reporting of economic evaluations, the current limitations of evaluations can be addressed and lead to better study [9]. It is important to note that the standardization of reporting and other policies in the United States shared in the bulk of the estimated $2 trillion savings [27]. We anticipate that the standardization of reporting would lead to a progressive improvement in the quality of submissions over time and provide the Egyptian health care system with data often unavailable in the past.

In developing those recommendations, we chose to build on the learning experience from other countries and modify and adapt the knowledge acquired to fit the Egyptian setting. In doing so, duplication of efforts and use of resources much needed elsewhere are avoided. As a rule, certain elements of HTA reports are transferable, but adjustment to local data is absolutely necessary [16]. Copying recommendations based on international HTA without local adjustment may do more harm than good. Putting this into consideration, our recommendations were tailored to the current settings and environment in Egypt while using the current guidelines as an initial benchmark. Our starting point is built on many years of experiences and expertise worldwide.

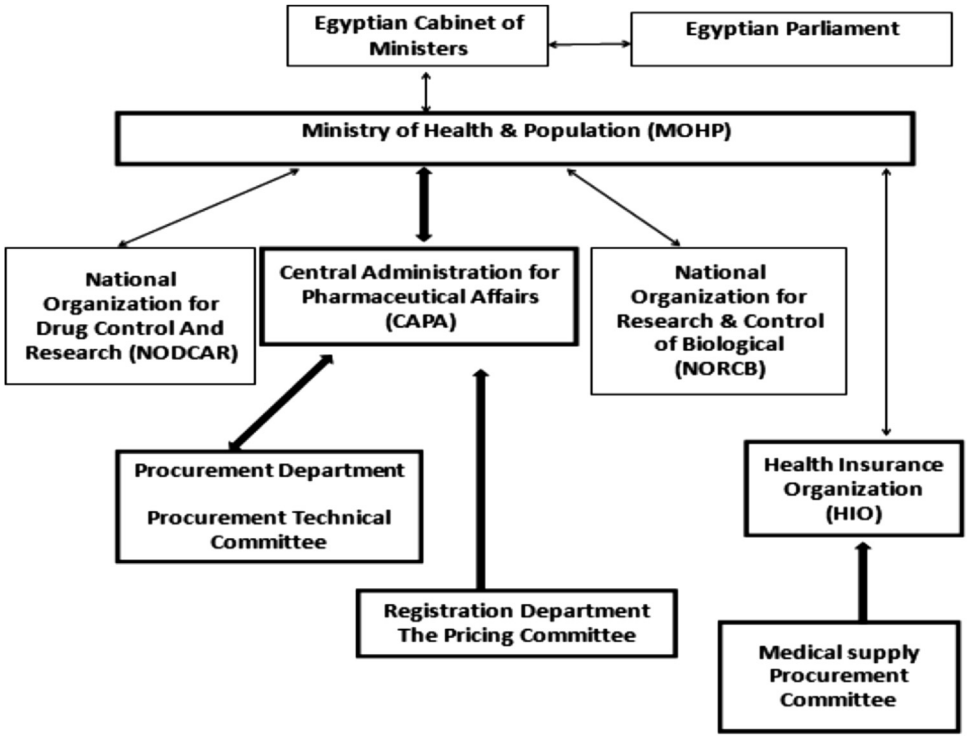

Fig. 2 – The Egyptian pricing and reimbursement decision-making processes [26]. Bold boxes, decision-making bodies; boxes, decision influencer bodies; bold arrows, required step in the decision-making process; arrows, may or may not affect decision.

Table 3 – Key elements of the recommendations for reporting pharmacoeconomic evaluations in Egypt.

Key elements	The Egyptian recommendations	Differences/ similarities across the national guidelines reviewed	Rationale for inclusion in the Egyptian setting
Perspective	It should be relevant to the research question and adapted to benefits gained by the health care system.	Common	It is a common agreed-upon element that captures all the benefits when data are available representing the most efficient use of the finite resources.
Indication	It should be used in the approved indications.	Common	According to the Egyptian Ministry of Health regulations, the use of the product in unapproved indications is forbidden.
Choice of comparator	Comparators should be policy relevant. The widely used and reimbursed health care technology for a given patient group is the preferred option.	Different	Because of policy-related problems such as drug supply shortage, we have to use the available technologies.
Target population	Both those who are insured and uninsured by the Egyptian health care system.	Different	Because of the existing widespread uninsured population that is covered by other forms of health coverage, there is a need to assess the effectiveness among different categories of access to health care.
Subgroup analysis	Only for those for whom clinical effectiveness and cost-effectiveness may be expected to differ from that of the overall population.	Common	When a distinct group differs from the overall population, a subgroup analysis is essential to reflect the actual clinical benefit and provide an accurate estimate of the cost-effectiveness of the therapy across all population groups to better inform decision on reimbursement.
Preferred analytical technique	Any of CMA, CEA, and CUA considered.	Different	It depends on the research question. When the clinical benefit is interpreted as naturalistic clinical outcomes, CEA is the preferred method while CUA is the second option because the concept of using QALYs might not be well understood by the majority of decision makers.
Time horizon	It should be ensured that the chosen outcome and the resource consumption of the treatment alternatives are observable in this period.	Common	To accurately reflect the course of the disease and the total effects of the interventions.
Choice of outcome measure	Primary outcome measures are the first choice. CEA, where the intermediate marker is chosen, must have a validated, well-established link with an important hard end point. In CUA, outcomes are measured in QALYs gained.	Common	It depends both on the indication and on the research question.
Preferred method to derive utility	The direct use of the EQ-5D questionnaire, SF-6D, or similar generic measures is recommended.	Common	They are easy to use and interpret and are relevant to the Egyptian public educational level and preferences. After a period of time allowing knowledge building and according to the learning curve, more sophisticated instruments might be considered.
Synthesis of clinical and economic evidence	Evidence synthesis has to be based on objective, systematic, and reproducible search criteria. The results of meta-analysis are preferable with the heterogeneity of data accounted for. Economic evidence should be synthesized from systematic review of the local data sources and the best available evidence.	Common	Meta-analysis based on large randomized controlled trials is the highest hierarchy of clinical evidence and is recommended for clinical benefit evidence. However, economic benefit evidence is nontransferable among the countries and should be obtained from local data sources and the best available evidence.

Table 3 – *continued*

Key elements	The Egyptian recommendations	Differences/ similarities across the national guidelines reviewed	Rationale for inclusion in the Egyptian setting
Costs to be included	Direct medical costs as well as additional costs, savings, or other benefits when data are available.	Different	In most cases, data and information on indirect costs are lacking in Egypt; therefore, direct costs estimation is recommended.
Sources of costs	Primary data collection; if unavailable, secondary data sources can be used such as local administration, accounting data, and patient chart review. Official sources of unit cost data for products (e.g., tender lists) are preferable.	Common	Both estimated consumption of resources and their unit prices must reflect real-world settings in Egypt because relative and absolute price levels differ among countries.
Modeling	Modeling options include decision trees and Markov models. The model should be described in detail and should correspond to real practice of patient management.	Common	These models are easy to use, interpret, and aggregate the expected costs and short- and long-term outcomes captured in the most appropriate time horizon relating to the Egyptian population and subpopulations.
Discounting costs and outcomes	A discount rate of 3.5% per year should be used for costs and outcomes.	Common	Because constant prices and outcomes are used in the economic evaluation, there is no need to take into account inflation in the discount rate.
Uncertainty	Critical component(s) in the calculation should be varied through a relevant range or from the worst case to the best case. DSA should be required, while PSA remains optional.	Different	With the current level of knowledge, results of PSA are difficult to interpret by personnel reviewing the studies for coverage decisions.
Equity issues	All lives, life-years, or QALYs should be valued equally, regardless of the age, gender, or socioeconomic status of individuals in the population.	Common	All patients should have a fair participation opportunity and obtain the expected treatment outcomes.
Generalizability	The generalizability and the extent to which the clinical efficacy data and the economic data are representative should be identified and discussed.	Common	Because of the presence of wide regional differences in health care practice among urban and rural areas, generalizability of the studies should be discussed in detail.
Presenting results	Total costs and health outcomes must be reported separately, and the aggregated result be explained. ICER has to be calculated. The probability that the intervention is cost-effective at a range of threshold values should be reported and displayed graphically.	Common	Detailed information should be provided to facilitate the interpretation of results, thus allowing for a more transparent and uniform process for the final coverage decision.

CEA, cost-effectiveness analysis; CMA, cost minimization analysis; CUA, cost-utility analysis; DSA, deterministic sensitivity analysis; EQ-5D, EuroQol five-dimensional; SF-6D, six-dimensional health state short form (derived from short-form 36 health survey); ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years.

Key elements common across all national guidelines reviewed were included in the recommendations. Other key elements differed between the various guidelines such as the choice of comparator, preferred analytical technique, target population, costs to be included, and uncertainty. Through a consensus approach between all focus group members for these elements, we recommended the best fit to Egyptian settings that are applicable to the current Egyptian environment. A summary of the key elements of the recommendations and the rationale for their inclusion within the Egyptian setting are presented in Table 3 highlighting the elements that were common across all guidelines and the ones that varied.

HTA implementation in Egypt, however, is significantly challenged by the diversity and heterogeneity of the health care system, limited tradition for national treatment guidelines, and limited availability of epidemiological, health outcomes, and cost data. Data for economic evaluations are low quality, region and provider specific, unavailable in electronic records, and, in most cases, not updated. So, the common opinion is "HTA cannot be implemented in Egypt." In fact, there are no perfect data for health care research; we have to assess realistically how wrong they have to be not to be considered useful. Having some data is better than having no data at all; conducting pharmacoeconomic evaluations and outcomes research in Egypt would also greatly improve the quality of current data.

Therefore, it will be important to evaluate the effect of the implementation of these recommendations on reporting in future economic evaluations in a manner similar to Consolidated Health Economic Evaluation Reporting Standards (CHEERS): ISPOR Task force report [28]. As methods for the conduct of economic evaluation continue to evolve, it will also be important to revisit our recommendations. These recommendations were presented to the Assistant Minister of Health, and initial steps required to start building the capacity of the pharmacoeconomic unit are underway. A young generation of government personnel is enthusiastic to enter this field; recent graduates from the first health economic diploma program in the Middle East are keen to facilitate the implementation of HTA in Egypt.

Conclusions

Worldwide, health care decision makers are challenged to set priorities in an environment in which the demand for health care services outweighs the allocated resources [29]. Effective pharmaceutical pricing and reimbursement systems, based on HTA that encompasses economic evaluations, are essential to an efficient sustainable health care system [30]. The MOHP was encouraged to establish a pharmacoeconomic unit, as an initial step, for the support of pricing and reimbursement decisions. We anticipate that the standardization of reporting would lead to a progressive improvement in the quality of submissions over time and provide the Egyptian health care system with health economic evidence often unavailable in the past. Therefore, recommendations for pharmacoeconomic evaluations provide an essential tool for the support of a transparent and uniform process in the evaluation of the clinical benefit and costs of drugs that do not rely on the use of low acquisition cost as the primary basis for selection. Eventually, these recommendations will help inform the health care decisions in improving health care systems and achieving better health for the Egyptian population.

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