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Central Administration for
Pharmaceutical Affairs
General Directorate of Hospital Pharmacy
Pharmacoeconomic Unit

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Guidelines 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 [1].

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 impact on specific subgroups where appropriate. Secondary questions that relate to the primary study question should be clearly stated [2].

Perspective should be relevant to the research question and adapted to benefits gained by the health care system. The perspective adopted should maximize health gain for the population while representing the most efficient use of the finite resources available to the Ministry of Health [3]. 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 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 tender list at the time when 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, 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 [1].

Specific subgroups should be identified for those whom clinical and cost-effectiveness may be expected to differ from that of the overall population. Stratified analysis used to quantify the differences in cost-effectiveness that may exist in different subgroups is recommended as 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 [4].

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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. Cost-effectiveness analysis, 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, bone fracture) [5]. As the measure of primary clinical outcome may differ in different therapeutic areas, cost-effectiveness analysis cannot be used to compare or rank the cost-effectiveness of a broad set of products.

If quality of life of patients is an important clinical outcome in the treatment course of patients, cost-utility analysis (CUA) is the preferred analytical approach. In CUA the health gain is expressed in a combined single measure of life years and health related quality of life (HRQoL), e.g., in quality adjusted life years (QALYs) [6]. Ignoring quality of life differences among products would provide less than complete data to decision makers to address the healthcare dilemma of where to allocate resources [7]. Adherence to reference case approach for estimating QALYs for inclusion in economic evaluations would facilitate comparability [8].

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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 [5]. A decision to use a shorter timeframe 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 [9].

Choice of Outcome Measure

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

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 EQ-5D, SF-6D 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 EQ-5D or similar generic measures can be useful to translate the findings into QALYs.

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Information on the changes in the health state should be reported directly by the patient or 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 [10].

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, 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 [11]. 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 from Egypt; if not available, secondary data sources such as local administration, accounting data patient chart review can be used.

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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 as relative and absolute price levels differ among countries [12].

Resource use and costs should be identified, measured in their natural units and values [13]. 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 non-medical 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 timeframe 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 [14].

Out of the two general approaches to determine costs, micro-costing and macro-costing, macro-costing is preferred [15]. The source of cost data must be reported in details. Data should be the most recently available, with the cost year specified. Retrospective input costs should be inflated to the most recent

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calendar year using the Consumer Price Index for health [16]. 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 full range of existing evidence [17]. 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: a) the model should be described in detail and should correspond to real practice of patient management, b) the model should be as simple as possible, and easily understood, c) 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, Markov models) [18].

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Additionally, 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 requires different structural assumptions. The internal validity of the model should be tested prior 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 one year should be discounted using standard methods [15]. For comparability of results across evaluations, it is important that a common discount rate is used. As 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 is 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 worst case to best case, and the results recalculated [9].

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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. However, in PSA, probability distributions are applied 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 for the stochastic approach, such as deterministic sensitivity analysis (DSA), examines how parameter variables (included as point estimates) impact the model output [19]. We propose, given the difficulty in interpreting the PSA, that DSA should be required, whilst 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 and cost-effectiveness should be itemized in tabular form with data sources transparently. Negative results should be reported. Incremental cost-effectiveness ratio (ICER) 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 also needs to be assessed [20].

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Where more than two products are being compared, the results should be presented in the order of increasing costs and the ICER calculated by comparing each product with the one above it, excluding those products that are dominated. Equity issues, affordability, resource constraints should be considered in judging the cost effectiveness of a product for reimbursement [16].

Tornado diagrams are useful tools to display DSA. If PSA 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 [5]

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 age, gender, or socioeconomic status of individuals in the population [8]. 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 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 is representative of the likely effectiveness and similarly, the extent to which economic data is representative of the costs and resource utilization [4]. 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 healthcare practice within Egypt. These areas of concern should be identified and discussed and the likely impact on the results and conclusions of the report should be highlighted [21].

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