Recommendations on Pharmacoeconomic guidelines for Turkey considering reference countries: A scoping review

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ABSTRACT

Objectives: Through the years, assessing the value for money or cost-effectiveness of treatments has become increasingly important. In this context, the price regulations have become stricter in Turkey in contrast to regulations on pharmacoeconomic (PE) assessments. Considering lack of guidelines on PE evaluations, an urgent need arises for pharmacoeconomic regulations in Turkey.

Methods: In this study, we conducted a scoping review on pharmacoeconomic guidelines with specific interest for Turkey’s reference countries. Our search covered PubMed, Web of Science, and Cochrane databases, without date restriction. In addition, to provide further background for recommendations on pharmacoeconomic guidelines, a brief review of the Turkish medicines’ reimbursement system and those in reference countries was conducted, in the framework of the respective healthcare systems, explicitly considering the “Health Systems in Transition” series published by World Health Organization. The comparison tool and relevant databases of the International Society for Pharmacoeconomics and Outcomes Research were also reviewed.

Results: After selection, 6 relevant publications were included in this review. Regarding review on reimbursement regulations in reference countries, only Greece came out as having no formal PE guidelines.

Conclusions: The set of recommended PE guidelines for Turkey were therefore based on France, Portugal, Spain, and Italy’s guidelines and literature data. Our recommended set of guidelines can form the basis for further discussion and help determining the final set for formal embedding in the Turkish regulatory procedure for reimbursement of drugs.

Public Interest Summary: Through the years, assessing the value for money or cost-effectiveness of treatments has become important. Therefore, the price regulations have become stricter in Turkey in contrast to regulations on pharmacoeconomic (PE) assessments. Since an urgent need arises for pharmacoeconomic regulations in Turkey, we conducted a scoping review on PE guidelines with specific interest for Turkey’s reference countries. Our search covered three comprehensive databases. In addition, to conduct a wider research on country specific reimbursement systems and other relevant publications. After selection of articles, 6 relevant publications were included in this review. Since, only Greece came out as having no formal PE guidelines, the set of recommended PE guidelines for Turkey were therefore based on other four countries’ guidelines and literature data. Our recommended set of guidelines can form the basis for further discussion and help determining the final set for Turkish regulatory procedure for reimbursement of drugs.

Introduction

Taking the definition of the World Health Organization (WHO) into account [1], in Turkey, the organized health system began with the foundation of The Ministry of Health (MoH) in 1920 which firstly aimed at restoration after World War I and also to establish the health system’s key components. Subsequently, many governmental regulations have taken place. The Social Security Institution “Sosyal Sigortalar Kurumu (SSK)” was established in 1946 to provide healthcare insurance to the workers in the private sector and blue collars in the public sector. In the 1960 Constitution Act, the healthcare services were identified as a fundamental liability of the government toward citizens [2]. In 1961,
The “Decree on Socialization of Healthcare Services” paved the way for the national healthcare system. Subsequently, in 1965 healthcare services became embedded in the five-year development plans [3]. In the 1980s, the Ministry of Health accounted for primary and secondary health system services, and also there were intentions to establish a general health insurance system which failed. With the Constitution Act of 1982, health systems were defined and the responsibility of government in healthcare services was revised and shifted to the supervision and regulation of the services [2]. Until the 2000s, there were attempts to achieve slight changes and steps for reformation but because of various challenges like the economic crisis and changes in governments, these attempts remained without major impacts [4]. Even so, the plans for the general healthcare insurance system were mentioned from 1946 to the 2000s, it was not possible to put them into action [5].

In 2003, the “Health Transformation Program”, supported by the World Bank, was put into effect and it radically changed the healthcare system. Before this program, financing was multi-component and limited, there was a lack of coordination between the financing bodies and there was no correlation between the increase in the gross domestic product (GDP) and healthcare expenditure. Also, there was no common strategy and model to define the paying conditions [6]. As part of this transformation program, the reference pricing system was put in action with “The Decision Regarding the Pricing Regulation for Human Medicinal Products” in 2004. France, Italy, Spain, Portugal, and Greece were identified as reference countries for pricing medicines and price regulations were started to be implemented [7]. In 2017, the MoH announced the “The Statement of Pricing for Human Medicinal Products”, which is effective since then as the only regulation. Through this statement, the price regulations have become stricter [8]. While pricing regulations were developing, full pharmacoeconomic analysis/evaluation on cost-effectiveness did not proceed.

**Turkish reimbursement system**

Turkey’s regulations for reimbursement begin with specific rules for pricing. In this context, the price of pharmaceuticals is determined based on pricing in the reference countries. Turkish regulations define the reference price as “the lowest price in the reference countries” and if this is not applicable, then the pharmaceutical company must seek alignment with the prices in other countries which are in the European Economic Area (EEA). Notably, the lowest price in other countries provides the maximum. Yet the second situation is rare generally in Turkey, prices depend on the ones in the reference countries [7,8]. Currently, the prices are the same of the lowest price in the reference countries for branded medications, but it is different for generic drugs. For generic medications, the price is estimated as 60% of the lowest price in the reference countries [8].

After the pricing phase, the reimbursement process starts which is applied in two different ways. In particular, two reimbursement regulations are effective in Turkey. The “Social Security Medicine Reimbursement Regulation” defines the medicines and their posology for already financed medicines or newly submitted generic or branded medicines. This regulation is mostly used for generic medicines or branded medicines where their prices are calculated as per the standard discount rates. The second important regulation is “The Alternative Reimbursement Regulation”, covering the payment rules for healthcare services, inclusive innovative – potentially relatively expensive – drugs, and specifying which will be in the reimbursement list (positive list) or not (negative list) related to their added value. Also, the scope of this alternative regulation is specified to define the reimbursement method, promote, and ensure the availability of those products which cannot be locally manufactured or imported, named as “Foreign Medicines” and these have rules outside of reimbursement process [9]. In fact, this alternative regulation is mainly defining the submission process and form of commissions. However, it can be understood that there will be a confidential contract for the reimbursement model and this model will be decided by the commission, which is more of a bureaucratic commission, rather than a technical one. Typically, the technical form of the agreement is not included in regulation and pharmacoeconomic evaluations are not mentioned at all.

Apart from these, there is a guideline defining the reimbursement dossier submission requirements for pharmaceutical companies. The main approaches for the reimbursement process in Turkey, as defined in the submission procedure, offers different ways for two different categories. For generic medications, there are three main points: if the branded medication is on the reimbursement list, presenting cost analysis is not needed for generic medications and fixed discounts are applied. Comparative prices must be presented for generic medications to explain the rationale of the price. Finally, generic medications have to meet some requirements concerning price justification. Yet, there is no clear regulation for cost minimization analysis (CMA) which plays a significant role in the evaluation of generic medications. For branded medications, these requirements are different at certain points, which are mainly a part of the rules for dossier submission. The results of the clinical trials and possibly meta-analysis constitute the data which are retrieved from scientific articles for pharmacoeconomic (PE) evidence of branded medications. In the dossier, the rationale of the retrieved studies and information on direct costs must be given in detail. Also, additional information on other costs should be provided. The analysis based on calculated prices must be performed with CMA or cost effectiveness analysis (CEA) and should include proper sensitivity analysis. Evaluations with cost utility analysis (CUA) could be given additionally [10]. Notably, in submission procedure sensitivity analysis, CMA, CEA, and CUA are mentioned without an explanation, yet guidelines for how to conduct and formation of data are missing. For example, specifics of the perspective, choice of comparator, preferred analysis, outcomes to be measured, and specific pharmacoeconomic parameters to be used are not defined at all.

Right now, Turkey does not have a set of pharmacoeconomic guidelines and pharmacoeconomic assessment is still not required by Social Security Institution during reimbursement processes. Pharmacoeconomic assessment seems a logical next step in further optimizing the Turkish drug reimbursement process. Assessing the value for money or cost-effectiveness of treatments has become increasingly important in the last decades. Although pharmacoeconomic assessments are sometimes seen as an obstacle for new treatments, the economic perspective helps efficient and optimized allocation of resources and provides tools to ensure funds are directed to those patients who benefit the most from new therapies and support value-based pricing. To further support uptake of pharmacoeconomic assessments, an urgent need exists for pharmacoeconomic regulations in Turkey. One aspect of this concerns the design of guidelines for good pharmacoeconomic research, as existing for many countries around the globe already [11]. For example, pharmacoeconomic guidelines exist in almost all of Turkey’s reference countries.

In this study, we conducted a scoping review on pharmacoeconomic guidelines with specific interest for Turkey’s reference countries to potentially base the Turkey’s set upon. Additionally, we aim to make a set of recommendations for pharmacoeconomic (PE) guidelines for Turkey with intent of supporting drug assessments.

**Methods**

To provide an initial overview on the research topic, a scoping review research was planned to identify key characteristics of the guidelines and identify potential knowledge gaps [12,13]. Therefore a protocol-driven literature research was conducted between 22.03.2021 and 30.03.2021, considering the PRISMA Statement for Scoping Reviews (see supplementary file) [14]. PubMed, Web of Science, and Cochrane databases were used without time limitation, with the search terms “pharmacoeconomic guideline, pharmacoeconomics guideline, pharmacoeconomic guidelines, pharmacoeconomics...”
guidelines”.

To provide further background for recommendations on PE guidelines, a brief overview of the Turkish medicines’ reimbursement system and those in reference countries was conducted. Reference countries were identified as per the regulation “The Decision Regarding the Pricing Regulation for Human Medicinal Products” prepared by Council of Ministers [7]. To ensure coherent suggestions on the PE guidelines, the healthcare systems of the reference countries were reviewed as far as considered relevant, explicitly considering the “Health Systems in Transition” series published by WHO, which are country-based reports and provide detailed information about health systems in that country [1,15-17].

Additionally, relevant announcements on PE guidelines in reference countries were studied. Notably, the key features of the reference countries’ guidelines are considered to form the basis for a set of PE guidelines in Turkey. In particular, tool and database of International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for pharmacoeconomic guidelines are used as core information to compare the guidelines in reference countries within the scope of the purpose of guidelines, perspective, choice of comparator, time horizon, preferred analytical technique, costs to be included, modeling, preferred outcome measure and the preferred method to derive utilities [11].

Eligibility criteria

Except commentaries, correspondences, editorials, newspaper articles, and other forms of popular media, all articles were included. Articles that are not written in English and those considered not relevant to the country’s guidelines of health technology assessment or pharmacoeconomics evaluation were also excluded. Restrictions for the study type or research method were not applied.

Study selection

All results were screened by two researchers (LY and BSS) independently to eliminate bias in the selection. After screening the titles and abstracts, both researchers read the full text of the retrieved records and determined if each record met the inclusion criteria. In case of initial disagreement, the final decision on including a record was made by the two researchers mentioned with consensus.

Data charting

After final selection, included records were charted as per their author(s), title and publication year and country. Also, to present the individual aspects of countries’ guidelines, common points of these guidelines on perspective, comparator, analytic technique, evidence source, outcome measures, costs, time horizon, and discounting were added as separate columns to the chart. The data chart was prepared by one author, but the details presented in the chart were determined by all researchers with a consensus.

Limitations

The authors of this paper are only qualified in English as second language, the scientific papers other than English language were
omitted. Also, the gray literature was not included as we wanted to base our findings and inferences on peer-reviewed information only, taking reliability of the information explicitly into account.

Results

Researchers reached 3388 records identified from 3 databases in total. After removing duplications and exclusion for the language criterion, 2603 records remained. After title and abstract screening, 2430 records are excluded. Eventually, 173 were included in the review (See Fig. 1). These 173 records were included in full text screening. There were certain exclusion reasons for 167 of those 173 records. Notably, 15 were excluded because of article type as they concern an editorial, correspondence, or commentaries, 4 were excluded because they addressed a specific situation like oncology and anti-hypertension, 2 of them were about ethical issues and reporting/conducting studies and 4 of those were on generalisability of pharmacoeconomic evaluation studies. Although 140 of them touched on the guidelines, none of them mentioned PE guidelines as the main topic and were excluded for that reason, and 2 were about clinical guidelines.

Synthesis of data obtained from included records is given in Table 1, including information about the article and the characteristics of pharmacoeconomic evaluation guideline as per the article.

Healthcare systems’ characteristics

To provide a clear suggestion on PE guidelines, we reviewed all the reference countries’ healthcare systems from the perspectives of healthcare expenditure, revenue source, coverage, the existence of out-of-pocket payments, and the population size of the country. The relevant comparisons with the review of 7 references, are given in Table 2. All reference countries have points in common in terms of healthcare financing, coverage, and out-of-pocket payments. While healthcare expenditure is similar in reference countries, Turkey’s expenditure is approximately 7% of GDP, clearly below the percentages for reference countries. Whereas revenue sources of Spain, Portugal, and Italy are taxes, in Turkey, Greece, and France those are specified as income-based contributions. Also, differences in population sizes are obvious [24].

PE guidelines in reference countries

As one of the Turkish reference countries, only Greece has no PE guidelines. The other four countries (France, Italy, Spain, and Portugal) providing reference for the pricing in Turkey have publicly available pharmacoeconomic guidelines. However, these four reference countries’ sets of guidelines differ in terms of some key features (Table 3). Notably, only the French guideline covers all the key features concerning perspective, comparator, use of randomized clinical trials (RCTs) and meta-analyses, discounting costs and effects, preferred outcome measures in terms of quality adjusted life years (QALYs), assessing utility and modeling (time horizon and model type) [27].

Italian, Spanish, and Portuguese guidelines all define four main methods of analysis - CMA, CEA, CUA, CBA - but only France additionally has the cost-consequence analysis [28]. Italy has a guidance on reimbursement and pricing dossier submissions, which may potentially not be labeled as a full set of PE guidelines [29]. Similarly, Spain has a recommendation guide within the scope of the economic evaluation of health technologies [30]. In Portugal’s PE guideline, which was published in 1998, the perspective of evaluation is stated as societal, and the comparator treatment should be the most used. The former is rather unique, the latter is grossly aligned with other countries. It defines the CMA, CEA, CBA, and CUA analysis as methodologies. It refers to “quality of life measurements” but a clear specification seems to lack [31]. The French guideline states that the economic evaluation should mimic real-world conditions as close as possible and define a collective perspective that covers all stakeholders in the health system [27]. Also, in the French guideline, it is required to include a systematic review of evidence. Preferred outcomes measures are defined as life years in CEA and QALYs in CUA, which is most precisely described in Spain’s PE guideline [30].

Recommendations for Turkish PE guidelines

Based on characteristics of Turkey’s reference countries’ health systems and PE guidelines, below we recommend a set of contemporary guidelines for Turkey. From the above, it flows that although there are common aspects of health systems and PE guidelines, there are also specific differences between countries. Yet, we can notice some common points in all guidelines. For example, the study perspective is commonly defined as a societal perspective. Since Turkey has a public health insurance for all citizens, next to this societal perspective, potentially also a governmental perspective could be taken into consideration when defining the perspective in the new guideline.

Comparison between interventions or choice of the comparator is at the heart of all PE studies and guidelines. Next to the evaluation of effectiveness, it is mostly needed to define a therapy in pharmacoeconomic terms. In such a manner, the most important question will be which therapy should be a comparator. Since we have a clear categorization between branded and generic medication in Turkey, the choice of the comparator will be based upon it. For branded medication which is the new therapy that enters Turkish market for the first time, the evaluation should be made in consideration with the existing standard therapy. On the other hand, since generic medications have more than one bioequivalent medication, the evaluations should be made concerning cost analysis or CMA.

While conducting the pharmacoeconomic evaluation, all consequences should be covered. Time horizon is one of the critical aspects for seeing all results and benefits of a treatment. Although it is hard to define a certain duration, it can be stated that it should cover all aspects of the treatment as defined in the reference countries’ guidelines as well as be long enough to cover all relevant costs, savings, and health gains.

The analytical technique is another key point of the evaluation, as it defines measurement tools and outcomes. All techniques have their own places in pharmacoeconomic evaluations and in this context all techniques should be welcomed. As it can be noticed, all techniques have the common word, which is “cost”. Thus, costs are one of the main aspects of the techniques and they should be clearly defined in an evaluation. Since the costs can affect the results significantly, all costs should be required and if there is any missing cost, justification should be given. Similarly, outcomes measurement reflects a relevant determinant as well as costs. Although measurements can be conducted with different tools, they should match with the analytical technique, as it defines the unit of measurement. QALY’s piece together the two dimensions of the health outcomes, the life years gained and the quality of life. Thus, the QALY’s should be the preferred base for the evaluation, with validated and reliable scoring tools underlying its measurement, such as EQ-5D questionnaires.

Discounting in costs and health benefits is still controversial, both among countries and scientists. According to Hacker et al., 3% is a standard discount rate in advanced economies. But also discount ratio at 4% and 5% have been used in upper-middle-income and lower-middle-income countries respectively [37]. As Turkey classifies as an upper-middle-income country by the World Bank, the 4% ratio should be considered [38]. Nevertheless, sensitivity analysis is required as it shows the robustness of the evaluation for the discount rate, inclusive differential discounting. Notably, sensitivity analysis is required for all relevant parameters.

Recommendations on key features of Turkish national PE guidelines are summarized in Table 4 as a synthesis of this comprehensive review.
Table 1
Synthesis of data obtained from included records.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title and Year of Publication</th>
<th>Country</th>
<th>Perspective</th>
<th>Comparator</th>
<th>Analysis Technique</th>
<th>Evidence Source</th>
<th>Outcome measure</th>
<th>Cost</th>
<th>Time Horizon</th>
<th>Discounting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irina Cleemput et al. [18]</td>
<td>Belgian Methodological Guidelines for Pharmacoeconomic Evaluations: Toward Standardization of Drug Reimbursement Requests (2009)</td>
<td>Belgium</td>
<td>Health-care sector and in the health gains for society</td>
<td>Prior treatment was proven effective. Also, multiple comparators can be applied if relevant</td>
<td>CEA, CUA, CMA, CBA</td>
<td>RCTs and models</td>
<td>Life years gained and QALYs</td>
<td>Direct and indirect costs</td>
<td>Depends on treatment but should be in accordance with the expected consequences and benefits from treatment</td>
<td>3%</td>
</tr>
<tr>
<td>Devidas Menon, et al. [19]</td>
<td>Canada’s New Guidelines for the Economic Evaluation of Pharmaceuticals (1996)</td>
<td>Canada</td>
<td>Societal</td>
<td>Existing treatment</td>
<td>CMA, CCA, CEA, CUA, CBA</td>
<td>All sources are accepted.</td>
<td>HRQOL, Quantity and quality outcomes</td>
<td>Direct and indirect costs</td>
<td>Should be made to extend all consequences</td>
<td>5%</td>
</tr>
<tr>
<td>Takeru Shiroiwa, et al. [20]</td>
<td>Development of an Official Guideline for the Economic Evaluation of Drugs/Medical Devices in Japan (2017)</td>
<td>Japan</td>
<td>Public healthcare payer’s perspective</td>
<td>Technology reimbursed by public health insurance, widely used in clinical practice and expected to be to a large extent</td>
<td>CEA, CUA</td>
<td>Systematic reviews</td>
<td>QALY</td>
<td>All costs including paid by public insurance, central and local governments, and patients; loss of productivity</td>
<td>Long enough to evaluate the new technology</td>
<td>2%</td>
</tr>
<tr>
<td>Livio Garattini, et al. [21]</td>
<td>Dutch guidelines for economic evaluation: ‘from good to better’ in theory but further away from pharmaceuticals in practice? (2017)</td>
<td>The Netherlands</td>
<td>Societal perspective</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Systematic reviews based on RCTs</td>
<td>ICER with life years gained and QALYs</td>
<td>Direct costs for patient and family, indirect costs</td>
<td>Lifetime. But if it is not relevant, justifications should be provided</td>
<td>4% for costs and 1.5% for future effects</td>
</tr>
<tr>
<td>SeungJin Bae, et al. [22]</td>
<td>Korean Guidelines for Pharmacoeconomic Evaluation (2013)</td>
<td>Korea</td>
<td>Limited societal perspective</td>
<td>Not specified</td>
<td>CUA, CCA, CBA, CMA</td>
<td>Systematic reviews</td>
<td>QALYs</td>
<td>Direct costs</td>
<td>Should be long enough to present all consequence</td>
<td>Not specified</td>
</tr>
<tr>
<td>Ewa Orlewska and Piotr Mierzejewski [23]</td>
<td>Project of Polish guidelines for conducting pharmacoeconomic evaluations in comparison to international health economic guidelines</td>
<td>Poland</td>
<td>Societal</td>
<td>The most commonly used treatment or the cheapest or most effective product based on case</td>
<td>CEA or CUA</td>
<td>RCTs</td>
<td>ICER</td>
<td>All relevant costs</td>
<td>Should cover all consequences</td>
<td>5%</td>
</tr>
</tbody>
</table>

CMA Cost Minimization Analysis, CEA Cost Effectiveness Analysis, CUA Cost Utility Analysis, CBA Cost Benefit Analysis, CCA Cost Consequence Analysis, QALY Quality Adjusted Life Years, HRQOL Health Related Quality of Life, ICER Incremental Cost Effectiveness Ratio RCT Randomized Clinical Trials
Discussion

Although there are various steps in implementations in healthcare systems, pricing and reimbursement are the key steps for a new therapy to be available on the market and providing access to patients. Reimbursement is the crucial step in whether patients can access therapies via the national health systems. Additionally, healthcare-costs are increasing since new and more expensive therapies are presented to the market. Because the costs of new medicines/drugs are higher than conventional medicines, non-optimal allocation of funds potentially leads to limited access to recent medicines [39]. Thus, all over the world, governments are trying to make policies more efficient with the aim of enhancing resource allocation, approving the most cost-effective treatments in such a limited budget. Next to governments, in such an environment the industry will also benefit when in planning the R&D activities early economic analysis is included [22].

External price referencing (EPR) concept is a common method to control the pharmaceutical prices which is a price regulation considering prices in other countries. This method mostly highlighted with its price-converging effect, but at the same time it also led to higher pharmaceutical prices considering other healthcare service-related costs in low-income countries. The industry tends to determine their marketing strategies based on the countries which provide higher prices [40]. In Turkey’s pharmaceutical pricing regulations, it is clearly stated that drug prices are determined as the lowest price in the reference countries in Euro currency. The exchange rate to Turkish Lira is fixed by the Turkish Medicines and Medical Devices Agency (TMMDA) and TMMDA announces the rate in the first 15 days of each year [8]. This system has a positive impact on the healthcare budget. But the industry is affected on the contrary. Consequently, the industry is facing currency risk and this risk leads to presumed inability for adequate returns of investment in new projects [41].

Pharmacoeconomic analysis can help to achieve fair prices, based on value-based assessments, both satisfying the industry and controlling the health-care budgets. All in all, recent developments in the pharmaceutical industry and introductions of advanced contemporary therapies have made pharmacoeconomic assessments a necessity [42].

In this study, we conducted a scoping review for pharmacoeconomic guidelines and, also reviewed the reimbursement guidelines in Turkey’s reference countries, in the absence of any comprehensive set of Turkish PE guidelines. It was seen that all the pharmacoeconomic guidelines mainly focused on general situations and draw a frame for the general issues rather than being very specific. Although there are complex issues related to end of life treatments, rare diseases and willingness-to-pay, we recommend as a starting point to create a PE guideline for the general framework as a basis for next steps. After the implementation and development of policies for general issues, these more specific issues could be taken into consideration efficiently. Also, budget impact analysis could be considered as a subject of another guidance, aligned with the PE guidelines [43]. Even though the existing procedure in Turkey defines the requirements for submission, it is not providing guidance on methodologies for evaluations.

In considering the differences among countries as well as the health systems, it is impossible to copy an existing guideline and expect to implement it efficiently. Hence, we considered it necessary to create a new set of rules to define the requirements and key points of pharmacoeconomic assessment specifically for Turkey. Notably, guidelines should optimally be aligned with the requirements of the Social Security Institutions in Turkey. Besides the alignment, the workforce and qualification of the labor force of the stakeholders should be noted as a key factor for implementation [44].

When pharmacoeconomic evaluations are taken up for new technologies, paving the way for effective resource allocations, the willingness-to-pay (WTP) threshold soon becomes an unavoidable debate. Recently, defining the WTP threshold nationally, as per the GDP per capita of the country, has been suggested [19]. Considering this WHO’s threshold for cost effectiveness, the interventions that cost less than three times national annual GDP/capita could be concluded as cost effective. If the intervention costs less than once national annual GDP/capita it could actually be concluded as highly cost-effective [45].

Conclusion

Although we expected to find abundant information on the other country’s guidelines, it appeared there was limited information on PE guidelines considering publications in English. Therefore, the suggested set of guidelines for Turkey could only be based on a limited number of publications from the scoping review. Such an integrated and aligned set of guidelines will enhance decision making on drug reimbursement and sets the scene for more effective health technology assessment and optimal allocation of health-care resources. Our recommendation for a set of guidelines can form the basis for further discussion and determine the final set for embedding in the Turkish regulatory procedure for reimbursement of drugs. Thus, the results of this study will pro-actively be shared with the relevant authorities. To achieve broad acceptance, all aspects of these recommendations should be discussed with experts and
Some key features from Turkey’s reference countries’ PE guidelines[11,27-29,32–35].

<table>
<thead>
<tr>
<th>Countries Guideline</th>
<th>France</th>
<th>Italy</th>
<th>Portugal</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose of the document</td>
<td>Provide methodological and reporting guidelines for PE evaluations</td>
<td>Provide information for pricing and reimbursement submission dossier</td>
<td>To form a frame for methodology and define the requirements that must be provided to decision-maker in the reimbursement process</td>
<td>Provide methodological and reporting guidelines for PE evaluations</td>
</tr>
<tr>
<td>Perspective</td>
<td>A collective perspective that covers all stakeholders in the health system and individuals who will be affected by the final decision</td>
<td>As a base, Italian National Health Service. If appropriate societal perspective also welcomed</td>
<td>Societal perspective, considering patients, families, and other parties</td>
<td>A societal perspective is recommended. It is also recommended to include the perspective of the other stakeholders and, National Health System (NHS) in the analysis. Societal and NHS perspectives should be presented separately</td>
</tr>
<tr>
<td>Choice of comparator</td>
<td>All interventions competing with the new therapy should be identified. The choice of comparator must be justified</td>
<td>Should be standard of care within the Italian healthcare setting (including most widely used therapies or national treatment strategies etc.)</td>
<td>The most common treatment, less expensive and most efficacious</td>
<td>Current health interventions with standard technology</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Long enough to reflect all outcomes</td>
<td>5, 10 years or lifetime</td>
<td>Depends on the duration of treatment and expected consequences</td>
<td>Should allow obtaining all relevant differences in costs and the effects of health treatments and resources</td>
</tr>
<tr>
<td>Preferred analytical technique</td>
<td>Anyone of CMA, CEA, CUA, CBA, and CCA</td>
<td>CEA, CUA</td>
<td>Any scientific recognized economic evaluation technique can be used such as CMA, CEA, CUA, CBA</td>
<td>Any of the four analysis methods (CMA, CEA, CBA, CUA)</td>
</tr>
<tr>
<td>Costs to be included</td>
<td>Depends on the study, all relevant costs should be presented but indirect cost should be reported separately</td>
<td>From a societal perspective, the human capital method should be used for indirect costs</td>
<td>All relevant costs should be identified</td>
<td>With the description of chosen perspective, the physical units of resources used should be considered separately. Other relevant costs could be included as per the perspective requirements</td>
</tr>
<tr>
<td>Modeling</td>
<td>Allowed, requires details</td>
<td>Allowed, requires details</td>
<td>Allowed, should present all aspects</td>
<td>Should serve the aim of the study, must be present in a clear and comprehensive manner</td>
</tr>
<tr>
<td>Preferred outcome measure</td>
<td>Outcomes like QALY, HRQL, etc.</td>
<td>Effects of intervention including a reduction in mortality, slow down of progression</td>
<td>If available effectiveness, if not then efficacy could be used</td>
<td>QALY, willingness to pay, and other relevant outcomes whichever possible</td>
</tr>
<tr>
<td>The preferred method to derive utility</td>
<td>Standard gamble or time-trade off</td>
<td>Standard gamble or time-trade off</td>
<td>For CUA value-based methods and contingent valuation method for CBA</td>
<td>Direct or indirect measurements including validated surveys, questionnaires, etc.</td>
</tr>
<tr>
<td>Discounting costs and outcomes</td>
<td>Social discount rates fixed at 4%, but if the time horizon less than 30 years with a reduction to up to 2%</td>
<td>An annual discount rate of 3% (between 0% and 5% in sensitivity analysis)</td>
<td>5% (0% and 5% can be applied to the sensitivity analysis)</td>
<td>An annual discount rate is 3% but in sensitivity analysis, 0% and 5 %?</td>
</tr>
<tr>
<td>Sensitivity analysis: parameters and range</td>
<td>Structural uncertainty, parameter uncertainty (such as related to measuring or sampling errors), or uncertainties related to basic methodological choices</td>
<td>Surrounding effectiveness, safety, use of resources, costs, and utility parameters</td>
<td>Key parameters with values that are subjected to uncertainty</td>
<td>Not specified</td>
</tr>
<tr>
<td>Sensitivity analysis: methods</td>
<td>Probabilistic sensitivity analysis, for justification of parameters univariate deterministic analysis, should be used</td>
<td>Univariate deterministic analysis with a tornado diagram</td>
<td>Not specified</td>
<td>Not specified but one way or multiway sensitivity analysis, threshold analysis could be used</td>
</tr>
<tr>
<td>Incremental analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Required</td>
<td>Yes</td>
</tr>
<tr>
<td>Portability of results (Generalizability)</td>
<td>When the economic evaluation study relies on international data or national data for a country other than France, the authors should demonstrate that these data may be transferred with sufficient plausibility to the French context</td>
<td>Studies must refer to the national context</td>
<td>Yes, the origin of the data used, and the hypotheses adopted should be specified</td>
<td>Transparency in methods, data, and results is essential to assess the validity of the analysis. It can also help healthcare agents generalize or transfer the elements of economic evaluation to new contexts</td>
</tr>
</tbody>
</table>

CMA Cost Minimization Analysis, CEA Cost Effectiveness Analysis, CUA Cost Utility Analysis, CBA Cost Benefit Analysis, CCA Cost Consequence Analysis, QALY Quality Adjusted Life Years, HRQOL Health Related Quality of Life

Committees including people from both the private sector, scientists working in the health economics area, public decision-makers, physicians, and pharmacists. Also, to enhance the professional know-how for all stakeholders, their knowledge should be improved for effective implementation of the guidelines.

**Funding**

No research funding is received from any institution for this study.

**Ethical approval**

Not required

**Patient consent**

Not required
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Table 4

<table>
<thead>
<tr>
<th>Recommendations on key features of Turkish national PE guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key features</strong></td>
</tr>
<tr>
<td>A collective perspective should be applied to cover impacts on the private sector, governmental bodies, and the national healthcare system, both within the societal and governmental perspective.</td>
</tr>
<tr>
<td>Basically, for generic medication, it should be based on the cost analysis or CMA. Brandied medication should be taken into consideration with proof of cost-effectiveness of new technology or treatment.</td>
</tr>
<tr>
<td>The time horizon must be determined as per the expected consequences and benefits. It must be adequate to cover all results of the interventions and justification on the decision for the time horizon should be provided in the dossier.</td>
</tr>
<tr>
<td>All techniques should be welcomed as their place in health economics is unquestionable. Yet, a preference could be stated for CUA with costs per QALY for comparative purposes.</td>
</tr>
<tr>
<td>Although it can be complex to include all costs, it is necessary to identify the costs since they play a vital role in the assessments. Thus, all costs, direct and indirect, must be included, both medical and non-medical. A valid argument should be presented if any cost could not be involved in the evaluation.</td>
</tr>
<tr>
<td>Measure tools could be used based on the preferred analytical technique. In particular, QALYs based on EQ-5D assessments. For clinical outcomes, hard endpoints are preferred, that allow correlation with quality of life.</td>
</tr>
<tr>
<td>Sensitivity analysis is required as it presents the robustness of results and identifies those variables those affect the results most.</td>
</tr>
<tr>
<td>Discounting should be determined and discussed while creating the new guidelines. Yet, equal discounting at 4% could be a starting point. It should be required to evaluate differential discounting in sensitivity analysis to show consequences in different situations.</td>
</tr>
</tbody>
</table>

Acknowledgements

Not applicable

Declaration of Competing Interest

None declared

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hjpt.2022.100682.

References

[31] Agenzia Italiana Del Farmaco. Guidance to applicants for the submission of pharmacoeconomic analyses within the pricing and reimbursement dossier. 2020; (July)1-20.


