GUIDELINES FOR PHARMACOECONOMIC EVALUATION FOR SERBIA

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INTRODUCTION: Facing rising costs for medicines, national health insurance funds all over the world are looking for a way to prioritize the allocation of available resources to ensure the highest possible level of health to the population they serve. Pharmaco economists had long argued that all decisions about the use of public funds should be based on careful evaluation of both the effects of intervention and on its costs, in order to choose between competitive therapeutic options. Economic evaluations are tools that health economists use to assess effectiveness of therapeutic interventions. The need for the first guidelines for pharmacoeconomic evaluation in Serbia emerged as a result of permanent changes in the Serbian health system and in the world.

The guidelines are primarily intended for those who conduct pharmacoeconomic studies, Serbian decision makers and policy makers who are responsible for funding decisions regarding medicines (professionals from the Republic Institute for Health Insurance, from Ministry of Health, Health technology assessors). In addition, guidelines are intended for academics, scientific researchers in the field of pharmacoeconomics, health care professionals and associates who participate in the processes of managing the systems, subsystems, segments of health care, experts from the pharmaceutical industry (health economics & market access, marketing & sales departments), pharmacists from hospital and public pharmacies, patient groups, as well as those who are interested in the field of pharmacoeconomics.

OBJECTIVE: To provide methodological and reporting guidelines for pharmacoeconomic evaluation (PE) for Serbia.

- To assist the “doers” of economic evaluations (EE) to produce economic information that is relevant and useful to decision makers in Serbian health care system
- To explain the principles of good practice in the development of PE evaluation
- To provide sets of standards for the conduct and reporting of high quality EEs that can be reviewed and compared by decision makers

METHODS: A group of researchers specialized in economic evaluation of medicines developed the PE guidelines, following the initiative of other countries in this framework, to provide recommendations for the standardization of methodology applicable to economic evaluation of medicines in Serbia. The guidelines were written in accordance with the best European and international guidelines, with respect to the existing legislation in Serbia. Guidelines are based on a “reference case” (RC) which includes set of preferred methods which analysts should follow when conducting PE for each

component of the economic evaluation. Additional analyses, apart from RC, are also allowed but they have to be separated and differentiated from the RC analysis. Pharmacoeconomists and healthcare decision makers have to assess both RC and additional analyses.

RESULTS:

Components of PE evaluations	**Reference case**
Study question	The question should be well defined, stated in an answerable form, and relevant to the decision that should be taken. Define the patients or population, intervention, comparators and outcomes (PICO) relevant to the study question.
Literature review	Each pharmacoeconomic evaluation should consist of systematic review of available up-to-date clinical and economic studies on the studied medicine following the guidelines of the Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/report4.htm for clinical reviews, http://www.york.ac.uk/inst/crd/report6.htm for economic reviews). The review should moreover contain the search strategy, study selection criteria and procedures followed for selecting studies, study quality assessment, data extraction sheets, and a synthesis of the evidence found. The methodology used for the literature search should be clear and reproducible. The review should reveal the up-to date evidence for clinical effectiveness of the product and its cost-effectiveness relative to its comparator(s). The evidence should be critically appraised, its quality assessed and data presented in data extraction sheets. A clear and concise synthesis, substantiated with references, should be provided. Ongoing studies should be mentioned.
Perspective of the evaluation	The reference case analysis should only include direct health care costs from the perspective of the health care payer. This includes payments out of the government's health care budget as well as patients' co-payments. Health outcomes should be measured in patients but valued from a societal perspective.
Target population	The study question should specify the target population(s) for the intervention and its expected use. Relevant subgroups need to be defined. If the implications of the drug on the effectiveness and/or costs differ between subgroups, separate subgroup analyses should be performed, provided that appropriate (statistical) justification for subgroup analysis is provided. Post-hoc subgroup analyses are only allowed if the costs between the subgroups are proven to be different based on appropriate statistical analyses. Relative effectiveness should be assumed equal across subgroups in this case.

<table>
<tr><td></td><td>Epidemiological data for Serbia should be presented if available for both the entire target population and the relevant subgroups.</td></tr>
<tr><td>Comparator</td><td>The drug should be compared with the most relevant alternative treatment for the proposed indication of the drug.

The most relevant alternative treatment is either the treatment that is most likely to be replaced by the new treatment or, in case of add-on treatments, the current treatment without the add-on product. If this treatment cannot be identified, the recommended treatment according to the Serbian clinical guidelines should be used as a comparator. In some cases, multiple treatments will have to be included as comparator.</td></tr>
<tr><td>Analytic technique</td><td>Cost-effectiveness analysis (CEA) should be used if improving life expectancy is the main objective of the treatment and also the most important outcome from the patient point of view or if there is a clearly identified dominant clinical outcome parameter that is relevant to the patient and there are no other patient relevant outcome parameters expressed in different units.

Cost-utility analysis (CUA) should be used if the treatment has an impact on health-related quality of life that is significant to the patient or if there are multiple patient-relevant clinical outcome parameters expressed in different units.
Results should be expressed as incremental cost-effectiveness (ICER) or cost-utility ratios (ICUR) with their associated distribution.</td></tr>
<tr><td>Study design</td><td>Pharmaconomic evaluations should be based as much as possible on data from head-to-head comparisons between the study product and the comparator (RCTs and non-interventional studies). Modeling should be applied if there are insufficient data from available literature for economic evaluations.</td></tr>
<tr><td>Calculation of costs</td><td>The identification, measurement and valuation of costs should be consistent with the perspective of the health care payer.
Non-health care costs or unrelated health care costs should not be included in the reference case analysis.
Validated sources should be used for the unit costs (In table bellow are relevant institutions and internet web sites where can be found data for pharmacoeconomic evaluations in Serbia).

<table>
<tr><th>Institution</th><th>Internet web site</th></tr>
<tr><td>Republic Institute for Health Insurance</td><td>www.rzzo.rs</td></tr>
<tr><td>Ministry of health Republic of Serbia</td><td>www.zdravlje.gov.rs</td></tr>
<tr><td>Medicines and Medical Devices Agency of Serbia</td><td>www.alims.gov.rs</td></tr>
<tr><td>Institut of Public Health Serbia „Dr Milan Jovanović Batut“</td><td>www.batut.org.rs</td></tr>
<tr><td>Statistical Office of Republic of Serbia</td><td>www.stat.gov.rs</td></tr>
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	Ministry of Finance of Republic of Serbia	www.mfin.gov.rs
	National Bank of Serbia	www.nbs.rs
Valuation of outcomes	Outcomes should be expressed in terms of final endpoints instead of intermediary outcomes. CEA: LYG for chronic conditions or acute conditions with long-term sequelae or a relevant short-term outcome in case of acute conditions without long-term sequelae. CUA: QALYs, with quality of life weights based on empirical data obtained with a generic quality of life instrument for which public preference values exist. For EQ-5D description, values from general population are available na web-site www.economicsnetwork.ac.uk/health/EQ_5D_index_calculator.xls. Use values of Slovenian idexes is recommended, if EQ-5D is used.	
Time horizon	Lifetime for chronic conditions or acute conditions with long term sequelae or duration of the treatment or disease and its consequences for acute conditions without long term sequelae.	
Modelling	Modelling should be applied if the available data are insufficient to allow a full assessment of the cost-effectiveness or cost-utility of a product. Models should be based as much as possible on data from clinical studies comparing the study medication and the comparator, data from validated databases and/or data from literature. Guidelines for good modelling practices, developed by the modelling task force of ISPOR, ought to be followed whenever a model is built. A justification for modelling should always be provided and the structural hypotheses, assumptions and sources of information should be presented in a clear and transparent way. Model inputs and outputs should be consistent with existing data and have face validity.	
Handling uncertainty	The uncertainty surrounding the cost-effectiveness/cost utility estimates should be analysed using appropriate statistical techniques. Interval estimates should be presented for each uncertain parameter in the economic evaluation. The different aspects of uncertainty in the evaluation should be addressed, including methodological uncertainty and data uncertainty. For models, probabilistic sensitivity analyses should be presented. A cost-effectiveness plane and cost-effectiveness acceptability curve or –for dominant interventions - the net monetary benefit function, should be presented. A Tornado diagram should show the most important contributors to the variability of the estimated incremental cost-effectiveness/cost-utility ratio.	
Discount rate	Future costs should be discounted at a rate of 3%; future benefits at a rate of 1.5%.	

CONCLUSION: First Serbian PE guidelines were developed as results of changes in Serbian health system and the need for better and more complete economic information by decision makers. By providing standards for conducting and reporting of economic evaluations, guidelines can address current needs and requests of Serbian health care system, will be of great help decision makers and enable more optimal use of health care resources.

REFERENCES

Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. 3rd edition. Oxford: Oxford University Press, 2005.

http://www.ispor.org/PEguidelines/index.asp

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