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METHODOLOGICAL BASICS OF ANALYSIS OF "COST-EFFECTIVENESS"

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Summary: *The paper presents the basic methodology for the conduct of analysis of «cost-effectiveness» and incremental analysis of «cost-effectiveness». Among other aspects, the mathematical apparatus of these species of pharmacoeconomic analysis is discussed, their semantic content is described. In the scopes of the paper we focus on the order of these types of analysis, with a brief description of each stage and its features. In particular, the requirements of the selection of compared alternatives are illustrated, as well as the importance of the selection of effectiveness criterion and types of accounted costs are stressed. The approach toward the results in the frames of each considered types of pharmacoeconomic analysis is described in details. In conclusion, a detailed graphic of the algorithm on the described types of the analysis is illustrated.*

Keywords: *Pharmacoeconomics, cost-effectiveness/efficacy, methodology of pharmacoeconomic analysis, incremental cost-effectiveness ratio, threshold of willingness-to-pay, interpretation of results of the (incremental) "cost-effectiveness" analysis, decision-making in the health system*

The cost-effectiveness/efficacy analysis along with the "budget impact" analysis is considered as one of the most commonly used methods in pharmacoeconomic studies. Preconditions determining such a widespread of the considered method in pharmacoeconomic analysis are based on a range of factors. In the line of the budget deficit in the health care system, which obtains higher importance, the assortment availability of the health technologies, including innovative, high-performance and high-cost technologies, is increased. Hereby, the health managers, following the overall aim of providing the population with the best medical assistance, are obliged to select optimal technologies which correspond to the specific conditions of the exact health care system both in terms of clinical efficacy and based on the economic availability criterion.

In regards to budget restrictions of the health care system and market economy conditions, the unit cost of achievable effect or unit price per unit of effectiveness of the technology, compared to alternatives, is seen as the most important criterion in the health technology selection among the alternative solutions. The comparison of the unit prices of efficacy of alternative technologies is a subject of the pharmacoeconomic analysis of "cost-effectiveness". Actually, the analysis of "cost-effectiveness" is a fundamental principal of pharmacoeconomics: the move from the treatment price to the treatment result.

The authors suggest the following definition of the term of "cost-effectiveness" analysis: the "cost-effectiveness/efficacy" analysis is a pharmacoeconomic method allowing to determine the optimal health technologies based on the criterion of achievability of the settled therapy aims (diagnostics, prevention, rehabilitation) through the comparison of the evaluations of the results and costs for two and more health technologies, the efficacy of which is different, but results are measured by the same units.

According to the abovementioned definition, the mathematic interpretation of the "cost-effectiveness" analysis will be the equality or inequality of the cost relations, having monetary value, and the clinical effectiveness, presenting the meaning of the selected efficacy criterion of the compared health technologies [1].

$$CER = \frac{Cost}{Ef}, \text{ where:} \qquad \text{Formula (1)}$$

CER – coefficient of "cost-effectiveness" of technology;
Cost – costs associated with technology in terms of money;
Ef – clinical effectiveness of technology, expressed in appropriate units.

$$CER_1 = \frac{Cost(1)}{Ef(1)} \begin{matrix} > \\ = \\ < \end{matrix} CER_2 = \frac{Cost(2)}{Ef(2)} \begin{matrix} > \\ = \\ < \end{matrix} \cdots \begin{matrix} > \\ = \\ < \end{matrix} CER_n = \frac{Cost(n)}{Ef(n)}, \text{ where:} \qquad \text{Formula (2)}$$

CER1, CER2, CERn – coefficients of «cost-effectiveness» of the compared alternative technologies;
Cost(1), Cost(2), Cost(n) – costs associated with comparing alternative technologies;
Ef(1), Ef(2), Ef(n) – efficacy provided by comparing alternative technologies and expressed in the same units.

In the scopes of pharmacoeconomic studies, it is often appropriate not only to determine the coefficients of "cost-effectiveness", reflecting the unit cost on the effectiveness of the studied health technologies, but also to calculate of the cost of an additional unit of effectiveness in a more efficient technology.

To achieve the settled objectives, the incremental analysis of "cost-effectiveness/efficacy" is designed. The results of the incremental analysis of "cost-effectiveness/efficacy" are presented through the corresponding coefficient: the incremental analysis of "cost-effectiveness/efficacy" defines the ratio of difference of costs for 2 compared alternative technologies in regards to the difference of their efficiency. Thus, it's worth mentioning that the incremental analysis of "cost-effectiveness/efficacy" can evaluate the technology only in pairs, while the analysis of the "cost-effectiveness" can simultaneously consider more than two technologies. See the formula for calculating the incremental ratio of "cost-effectiveness" below:

$$ICER = (Cost(1)-Cost(2))/(Ef(1)-Ef(2)), \text{ where:} \qquad \text{Formula (3)}$$

Cost(1), Cost(2) – costs associated with compared alternative technologies;
Ef(1), Ef(2) – efficiency provided by comparing alternative technologies and expressed in the same units.

The methods of pharmacoeconomics are considered as highly specialized tools designed to reach specific objectives and terms. The analysis of "cost-effectiveness" is used in terms of necessity of selection of the best technology for the exact health care system among several potentially available health technologies. The criterion of optimality considerers the cost of effectiveness of the determined technology. The proof for the use of the incremental "cost-effectiveness" analysis is grounded in the necessity to identify the results of "cost-effectiveness" analysis, which can be applied when the technology with the best clinical effectiveness is characterized with the higher coefficient of "costs-effectiveness" in comparison to less higher technology of clinical effectiveness.

According to the abovementioned formulas, it's obvious that the analysis of "cost-effectiveness" and the incremental analysis of "cost-effectiveness" use the results of the prior analysis of efficacy and costs with the aim to define the unit costs of effectiveness or unit costs of effectiveness with additional units presented by the compared technologies. In this line, the methodology of the "cost-effectiveness" and incremental "cost-effectiveness" analysis can be described by the following structure (figure 1).

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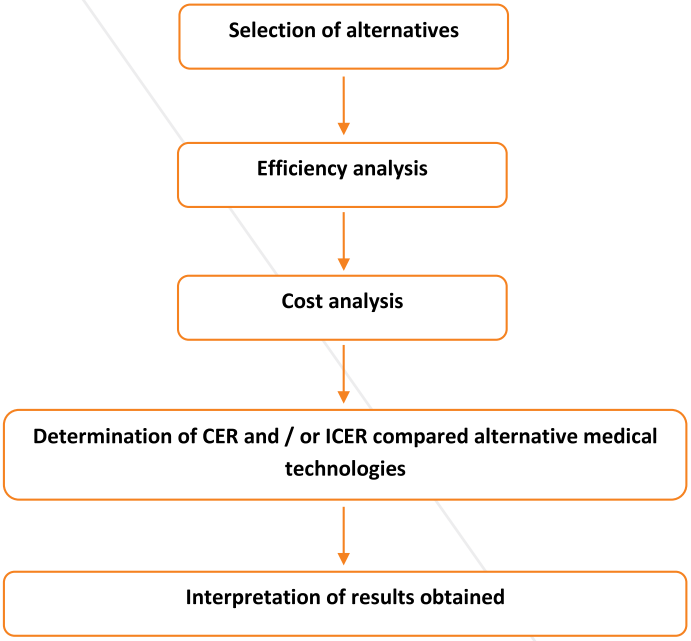
Figure 1. Stages of the analysis of «cost-effectiveness» and incremental analysis of «cost-effectiveness»



The selection of alternatives is prior to the implementation of the described types of pharmacoeconomic analysis. Taking into account the comparative approach, grounded on the discussed pharmacoeconomic analyses, the appropriateness of alternative selection procedures has a significant impact on the results of the "cost-effectiveness" analysis and incremental analysis of "cost-effectiveness" [5,6]. The best alternatives for a comparison of the discussed health technologies are the following (in decreasing order):

1. the golden standard of technology in the exact field of medicine;
2. the routine practice in the exact field of medicine;
3. the technologies, according to treatment protocols, guidelines and standards;
4. in the absence of the abovementioned alternatives - best supportive care or historical controls.

In accordance with the algorithm, the first and immediate stage of the analysis of "cost-effectiveness" or incremental "cost-effectiveness" analysis is the efficacy analysis. The counting of the costs is concluded based on the results of the efficacy analysis. After considering the costs and effectiveness of health technologies, the corresponding coefficients are counted, and further their interpretation follows.
The analysis of "cost-effectiveness" like the incremental analysis of "cost-effectiveness" along with its available mathematic apparatus is characterized by a range of restrictions and assumptions to be necessarily considered in order to obtain appropriate data. The above mentioned will be presented in this paper by the authors.

Peculiarities of conducting the incremental analysis of "cost-effectiveness" on the stage of efficacy analysis

In the beginning of the article it's presented the English transcription of the term of "cost-effectiveness/efficacy" analysis. It was described by the two phrases:

1. cost-effectiveness analysis;
2. cost-efficacy analysis.

In Russian translations both terms have the same meaning, at the same time in the pharmacoeconomic context the words "effectiveness" and
"efficacy" have different meanings, which is important to highlight in this article to avoid the misunderstandings when reading English texts.
In Russian the words "effectiveness" and "efficacy" correspond to the meaning of the word effectiveness (clinical), but in English the word "effectiveness" reflects the effectiveness in real practice, and term "efficacy" is related to the effectiveness in clinical studies. So, the existence of the two terms mirrors the two competitive approaches in regards to the evaluation of effectiveness: according to the first approach, the data on effectiveness obtained through practice is more valuable; the second approach, currently the dominant one, focuses on the significance of the obtained data through the clinical studies. The advantage of the first approach can be concluded in the fact that the obtained data illustrates the real effectiveness of a technology, non in the "ideal" conditions of clinical studies. The advantage of the second approach relates to the high standardization and statistic significance of the data in terms of minimization of backside factors (for example, characteristics of population and compliance of patients) over the results of the effectiveness evaluation [8].
In terms of the "cost-effectiveness" analysis, it's more than important to choose appropriately the criterion of effectiveness taking into consideration the characteristics of the studied nosology, especially in such cases when the data on surrogate endpoints is the only available one. Taking into account the fact, that the result of the analysis of "cost-effectiveness" analysis or incremental "cost-effectiveness" analysis is the cost effectiveness per unit, respectively, or cost of additional efficacy unit, it seems clear that these costs should reflect the cost for the target achievements in the current nosology.
The use of hard endpoints as effectiveness criteria (life years gained) in the analysis of "cost-effectiveness", and in terms of their data availability for the experimental technology, is characterized by the highest degree of credibility. The incremental analysis of "cost-effectiveness" based on criterion LYG allows not only to determine the value of the life years gained in a more efficient technology, but also provides an opportunity to carry out an independent assessment in the analysis of the threshold of "willingness-to-pay".
Also, during the (incremental) analysis of "cost-effectiveness", the time horizon is necessary to correlate data based on their effectiveness and cost. In this case, the determining factor in determining the time horizon of the analysis of "cost-effectiveness" is the time horizon, which characterizes the performance data. So, if the value of the criterion of efficacy was obtained by the results of a two-year observation of patients, the costs should also be established for the biennium. The change in the time horizon of the (incremental) analysis of "cost-effectiveness" under these circumstances, as in the direction of reducing it, for example, to a year, and in the direction of its increase, for example, up to 5 years, will be incorrect. If the time horizon of pharmacoeconomic studies extends one year, the discounting of results of the (incremental) analysis of the "cost-effectiveness" should be carried out [4,5].
A particular attention in the implementation of the (incremental) analysis of "cost-effectiveness" analysis stage should be given to the effectiveness of the method of expression values of the criterion of efficacy, since they have a different focus on the presentation of results. For example, in practice, results of clinical trials are presented in the following forms:

- the risk ratio;
- the odds ratio.

*Relative risk or hazard ratio (**Risk Ratio**)* is defined as the risk of occurrence of the outcome in a group of application of this technology to the risk of occurrence of the outcome in the control group. The risk of occurrence/non-occurrence of the outcome is the ratio of the number of trials as a result of which outcome was the total number of trials for this group.

*The odds ratio (**Odds Ratio**)* - is the ratio of the chances of the outcome in a group of this technology (the impact of this factor) to the chance of occurrence of the outcome in the control group. In this case, "by chance" means the ratio of the number of trials in which the outcome was due to the number of trials, in result of which the outcome was not observed.

From these definitions it follows that it would be incorrect to compare the two technologies, where the effectiveness of the one is expressed in the form of relative risk, and the other - in the form of odds ratios. In this regard, it is necessary to take into account that the values of the effectiveness criterion for all compared alternative technologies in the (incremental) analysis of «cost-effectiveness» should be expressed in a uniform way.

Peculiarities of (incremental) analysis of the «cost-effectiveness» at the stage of the analysis of costs

The character of the accounted costs - direct medical, direct nonmedical, indirect, - obviously, has no effect on the calculation during the (incremental) analysis of "cost-effectiveness" and is determined at the time of the study design, based on the point of view of the payer and the level of the health system. However, while studying the methodology of the analysis of «cost-effectiveness», a significant impact factor of fixed costs (compared to all health technologies) is revealed in terms of calculating the ratio of "cost-effectiveness". At the same time, the greater is the share of fixed costs in the total expenditure under the above

technologies, the greater degree of impact has their account over the coefficient of "cost-effectiveness".
A vivid illustration, revealing the abovementioned impact, can be considered the analysis of "cost-effectiveness" of medications used in nephrology practice in patients with end-stage renal disease (IV-V stage of chronic kidney disease). In the example of the Figure 2 is placed a graph showing the ratio of costs (annual rate) and efficacy (i.e., actually the coefficients of "cost-effectiveness") for the two medicines, A and B, excluding the cost of renal replacement therapy (RRT) and the costs for it. The following figure graphically clearly reflected the change as for the coefficients of "cost-effectiveness" themselves and the difference between the coefficients, characterizing the proposed A and B formulations, when included in the calculation of the cost of renal replacement therapy (costs of renal replacement therapy greatly exceed the cost of medicines A and B, because the renal replacement therapy, in fact, is the most expensive part of the treatment of patients with end-stage renal failure).

The final decision on the inclusion (or exclusion) of fixed costs into (from) the analysis of "cost-effectiveness" should be based on a given design and pharmacoeconomic study's focus: keeping fixed costs in the analysis of "cost-effectiveness" implies a broader and more comprehensive view on the studied problem, while exclusion of fixed costs from the analysis can more accurately determine the effects of the studied specific health technologies.
However, it should be noted that the results of an incremental analysis of the "cost-effectiveness" are not affected by the fixed costs: during the calculation of the incremental ratio of "cost-effectiveness" the fixed costs are offset by the step of determining the difference between the cost of the two technologies under consideration [2,3].

Restrictions during the (incremental) analysis of «cost-effectiveness»

Based on the mathematical definition of the coefficients of "cost-effectiveness" and incremental ratio of "cost-effectiveness", the value of the efficacy criterion (or the difference between the values of the effectiveness criteria in the case of incremental coefficient) can not be zero, because the latter is in the denominator terms of costs and efficacy. The above limitation in some cases makes impossible to conduct one of the species of the analysis.

$$CER = \frac{Cost}{Ef}, \text{Ef} \neq 0 \qquad \text{Formula (4)}$$

$$ICER = \frac{Cost(1)-Cost(2)}{Ef(1)-Ef(2)}, (\text{Ef(1)-Ef(2)}) \neq 0 \qquad \text{Formula (5)}$$

With regard to the analysis of incremental "cost-effectiveness" there is an additional limitation. Incremental coefficient of "cost-effectiveness", representing the ratio of the differences of costs and efficiencies can take negative values (when one of the compared alternative health technology requires less costs and provides better clinical efficacy). Given the logical sense of the incremental ratio of "cost-effectiveness", which represents the cost of an additional unit of effectiveness in a more efficient technology, it becomes obvious that, if the incremental coefficient obtains negative value, it will lose its meaning, since the value can not be negative. From the above, it follows that in a situation in which one of the two comparable health technologies are characterized by higher efficacy parameter and is accompanied by a lower cost than the other, the incremental analysis of "cost-effectiveness" is not performed.

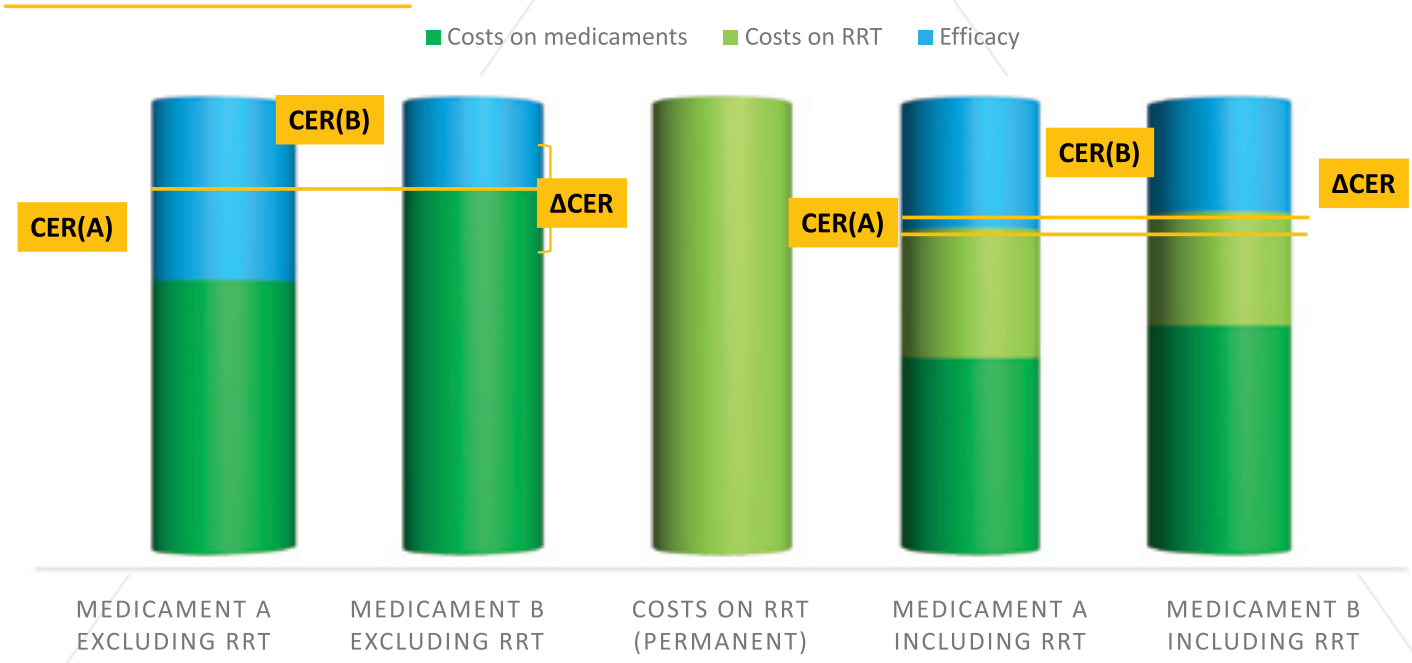
$$ICER \geq 0 \qquad \text{Formula (6)}$$

Interpretation of results of the (incremental) analysis of the «cost-effectiveness»

The stage of interpretation of the data obtained during the ongoing (incremental) analysis of "cost-effectiveness" is no less important in a pharmacoeconomic study than the anterior stages of analysis of effectiveness and costs. The Importance of interpreting data of the (incremental) analysis of "cost-effectiveness" is based on the fact that it is formed during the conclusion drawn by the pharmacoeconomic evaluation, which is used by consumers in this information product for management decisions.
Taking into account the fields, where the results of pharmacoeconomic studies are used, mainly the field of decision-making in the health sector, the formalization and uniformity forms, provided to health professionals over the conclusions of pharmacoeconomic studies (conducted, including method (incremental) analysis of the «cost-effectiveness»), obtain specific significances. The said formalization and development of universally recognized single species of pharmacoeconomic findings can facilitate the process of using applied pharmacoeconomics by appropriate professional in decision-making and improve its quality, reducing the likelihood of discrepancies when considering different pharmacoeconomic studies. In this regard, the authors, based on the recommendations of the International Society for Pharmacoeconomics ISPOR [8] adapted to Russian conditions, developed a standard report on the results of the (incremental) analysis of "cost-effectiveness". From the standpoint of the analysis of "cost-effectiveness" of health technology, the following can be recognized:

- "***strongly preferred***" or "***dominant***" in the case, if it has a better efficacy and a lower value of coefficient "cost-effectiveness";
- "***profitable***", when the technology, providing better performance, is characterized by a high coefficient of "cost-effectiveness" and has the coefficient of incremental "cost-effectiveness", expressing the value of one gained year of life, not exceeding a value of 1 per capita GDP;

Figure 2: The example of the impact of fixed costs in the analysis of «cost-effectiveness»



- "***cost-effective***", when the technology, providing better performance, is characterized by a high coefficient of "cost-effectiveness" and has a coefficient of incremental "cost-effectiveness", expressing the value of one gained year of life, is not greater than the value adopted in the country threshold value of "willingness-to-pay";
- "***marginally acceptable***", when the technology, providing better performance, is characterized by a high coefficient of "cost-effectiveness" and has a coefficient of incremental "cost-effectiveness", expressing the value of one gained year of life, and is characterized by a value within the borders of the interval from one up to two threshold values of "willingness-to-pay";
- "***ineffective***" or "***unacceptable***", if the technology has a greater coefficient value of "cost-effectiveness" in the case of lower therapeutic efficacy, or if its incremental coefficient of "cost-effectiveness" exceeds more than twice the threshold of "willingness-to-pay" in the conditions adopted in this health system.

These conclusions, expressing the final result of the pharmacoeconomic evaluation studied by the method of the (incremental) analysis of "cost-effectiveness" of technologies, may be supplemented depending on the specific characteristics of pharmacoeconomic work by other interpretations that distinguish these or other options considered from the standpoint of the selected technology analysis. Thus, in the case of evaluating technologies for reducing the number of the surrogate point over hospitalizations, besides the formal conclusion of the dominance or "cost-effective" character of one of the technologies based on the calculated coefficients of "cost-effectiveness", it seems informative to compare the values of these coefficients that reflect the cost of preventing hospitalization by the appropriate technology to the hardware costs of hospitalization.

Illustrating and summarizing the information contained in this article, we propose the following algorithm of the analyses of "cost-effectiveness" and incremental analysis of «cost-effectiveness» (Figure 3).

Considering the analysis of «cost-effectiveness» from a position of its results in decision-making in the health system, we should note some of the limitations that characterize this method. The main limitation is the fact that the analysis of «cost-effectiveness» in its assessment uses only one criterion of efficacy and reflects the cost of achieving it, leaving the behind the framework of the method the following aspects of the health technology use:

- the amount of funds needed for the implementation of this technology;
- the ethical and social aspects.

The recent one, for example, gains the paramount importance in making decisions about providing care for patients with orphan diseases. Thus, it is recommended to use the (incremental) analysis of «cost-effectiveness» in combination with other methods of pharmacoeconomic analysis and enhanced information support for decision-makers, in particular, in the assessment of health technologies [7], an important element of which is the analysis of «cost-effectiveness».

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Figure 3. Algorithm on "cost-effectiveness" analysis and incremental analysis of "cost-effectiveness"