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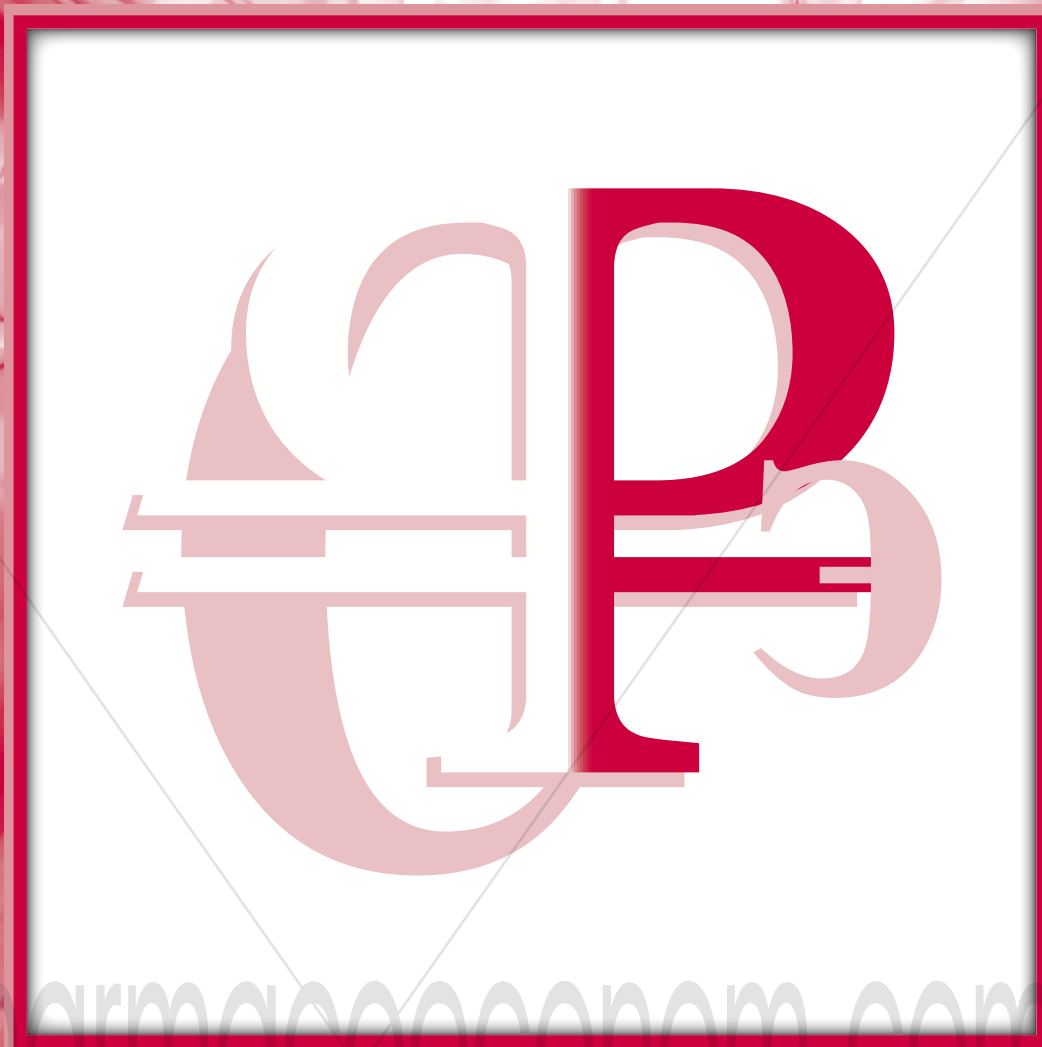
- ☐ КРИТЕРИИ ЭФФЕКТИВНОСТИ В ФАРМАКОЭКОНОМИЧЕСКОМ АНАЛИЗЕ

- ☐ РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

CRITERIA OF EFFICIENCY IN PHARMACOECONOMIC ANALYSIS

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Abstract: *The article aims to review issues of choice of drugs clinical effectiveness evaluation during pharmacoeconomic studies. It also includes effectiveness criteria classification in pharmacoeconomics. Special attention is paid to the description of the effectiveness criteria using both duration and quality of life: description of their methodological basis, advantages and limitations. The authors provide recommendations for the choice of effectiveness criteria, depending on pharmacoeconomic analysis method; the target audience for results of pharmacoeconomic analysis, and the characteristics of nosology.*

Keywords: *pharmacoeconomic analysis; effectiveness criteria; final endpoints; surrogate endpoints; «cost-effectiveness» analysis; «budget impact analysis»; QALY; DALY; LYG; overall survival.*

According to the essential principle of pharmacoeconomic analysis, which is transition from the treatment cost to the cost for treatment outcome, this pharmacoeconomic evaluation estimates the effectiveness of the drug.

At the same time, there is a need to determine effective evaluation of drugs in pharmacoeconomic analysis. The correct solution of the problem determines the adequacy of pharmacoeconomic studies. In the pharmacoeconomic analysis, any expression of the drug effectiveness is named the criteria of effectiveness or points (similar to the assessment of effectiveness in clinical trials).

Effectiveness criterion is an indicator that allows numerically expression the degree of potential benefit or harm from the use of medical technology [1-5. 15].

Classification of the effectiveness criteria in pharmacoeconomic analysis

Classification of the effectiveness criteria in pharmacoeconomics is made for convenience of choosing. Table 1 presents this classification of effectiveness criteria, and they are to be divided into surrogate endpoints and final endpoints.

> Surrogate endpoint is a measure of outcomes, used for indirect qualitative assessment of the effectiveness of medical intervention (diagnostic, therapeutic, or other) expressing biomarkers or the risk of significant events.

> Final endpoint is a measure of outcomes used in direct evaluation process of medical intervention (diagnostic, therapeutic, or other) based on the measurement of longevity and quality of life.

Each of these groups is divided into two subgroups (table 1).

The group of surrogate endpoints can be divided in subgroups of direct clinical effects (I) and mediated surrogate endpoints (II). Direct clinical effects include any indicators of life activity(biomarkers), used for evaluation of drug effectiveness(the level of glycosylated haemoglobin (HbA1C), prostate-specific antigen (PSA), calcium-phosphorus value (CaxP), blood pressure (BP), etc.). Examples of surrogate endpoints in subgroup (II) might include indicators of morbidity, disablement, etc. [1-4] (table 1).

Final endpoints group has subgroup (III) which indicates the longevity of patients. The subgroup includes indicators such as overall survival, median survival, survival without progression, survival rate, life years gained [4.9 -15].

The definitions of each of these final endpoints, characterizing the life expectancy of patients are presented below:

Overall survival (OS) is the period between diagnosis/treatment/inclusion in clinical trials, during which patients remain alive.

Median survival is the period of time from diagnosis/treatment/inclusion in clinical trials, during which 50% of patients remained alive.

Progression free survival (PFS) is the period of time from diagnosis/treatment/inclusion in clinical trials, during which the condition of the patients is not deteriorating.

Survival rate - percentage of people in a study who remain alive for a certain period of time.

The number of extended life years (life years gained, LYG) is the difference in life expectancy between two compared groups of patients [6].

Effectiveness criteria for evaluating duration and quality of life

Another subgroup (IV) of final endpoints includes indicators characterizing life expectancy and quality of life. This subgroup indicator example are quality

Table 1. Classification of the effectiveness criteria in pharmacoeconomics analysis

Effectiveness criteria type	Surrogate endpoints		Final endpoints	
Subgroups	(I)	(II)	(III)	(IV)
Description	Direct clinical effects	Mediated surrogate endpoints	Characteristic of survival	Characteristic of survival and quality of life
Example	HbA1C, PSA, CaxP	Morbidity, disablement	LYG, OS, FPS, median overall survival	DALY, QALY, HYE, HLY

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11

adjusted life year (QALY)[1], healthy life year (HLY), health year equivalent (HYE), disability adjusted life year (DALY).

Although the meaning of surrogate endpoints and final endpoints, that characterise life expectancy is intuitive and requires no detailed explanation, the variety of endpoints, characterizing both the duration and quality of life requires further consideration.

Understanding of the fact that for patients the quality of life itself has the same weight as life expectancy became a prerequisite for formulating a IV subgroup criteria for evaluation of drug effectiveness. This approach can be explained with increasing possibilities of pharmacotherapy in conjunction with a dramatic increase of the cost and in fact, pharmacoeconomic analysis began to be used as a decision support tool in healthcare. Paradigm shift in decision-making, as stated above, moved from the price for treatment to the price for treatment outcome, attaches the highest importance of the outcome determined by price. Subgroup IV of effectiveness criteria is a special type of drug efficiency evaluation, with **the highest degree of credibility in pharmacoeconomic analysis**. Complex indicators in drug efficiency evaluation that take into consideration both longevity change and quality of life allowed to quantify and differentiate possible changes in the patient's condition, such as increase in life expectancy in a vegetative state, and the extension of full active life. On the other hand, effectiveness criteria of subgroup IV are **currently the universal indicators** for assessing the effectiveness of medicines. The first subgroup of surrogate endpoints, including various biomarkers, is entirely specific for a particular disease and drug, the second subgroup of surrogate endpoints also reflects the probability of occurrence or non-occurrence of a variety of important conditions for this disease. The group of final endpoints that take into account life expectancy, is relevant to diseases with a pronounced effect on survival rates. At the same time effectiveness criteria in subgroup III in case of ophthalmologic diseases is likely to be inadequate, because of the low fatality of ophthalmologic diseases. In this case, to provide prioritization of funding lines, it is necessary to compare the ratio of efficiency and consumable resources in different diseases, so that effectiveness criteria for the first three subgroups become unacceptable (table 2).

The use of the effectiveness criteria in subgroup (IV) (using both longevity and quality of life) allows the most equitable comparison between drugs applied in various medical fields, because their determination is based on measuring of the quality of life **by patients,** using unified scales.

The definition of effectiveness criteria in subgroup (IV) is based on utility theory, that develops tools to estimate consumers' propensity of choosing (consumer's preferences) of various alternative options. Thus, there is a presumption in the case of subgroup IV effectiveness criteria that the quality of human life can vary in different life periods from ideal level of health (usually taken as 1) to the level of death (usually equate to 0). Indicators that take into consideration both longevity and quality of life will be determined as the sum of the values of a certain quality of life works the condition of the patient and the time spent in this condition. The number of summands that amount is equal to the amount of patient states within the time period concerned (formula 1).

$$EIV = \sum_{i-k}((Q_i * T_i) ... + ... + (Q_k * T_k)), \text{где:} \qquad \text{Formula (1)}$$

EIV - effectiveness criteria of subgroup (IV)
Q_i - quality of life in condition i;
T_i - time stay in a condition i;
Q_k - quality of life in condition k;
T_k - time stay in a condition k.

Formula 1 demonstrates that the value of the effectiveness criteria in subgroup IV with evaluation of one year life for patients results may not exceed one (one year of life in a state of ideal health), but also can become less then 1 (if quality of life during the past year was not perfect).

There are several approaches to the measurement of the quality of life of patients and they can be divided into direct and indirect approaches. The former one includes the evaluation of the quality of life through visual analog scale (VAS), a method of temporary compromises (time trade-off - TTO) and method of standard risks (standard gamble - SG) [9, 11]. Using direct methods for the determination of the quality of life implies direct interviewing/ interaction with the patient. VAS is the the most basic and intuitive method of assessing the quality of life, the patient is offered to note his current well-being on a special quality of life scale (where 0 is a quality of life that corresponds to death, 10-quality of life, the corresponding absolute health) (fig. 1). The downside of the method simplicity is its primitiveness and low sensitivity, it should be preferably combined with other methods of assessing the quality of life.
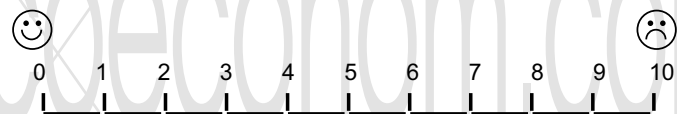

Figure 1. The visual analogue scale of quality of life

Table 2. Comparative analysis of the admissibility of the various effectiveness criteria

Nosology	Prostate cancer	Arterial hypertension	Glaucoma	Diabetes mellitus
Effectiveness criteria				
Surrogate endpoints (subgroup I)				
The value Of PSA	+	-	-	-
Blood pressure	-	+	-	-
Intraocular pressure	-	-	+	-
HbA1C value	-	-	-	+
Surrogate endpoints (subgroup II)				
Morbidity	+	+	+	+
Morbidity	Morbidity of each disease is different, effectiveness criteria are not compatible			
Final endpoints (Subgroup III)				
OS	+	+	-	±
Conclusion	There is no universally effective indicators among effectiveness criteria of I-III subgroups			

+ means the applicability of the effectiveness criterion to nosology assessment
- the nosology cannot be evaluated by this effectiveness criterion
± reduced sensitivity of this criterion to nosology

[1] In Russian literature may occur alternative translations of term QALY, such as quality-adjusted life year, quality adjusted life years gained, years of life adjusted for quality.

TTO and SG are currently regarded as basic methods of determining the quality of life. In case of TTO a hypothetical situation is offered to a patient with disease X: The drug Y for disease X completely cures this disease (provides quality of life equal 1), but cuts the life of the patient short. For example, a patient can expect to live for 10 years with disease X, with certain suffering, or by taking the drug Y, can be cured of disease X, but his lifetime will be reduced from 10 to 6 years with absolute quality of life. The patient is asked to determine the maximum   admissible lifetime reduction after taking the drug Y.

The patient with disease X in case of using SG can choose another hypothetical situation. The drug Y can completely cure this disease, but its administration is associated with the risk of mortality. Now therefore a patient may make a complete recovery from disease X or may die taking the drug Y. The patient is asked to determine the maximum acceptable risk level for the death caused by taking drug Y.

Direct methods of measuring the quality of life are to make an inconvenient process, seeing proposed in TTO and SG situations of choice often cause difficulties for patients in decision-making. In this regard, the most currently popular indirect methods of determining the quality of life are surveys/ questionnaires. Questionnaires/questionnaires do not require determination of patient preferences in hypothetical situations, such as using TTO or SG. Questionnaires/questionnaires contain detailed questions that characterize the quality of life, with clear answers (closed-form questions). Domains of questions characterize the quality of life in various aspects, such as[2] motility (the preservation of the motor activity of the patient), self-care (how the patient is able to care for himself or herself), activities of daily living (how easily the patient is dealing with everyday activity), pain (the expression of pain feelings), mood (concern, depression). The closed replies correspond to certain points, thus filling in the questions fully forms an integral assessment of patient's quality of life. The points for each of the replies are determined beforehand through the methods of TTO or SG when designing a questionnaire [14]. In case of use of questionnaires, a simplifying of procedure for assessing patients' quality of life can be achieved. Questionnaires for setting out the quality of life can be divided into generic for all diseases, and special, which are used to evaluate the quality of life in certain diseases so as to incorporate all the aspects of the patient quality of life with the certain state.

The vast majority of cases the approach of work with effectiveness criteria of subgroup IV is similar to other kinds with final endpoints and surrogate endpoints: pharmacoeconomic researchers are not engaged in defining effectiveness criteria values using the values obtained from clinical trials. There is a special direction in clinical trials working with applied methodology and the assessment of the quality of life for patients - patient reported outcomes (PRO).

Most of the work in the methodological apparatus for determination of the effectiveness criteria of subgroup IV was conducted in *80's-90's* of the last century. Several alternative tools were developed to assess the duration and quality of life - QALY (Quality adjusted life year), HYE (Health Year Equivalent), HLY (Healthy Life Years) and DALY (Disability Adjusted Life Year). Indicators of QALY, HYE and HLY make common sense and demonstrate life expectancy of good quality, while DALY has the opposite meaning, a lifetime with negative quality and potential years of life lost [7-14].

However, QALY, HYE and HLY are not quantitatively equivalent to each other.

The difference between QALYS, HYE and HLY is located in the process of determining quality of life.

The practice of using effectiveness criteria of subgroup IV has made QALY to be the most applied. The calculation formula for QALY takes into account the common approach to definition of effectiveness criteria of group IV and looks like the following:

$$QALYS = Ut * T$$, where: Formula (2)
QALY – quality - adjusted life year;
Ut - utility assigned to a duration, reflecting
the current quality of life;
T- time stay in its current state.

The formula describes the meaning that the quality of life in the effectiveness criteria of QALY is expressed in utility indicator. The QUALY is most often determined by indirect methods - questionnaires such as EQ-

D5, SF-36, HUI-3, etc. It is important to note that for the determination of the QALYS is not any assessment of the quality of life, but only the score obtained on the basis of special validated to QALYS instruments (the above questionnaires) [9. 11].

DALY has the negative meaning of QALY, is mainly used for estimating the burden of disease for international comparisons or comparison between different nosologies. However, the procedure for quantitative method of calculating DALY differs from QALY, and can be expressed with the following formula [7, 8, 10]:

$$DALY = YLL + YLD$$, where: Formula (3)
DALY- Disability-Adjusted Life Year ;
YLL-Years of Life Lost due to premature mortality
YLD-Years of Life Lost due to disability

$$YLL = n_z * L_z$$, where: Formula (4)

YLL-Years of Life Lost due to premature mortality
n_z-number of deaths aged Z;
L_z-life age age expectancy for people aged Z.

$$YLD = N_z * I_z * DW * L_z$$, where: Formula (5)
YLD-Years of Life Lost due to Disability
N_z-population aged Z;
I_z-morbidity of nosology for patients aged Z;
    DW- incapacity weighting factor;
    L_z-the duration of the disease.

The basic element of disability weights definition is the process of interviewing patients. Currently, these coefficients are calculated for a variety of diseases. The study Voigta K. et al, 2010 [7] describes the disability weights for more than 200 patient conditions.

Despite all the advantages of the above instruments for measuring the duration and quality of life, there is a critical view of subgroup IV effectiveness criteria in pharmacoeconomic analysis. Although endpoints, that take into account the duration and quality of life, are considered as the most universal and convincing efficiency criteria using principles of decision-making practices effectiveness criteria, they have some restrictions.

Universality of the QALY, particularly, as effectiveness criterion, occurs in comparison with other surrogate and endpoints. The lower value of the QALY as a measure of treatment for severe life conditions can be more valuable than bigger QALY in assessing the therapy of less serious diseases. Steps are currently being taken to improve the methodology of QALY, with the advent of correction factors on the severity of the disease.

Another problem of QALY indicator is non-linear growth: the higher is the initial quality of life of the patient, the more difficult is to increase it. For example, it is easy to raise the level of quality of life (for instance, with the value 0.2) for the person with a low one because of severe headache, by using an analgesic drug. At the same time, it is very difficult to increase the quality of life for the same amount of 0.2 for a healthy person, whose quality of life was originally highly enough (but not perfect).

First and foremost, it is necessary to take into account the dependence on patient age, considering the limitations of DALY. Taking into account years of life lost due to premature death, large values DALY the same nosology are given to younger patients, in comparison with elderly patients.

The above criticism of QALY and DALY does not diminish the role of effectiveness criteria in pharmacoeconomic analysis, however, it requires an understanding of their limitations when interpreting results [7-14].

The choice of one efficiency criterion or another when conducting pharmacoeconomic research depends on various factors, the most important of which are:
  • Applied methods of the pharmacoeconomic analysis;
  • Accessibility of data for efficiency criterion;
  • Specific feature of the nosology;
  • The target audience for pharmacoeconomic analysis.

First and foremost selection of effectiveness criteria in pharmacoeconomic study is determined by the method of pharmacoeconomic analysis.

[2]Here are the domains of the questionnaire EQ-D5

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The selection process for effectiveness criteria in «cost-effectiveness» analysis

Final endpoints are the most preferable in «cost-effectiveness» analysis among the effectiveness criteria. However, it is necessary to take into account the availability of data of performance criteria, which is often limited for endpoints, especially for innovative drugs. Innovative drugs are providing limited information about final endpoints because of the necessity of a patient follow-up for long period to receive a certain information about drug effect on life expectancy. It is not always possible because of drugs novelty. In this case, the pharmacoeconomic analysis is using surrogate endpoints of the subgroup I. The surrogate endpoints have to be chosen to become quantitatively linked to final endpoints (using modeling techniques). The approach is based on the assumption that the data of biomarkers/clinical endpoints level after medical intervention allow to predict changes of endpoints (fig. 2). A sufficient connection between surrogate and the final endpoints is a requirement for this assumption. The connection may have 3 levels of recommendations, depending on the source:

Level 1. The connection between surrogate and clinical endpoints is based on the results of clinical research;

Level 2. The connection between surrogate and clinical endpoints is based on the results of epidemiological/observational studies;

Level 3. The connection between surrogate and clinical endpoints is based on biological possibility (pathophysiological research or understanding of the pathogenesis of disorder);

The target audience plays an important role in «cost-effectiveness» analysis, determining the value of the unit effectiveness in case of a drug using. If the target audience includes clinical specialists (for example, the main freelance specialists), analysis of «cost-effectiveness» may use as a effectiveness criteria clinically relevant surrogate endpoints because this group of specialists has an understanding of importance of improving key health indicators related to a particular disease. For example, analysis of «cost-effectiveness» for a drug for the treatment of depressive disorders, prepared for main freelance psychiatrist would be justified usage of Hamilton scale values as effectiveness criterion. Specified indicator has high significance for psychiatrists in assessing the condition of the patient. They are able to evaluate the value of the indicator changes of the drug. On the other hand, public health managers suppose that the analysis of «cost-effectiveness» makes relevant use in case of final endpoints, because they value of surrogate endpoints is not so obvious and clear (fig. 3). In general, the use of surrogate endpoints as the only criteria

is a forced measure in the absence of data of endpoints for implementing pharmacoeconomic analysis [4.15].

The selection process for effectiveness criteria in «cost-utility» analysis

Analysis of «cost-effectiveness» as a form of «cost-utility» analysis allows using only effectiveness criteria of subgroup IV regardless of the target audiences, which will receive the results of pharmacoeconomic studies (fig. 3) [4.15].

The selection process for effectiveness criteria in «budget impact» analysis

It is therefore recommended for «budget impact» analysis to use surrogate endpoints of subgroup II - frequency of clinically significant events, associated with costs (fig. 3). «Budget impact» analysis can take into account surrogate endpoints of subgroup I if there is an established quantitative connection to effectiveness criteria for this analysis [4, 16].

The selection process for effectiveness criteria in «cost-minimization» analysis

A precondition for «cost-minimization» analysis is an equal clinical efficacy of compared drugs, thereon effectiveness criteria are disregarded. «Cost-minimization» analysis can include effectiveness criteria from surrogate endpoints of subgroup II (along the lines of «budget impact» analysis) however, due to the equality of clinically significant values for analysed drugs to compare frequencies specified effectiveness criteria should not affect the result of the analysis (fig. 3) [4].

Particularities of specific nosology must also be taken into account when selecting the effectiveness criteria: If the disease has little effect on the duration and/or quality of life, using final endpoints in pharmacoeconomic analysis may be appropriate. There is general recommendation for preferable usage of final endpoints for diseases that have a marked impact on the duration and quality of life(fig. 3) [4].

Conclusion

The selection of effectiveness criteria is an essential stage of pharmacoeconomic research; use relevant effectiveness criterion predetermines the usefulness of pharmacoeconomic analysis results. There are general recommendations of choosing effectiveness criteria in
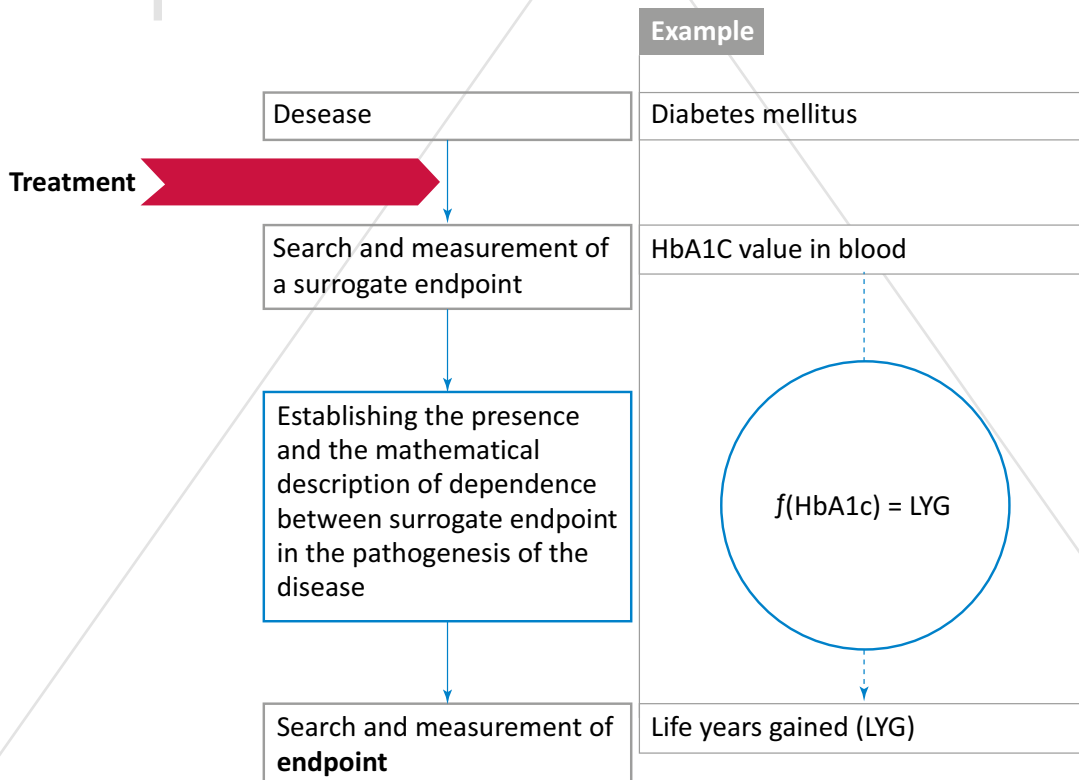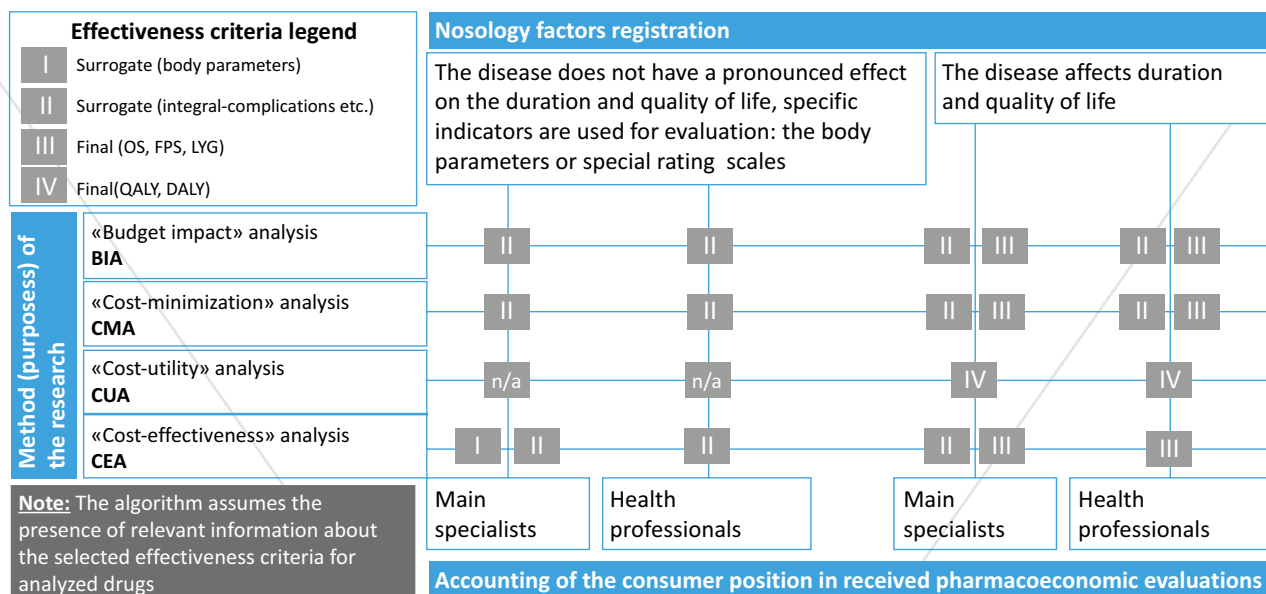

Figure 2. The use of surrogate endpoint as an effectiveness criteria of medical interventions for patients with diabetes mellitus

Effectiveness criteria legend	Nosology factors registration			

Figure 3. Effectiveness criteria selection algorithm in pharmacoeconomic analysis

pharmacoeconomic analysis; they include a priority of using final endpoints as indicators that take into consideration duration and quality of life. It is also essential to consider data availability, the pharmacoeconomic analysis method, the nosology features, and the target audience, to which results of the pharmacoeconomic research will be presented.

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