№1 Том3 2015

Фармакоэкономика

теория и практика

Pharmacoeconomics

theory and practice

№1 Volume3 2015

- **МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ АНАЛИЗА ЭФФЕКТИВНОСТИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ ПРИ ПРОВЕДЕНИИ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ**

- **IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ» – «ФАРМАКОЭКОНОМИКА – 2015» 16-17 марта 2015 г., УФА, AZIMUT ОТЕЛЬ УФА**

www.pharmacoeconom.com

METHODOLOGICAL BASICS OF EFFECTIVENESS ANALYSIS OF HEALTH TECHNOLOGIES IN PHARMACOECONOMIC STUDIES

Yagudina R.I., Babiy V.V.

Department of organization of medicinal provision and pharmacoeconomics, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation

Abstract:
The article presents the methodological basics of the effectiveness analysis in pharmacoeconomic studies of medicinal drugs or health technologies. In particular, the main challenge that researchers face is the defining criterion of the effectiveness of the evaluated alternatives is described. What is more, main positive and negative sides of using surrogate and final performance criteria, as well as provide methodological recommendations for their selection and evaluation.

Key words: *effectiveness analysis, effectiveness criteria, surrogate endpoint, endpoint, biomarker, clinical endpoint, pharmacoeconomic analysis, clinical endpoint, QALY, LYG*

Effectiveness analysis is one of the stages of pharmacoeconomic analysis (PA). It is used for criterion (indicator) selection, which could shot as accurately and fully as possible efficacy, safety and utility of studying health technology. Choosing the correct efficiency allows for the subsequent stages of PA to conduct a comprehensive assessment of the impact of technology on the overall burden of disease.

The main sources of information about the effects of the analyzed technologies are the results of clinical trials, where the drug's efficacy is usually expressed as indicators, using which the success of treatment in an individual patient is monitored in clinical practice (for example, blood biochemical parameters), and the safety of drug is assessed as mortality level and/or the number of adverse effects.

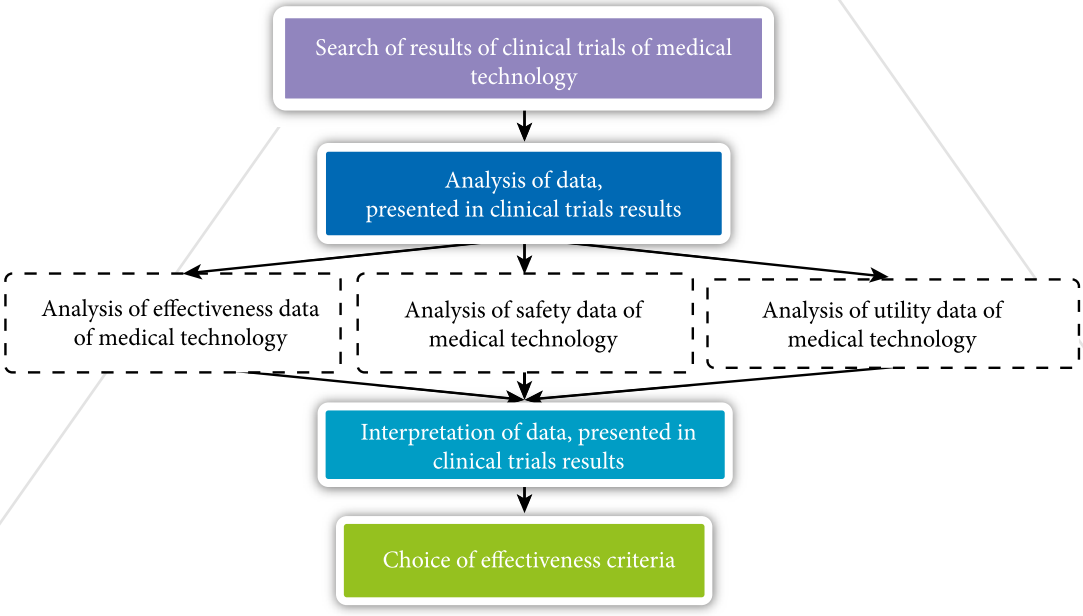
However, the information presented in this form is not always enough for the decision-makers (especially, if they are not specialists in this nosology). Moreover, for informed decision-making they need the results of PA, which take into account delayed effects of medical technology (e.g., changes in life expectancy), while carrying out clinical trials are not always possible.

The best and most common way to overcome the mentioned difficulties is pharmacoeconomic modeling. Mathematical models allow to predict the targeted consequences of medical technologies use (including delayed ones) on the basis of available results of clinical trials, as well as data on dependencies of targeted consequences medical technology use from the values of the performance indicator that was used in a clinical study. The consequences medical technology use is usually expressed as indicators, showing the duration and/or quality of life.

During effectiveness analysis of medical technology, we need to find answers to such questions as: Which criterion of effectiveness is the most reliable and will meet the aims of the work? How to measure this criterion? In which situations you can use the selected criteria? What time period allows the selected criterion of efficiency to make predictions?

In general, effectiveness analysis of medical technology includes the following stages: search, analysis and interpretation of data presented in the results of clinical studies (Fig. 1). As mentioned above, the outcome of this analysis will be the choice efficiency criterion.

Figure 1. Effectiveness analysis stages



Yagudina R.I. - tel 8(495)656-27-67, e-mail: yagudina@inbox.ru

Effectiveness criteria

Effectiveness criteria (effectiveness point) is an indicator that allows to numerically express the degree of potential benefit or harm from the use of medical technology. For example, the effectiveness criteria may be: hormones level in blood, tumor size, assessment of patients' health, assessment of patients' functional abilities, the life expectancy of the patient, etc.

In pharmacoeconomic analysis there are certain requirements to effectiveness criteria, namely, they must be reliable (to reflect the consequences arising from the medical technology use without bias), sensitive to possible changes in generally accepted and, if possible, should reflect remote in time results.

It was already noted, that there are the differences in approaches to effectiveness estimation and as a consequence the difference in the in-use effectiveness indicators in clinical and pharmacoeconomic studies. In English literature, there are three separate terms that denotes «effectiveness», but used in a different context:

• Efficacy – efficacy of medical technology in clinical trials;

• Effectiveness – effectiveness of medical technology in real practice;

• Efficiency – effectiveness of medical technology in pharmacoeconomic studies.

By analogy with above-mentioned separation used in PA conducting, effectiveness criteria can also be divided into:

• Surrogate endpoints – indicators that reflect the direct and indirect clinical effects (change of biochemical parameters, reducing the number of hospitalizations and so on);

• Final endpoints - indicators that reflect changes in health indicators at patients level (mortality, survival, life expectancy, disability, quality of life, etc).

A detailed description of the characteristics of each group are presented in table 1.

In general, the choice of effectiveness criteria (effectiveness points should be chosen accordance with the purposes of the study, characteristics of the analyzed population, characteristics of the disease (life-threatening or not), treatment features (palliative or therapeutic use), time and financial possibilities.

Table 1. Characteristics of the effectiveness criteria used in the pharmacoeconomic analysis

	Surrogate endpoints		**Final endpoints**	
	Direct clinical effects	**Intermediate clinical endpoints**	**Final endpoints of population level**	**Final endpoints of individual level**
Synonyms	Intermediate points		-	
	Biomarkers	Clinical endpoints, targeted clinical endpoints, clinical intermediate point, clinical indicators, clinical outcomes	-	-
Description	Indicator that reflects the qualitative and quantitative characteristics of biological processes, qualityes or various forms of pharmacological response that occurs after a medical intervention	Outcome of disease or medical intervention, expressed in the form of certain clinical conditions or phenomena	Indicators representing health indicators at the level of patients groups	The indicators reflecting the duration and/or quality of life of patients
Examples	Level blood glucose, blood pressure, forced expiratory volume, intensity of pain	Myocardial infarction, amputation, loss of vision, adverse event	Mortality, morbidity, disability	Quality-adjusted life year (QALY), life years gained (LYG)
Way of determination	Instrumental measurement, Survey methods	Observation, statistical method	Statistical method	Statistical method, survey methods, calculation method
Confidence level	High, if it measured using tools	Rather high, as results are formed basing on generalization of statistical data	Rather high, as results are formed basing on generalization of statistical data	Medium, as indicators are calculated. For calculations not all aspects may be taken into account
The level of practical significance	Low - allow us to conclude only on the stage of the disease and/ or sensitivity of biological processes to the ongoing medical intervention - not reflect the duration and quality of life of the patient - not allow us to directly evaluate long term results	Low -does not reflect the duration and quality of life of the patient - not allow us to directly evaluate long term results	Medium - not allow to quantify the patient's quality of life - allow us to directly evaluate long term results - reflect the effectiveness of treatment across the population	High - quantitative expressions of duration and/or quality of life of the patient - allow us to directly evaluate long term results - reflects the effectiveness of the therapy for average patient

Surrogate clinical endpoints

Surrogate clinical endpoint is the score used for indirect qualitative and quantitative assessment of the results of medical intervention, in cases where a direct comparison is impossible or unreasonable.

The term surrogate point combines effectiveness criteria, expressing direct (biomarkers) or indirect clinical effects of medical technology.

Biomarker is an indicator that reflects the qualitative and quantitative characteristics of biological processes, pathological processes or various forms of pharmacological response that occurs after a medical intervention. As biomarkers can be used: biochemical parameters, enzyme-linked immunosorbent indicators, quantitative and qualitative data on the substances in body tissues, data on the size of the organs/tumors, etc. It should be noted that the biomarker is used as a quantitative measure of any disorder, but not the disorder itself.

Naturally, the development of any pathological process as well as any medical intervention, accompanied by the change of numerous indicators in the body. However, to ensure that the indicator could be used as biomarkers (effectiveness criterion) of medical technology, it must meet obtain the following requirements [4]:

- specificity - it is preferable that the marker is the individual feature of a particular pathological process and is not influenced by internal and external factors;
- usability - a simple and clear measurement technique, which eliminates the bias;
- validity - selected for the evaluation of medical technologies biomarkers should correlate with the clinical target points (for example, disability) or, better, with endpoints (for example, with the number of extended life years) to allow estimation and prediction of the results. However, there are biomarkers of unknown validity, the use of which is based on general agreements in the medical and scientific practice, and biomarkers with probable validity, i.e. not estimated earlier publicly;

The use of biomarkers is usually used in cases when the clinical findings are rare/deferred (slowly progressive disease, prolonged observation which is not justified/consuming; rare diseases) or when the analysis focuses on life-threatening diseases for which there are no therapeutic alternatives. To date, there is no list of biomarkers that would be acknowledged as valid indicators of the effectiveness of medical intervention. Only a few biomarkers approved for use as performance criteria (for example, the level of glycosylated hemoglobin in diabetes mellitus).

Biomarkers are usually used in cases when the clinical findings are rare/delayed (slowly progressive disease, prolonged observation which is not justified/consuming; rare diseases) or when the analysis focuses on life-threatening diseases for which there are no therapeutic alternatives. To date, there is no list of biomarkers that would be acknowledged as valid indicators of the effectiveness of medical intervention. Only a few biomarkers are approved for use as effectiveness criteria (for example, the level of glycosylated hemoglobin in pat).

The use of biomarkers as performance criteria may lead to difficulties in the decision-making process, because presented in this form, the benefits of the analyzed medical technology is not so obvious. Therefore, this criterion can be used to evaluate medical technologies, mainly experts in specific nosology (doctors, researchers).

Clinical point (intermediate clinical effect) is the outcome of a disease or medical intervention, expressed in the form of certain clinical conditions or phenomena. Effects of medical technologies application, presented in the form of such effectiveness criterion, have high relevance for public health specialists and physicians. From the point of view of PA clinical endpoint can be used for more accurate assessment of medical technology (compared with the estimate made on the basis of biomarkers), because they allow to take into account the additional burden of the healthcare system due to adverse drug events, various complications etc.

As previously noted, in PA surrogate points are typically used in the modeling process implications of medical technologies. This approach is based on the assumption that the data on the level of biological markers/clinical endpoints, the change occurred as a result of medical intervention, allows to predict endpoints' changes (Fig. 2). The existence of a reasonable relationship between the surrogate and the final endpoints is a necessary condition for the validity of this assumption. Depending on the source, the connection can have three levels of evidence:

Level 1. The relationship between the surrogate and clinical points based on the results of clinical studies;

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

Level 3. The relationship between the surrogate and clinical endpoints based on biological features (from pathophysiological research or understanding of the pathogenesis of the disease).

In general, the use of surrogate endpoints as the only effectiveness criteria for medical technologies during PA is usually a least-evil solution in case of data absence required to build the data model.

Final endpoints

Final endpoint is a measure of outcomes that is used in direct evaluation process of medical intervention.

Figure 2. The scheme of a surrogate point using as an effectiveness criterion of medical intervention

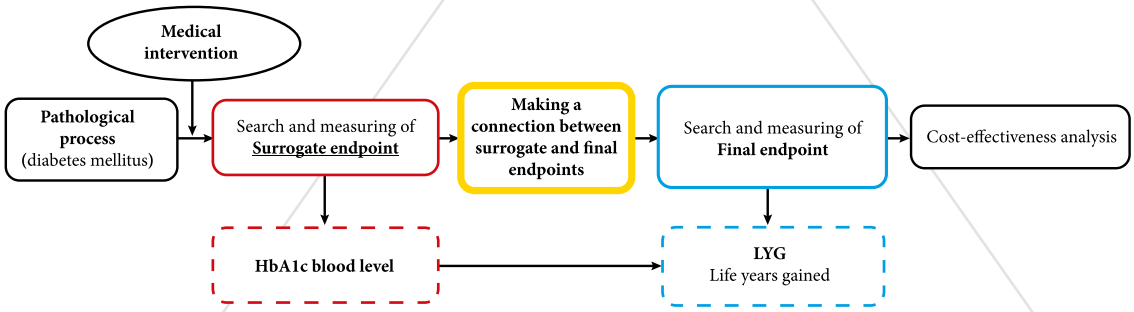
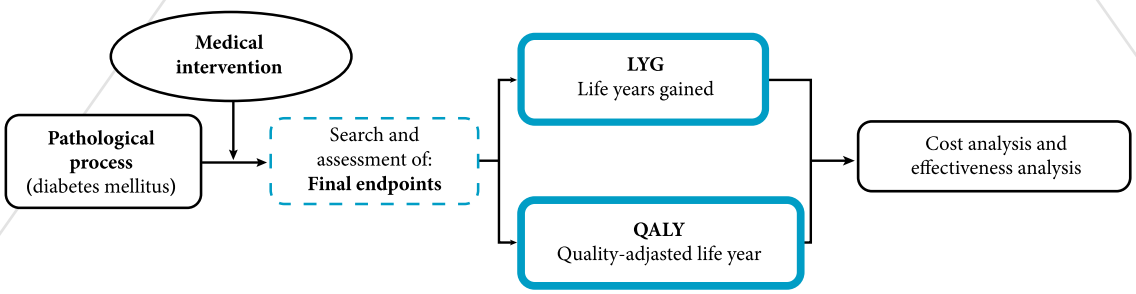


Figure 3. The scheme of the endpoint using as an effectiveness criterion of medical intervention



To estimate the value of final endpoints it is possible to undertake the clinical, epidemiological and others types of study, that could collect data for the direct effect of medical intervention on, for example, life expectancy. It should be noted, that due to the rather long duration of these studies, the long-term outcomes of medical technology are obtained. However, in pharmacoeconomic researches usually models gives the value of final endpoints.

Different types of final endpoints have different levels of importance during analysis and evaluation of medical technology. Endpoints that reflect survival/mortality are of higher importance due to lower rate of mistakes in measuring/calculation (compare to other types of final endpoints) and the goal of medical treatment (that is, life sustaining).

Final endpoints can be:

- Population-based final endpoints reflect the outcomes of medical intervention on a scale of population: disablement, morbidity, mortality etc.;
- Individual-based final endpoints reflect the outcomes of medical intervention on a scale of certain patient: life years gained (LYG), quality adjusted life years (QALY).

The latter two indicators are widely used in pharmacoeconomic analysis, especially in case of cost-effectiveness analysis.

Life years gained (LYG) reflect the impact of health care intervention in terms of its effect on mortality and life expectancy [34]. However, this type of endpoint does not take into account that health is more than just staying alive. Therefore, the indicator called quality adjusted life years (QALY) was made; it reflects the effect of medical technology on both mortality and quality of life.

Nevertheless, in some cases QALY does not reflect the clinical benefits of intervention (for example, the technology affects the symptoms, but not the disease).

Furthermore, quality of life is rather individual measure; it may vary within groups of patients and societies. Therefore, studies dedicated to estimation the quality of life should contain set of measurements.

Conclusion

Advanced analysis of effectiveness makes a solid basis for subsequent stages of pharmacoeconomic analysis. Through the fact that all endpoints have both positive and negative aspects, choosing of certain endpoint in the process of health technology assessment should be done individually. All sources of data on efficacy/effectiveness should be checked for common methods of evaluation, similar characteristics of cohorts, similar characteristics of environment. Besides, proper understanding of definitions of indicators in data sources is important (especially, if it is written on foreign language).

LYG (life years gained) and QALY gained (quality adjusted life years gained) are the most common types of endpoints in pharmacoeconomic analysis. In case of decision-making process, these indicators should be taken into account.

References

1. Khabriev R.U., Yagudina R.I., Pravdyuk N.G. Health technologies assessment. M.: LLC «Medical informational agency», 2013. – p.416.
2. Yabluchanskiy N.I. Surrogate and non-surrogate endpoints in drug clinical trials // «Drugs clinical trials in Ukraine» - November 3, 2006, Kiev.
3. Yagudina R.I., Yusupiova S.D., Nazarenko P.V. Usage of pharmacoepidemiologic studies in modern pharmacy
4. Yagudina R.I., Kulikov A.Yu., Serpik V.G. Pharmacoeconomics in ophthalmology. - M.: LLC «Medical informational agency», 2013. – p.304
5. Yagudina R.I., Serpik V.G., Sorokovikov I.V. Methodological basics of analysis of "cost-effectiveness" // Pharmacoeconomics: theory and practice. - 2014. - Vol.2, №2. - P.28-31
6. Biomarkers Definitions Working Group, Biomarkers and Surrogate endpoints: Preferred definitions and conceptual framework//Clinical Pharmacology & Therapeutics 2001; 69, 89–95
7. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials// Circulation. 1990; 82:1106-16.
8. Downing G.J. Biomarkers and surrogate endpoints: clinical research and applications// Amsterdam: Elsevier Scientific; 2000; 1-7.
9. Dumont GJ, de Visser SJ, Cohen AF, van Gerven JM. Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects// Br J Clin Pharmacol. 2005;59:495-510.
10. Echt S, Liebson PR, Mitchell LB, Peters R, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial// N Engl J Med. 1991; 324:781-8.
11. European network for health technology assessment. Endpoints used for REA of pharmaceuticals – Clinical endpoints. Guideline. URL: www.ema.europa.eu. Date of access: 10.05.14
12. European network for health technology assessment. Endpoints used for REA of pharmaceuticals – Composite endpoints. Guideline. URL: www.ema.europa.eu. Date of access: 10.05.14
13. European network for health technology assessment. Endpoints used for REA of pharmaceuticals – Surrogate endpoints. Guideline. URL: www.ema.europa.eu. Date of access: 10.05.14
14. European network for health technology assessment. Endpoints used for REA of pharmaceuticals – Health-related quality of life. Guideline. URL: www.ema.europa.eu. Date of access: 10.05.14
15. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. JAMA. 1979; 242:2562-71.
16. Fleming T.R. Surrogate Endpoints And FDA's Accelerated Approval Process// Health Affairs, 24, no. 1, 2005; 67-78.
17. Fleming T.R., DeMets D.L., Surrogate End Points in Clinical Trials: Are We Being Misled?// Annals of Internal Medicine 125, 1996; 7:605–613.
18. Fleming TR. Evaluating therapeutic interventions: some issues and experiences (with discussion and rejoinder)// Statistical Science. 1992; 7:428-56.
19. Fleming TR. Surrogate markers in AIDS and cancer trials// Stat Med. 1994; 13:1423-35.
20. Furberg CD, Berglund G, Manolio TA, Psaty BM. Overtreatment and undertreatment of hypertension// J Intern Med. 1994; 235:387-97.
21. Gordon DJ. Cholesterol lowering and total mortality. In: Rifkind BM, ed. Contemporary Issues in Cholesterol Lowering: Clinical and Population Aspects. New York: Marcel Dekker; 1994.
22. Herson J. The use of surrogate endpoints in clinical trials// Stat Med. 1989; 8:403-4.
23. Hine LK, Laird N, Hewitt P, Chalmers TC. Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction// Arch Intern Med. 1989; 149:2694-8.
24. Kozma C.M., Reeder C.E., Schulz R.M. Economic, clinical and humanistic outcomes: a planning model for pharmacoeconomic research. ClinTher. 1993;15:1121-32.
25. Mitchell A. Transforming Surrogate Outcomes: An Australian review//6th annual meeting HTAI, 21-24 June 2009, Singapore.
26. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project// J Clin Oncol. 1992; 10:896-903.
27. Packer M, Carver JR, Rodehoffer R, Ivanhoe RJ, DiBianco R, Zeldis SM, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group// N Engl J Med. 1991; 325:1468-75.
28. Packer M, Rouleau J, Swedberg K, Pitt B, Fisher L, Klepper M, et al. Effect of Flosequinan on survival in chronic heart failure: preliminary results of the PROFILE study [Abstract]// Circulation. 1993; 88(Suppl 1):I-301.
29. Preliminary Report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N Engl J Med. 1989; 321:406-12.
30. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991; 265:3255-64.
31. Psaty BM, Heckbert SR, Koepsell TD, Siscovick DS, Lemaitre R, Smith NL, et al. The risk of incident myocardial infarction associated with anti-hypertensive drug therapies [Abstract]// Circulation. 1996; 91:925.
32. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)// Lancet. 1994; 344:1383-9.
33. Report from the Surrogate to the Final Outcome Working Group to the Pharmaceutical Benefits Advisory Committee: a framework for evaluating proposed surrogate measures and their use to the submissions to PBAC, 24 Dec 2009.
34. Robberstad B. QALYs vs DALYs vs LYs gained: What are the differences, and what difference do they make for health care priority setting? Norsk Epidemiologi, 2005; Vol. 15 № 2.
35. Staner L, Clinical Research: Surrogate Outcomes in Neurology, Psychiatry and Psychopharmacology// Dialogues in Clinical Neuroscience, 2006;8:345-352.

36. Staner L, Luthringer R, Le Bon O. Sleep disturbances in affective disorders. In: Pandi-Perumal SR, Monti JM, eds//Clinical Pharmacology of Sleep, Basel, Switzerland: Birkhaüser Verlag; 2006:101-124.
37. Taylor R. The Use of Surrogate outcomes in Model-based Cost-effectiveness Analyses// 6th annual meeting HTAI, 21-24 June 2009, Singapore.