Medical Technologies
Assessment and Choice

Special Issue 2013

FOUNDING PARTIES

The Russian National Research Medical University named after
N.I. Pirogov (RNRMU) of Ministry of Health of the Russian
Federation

Foundation for the Development of Social Policy and Healthcare
“HELIOS”, Moscow

With support of the Committee for Social Policy and
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Publisher

Foundation for the Development of Social Policy
and Healthcare “HELIOS”, Moscow
Passed for printing on 20.10.2012
Format 60 x 90 1/8. Quires
Coated paper. Offset printing
Number of printed copies: 1000
Order N 1734
Printed Ltd Folium publishing company
The Federal Service for Supervision in the Sphere of Telecom, Information
Technologies and Mass Communications

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For contact information of all authors from former RCCEE&Ph please see page 3 of the cover.
INTRODUCTION

One of the principles of evidence-based medicine is the assumption that the decision to implement a particular medical technology should be based on a comprehensive analysis of all available scientific evidence of its effectiveness and safety rather than on expert opinion or personal clinical experience of physicians. The same applies to clinical guidelines, which should be in line with the principles of evidence-based medicine. Notably, the authors of such guidelines should state clearly the level of their certainty in the reliability of scientific evidence and the soundness of recommendations. Appropriate assessment systems have been created to indicate the level of certainty in the reliability of evidence and the soundness of clinical guidelines. These systems have been created to indicate the level of certainty in the reliability of evidence and the soundness of clinical guidelines with so-called “levels of evidence” and “grades of recommendations”. Both are normally indicated with Roman numerals or Latin letters and are meant to inform end users of guidelines (especially physicians, but also middle-level health workers, healthcare managers and patients) about the level of scientific evidence for the recommended action. A formalized systemic approach to the task of evaluating the reliability of evidence for the effectiveness of medical technologies and the soundness of recommendations helps to prevent faulty reasoning and promotes their critical acceptance and dissemination among healthcare specialists [10].

At present guidelines created and/or published in Russia indicate levels of evidence and grades of recommendations with Roman numerals or Latin letters. However, not all physicians are aware of the fact that there still doesn’t exist any unified grading system, and often even the essence of the process preceding the assignment of these letters and numbers remains unclear. As a result, the underlying meaning of phrases like “convincing evidence” or “based on the best available evidence” varies considerably between guidelines. Those specialists who have recently been trying to implement in a consistent manner the grading systems mentioned above are facing considerable difficulties, stemming from the lack of a standard approach to the creation of such systems.

The goal of this review is to analyze systems for grading evidence and recommendations created and currently used in other countries; the results of this analysis may help to create similar grading systems in Russia.

ESSENTIAL TERMINOLOGY AND CONCEPTS

Levels of evidence reflect the certainty that the detected effect of a medical technology is not an artifact. In line with epidemiological principles, the level of evidence is assigned based on three main criteria:
the quality, quantity and consistency of evidence (see the Table below) [1, 2]. The quality of evidence is a composite measure of the methodological quality of all available studies that addressed the relevant clinical issue (e.g. the effectiveness of a particular medical technology). The methodological quality of a study reflects the degree to which study design, its performance and the analysis of results may prevent the appearance or minimize the impact of systematic or random errors that might distort the true effect size and thus lower the reliability of results. An important concept is the hierarchy of study designs, which refers to the fact that some types of research design are more susceptible to systematic errors than other types, and therefore the results of such studies are intrinsically less reliable. It is now known that the results of randomized clinical trials (RCTs) and their systematic reviews or meta-analyses are the most reliable.

The methodological quality of studies is assessed with the help of various tools, primarily questionnaires or scales developed for particular designs of clinical trials. In 2002 researchers at the American Agency for Healthcare Research and Quality (AHRQ) performed a systematic search and discovered 20 systems for assessing the methodological quality of systematic reviews as well as 49 such systems for RCTs and 19 for observational studies [2]. At the moment there is no standard, universally accepted system for assessing the methodological quality of individual studies and groups of studies supplemented with an assessment of the quantity and consistency of evidence. An assessment of the level of evidence is thus a necessary, but not sufficient, precondition for writing clinical recommendations. Clinical recommendations are statements arising from a systematic analysis and intended to assist practicing physicians and patients in the choice of an appropriate treatment strategy in a particular clinical situation. Based on this definition, expert groups in charge of writing clinical recommendations should certainly take into account both the reliability of evidence and a number of other factors, such as the tradeoffs between benefit and harm of this medical technology, the generalizability of evidence (whether the evidence for its effectiveness applies to particular populations of patients and conditions of clinical practice), the values and preferences of patients, and the cost of treatment [3, 4]. Unlike levels of evidence, grades of recommendations reflect not only the certainty that the effect of the intervention is reliable but also the certainty that following these recommendations with result in more benefit than harm in a particular situation.

The process of developing clinical guidelines, from the assessment of the methodological quality of studies to the assessment of the level of evidence to the formulation of clinical recommendations, is presented in Fig. 1. The stages of assessing the level of evidence and formulating recommendations should be followed in the right order, but preferably they should be independent, so that the level of evidence and the grade of recommendation are assigned separately. Even though a high level of evidence is typically associated with a high grade of recommendation, a particular level of evidence does not always presume the same grade of recommendation. For instance, it has been demonstrated in high-quality RCTs that long-term administration of oral anticoagulants reduces the risk

<table>
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<tr>
<th>Criteria for assessing the reliability of evidence</th>
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<tr>
<td>Quality of evidence: a composite characteristic of the methodological quality of all available studies.</td>
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<tr>
<td>Quantity (volume) of evidence: effect size, number of studies, total number of patients in the sample.</td>
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<tr>
<td>Consistency of evidence: the degree to which the results of different studies are consistent.</td>
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Theoretically, the larger the effect size, the less likely it is that systematic and random errors arising in the course of the study may lead to a false conclusion. It is also obvious that with an increasing number of studies (provided that their methodological quality is high) the reliability of the observed effect increases. Furthermore, a larger total sample size makes the confidence interval for the effect estimate narrower, thus improving the precision of this estimate. In a word, the quantity of evidence determines our certainty in the fact that the observed effect was related to the tested intervention rather than random.

The consistency of evidence refers to the extent to which the results of different studies that looked at the effectiveness of the same medical technology (in different populations, with the same or different designs) are consistent. If the results of different studies are highly consistent, this means that the observed effect is reproducible and thus more reliable.

Grading of evidence begins with an assessment of the methodological quality of individual studies and groups of studies supplemented with an assessment of the quantity and consistency of evidence. An assessment of the level of evidence is thus a necessary, but not sufficient, precondition for writing clinical recommendations. Clinical recommendations are statements arising from a systematic analysis and intended to assist practicing physicians and patients in the choice of an appropriate treatment strategy in a particular clinical situation. Based on this definition, expert groups in charge of writing clinical recommendations should certainly take into account both the reliability of evidence and a number of other factors, such as the tradeoffs between benefit and harm of this medical technology, the generalizability of evidence (whether the evidence for its effectiveness applies to particular populations of patients and conditions of clinical practice), the values and preferences of patients, and the cost of treatment [3, 4]. Unlike levels of evidence, grades of recommendations reflect not only the certainty that the effect of the intervention is reliable but also the certainty that following these recommendations with result in more benefit than harm in a particular situation.

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Fig. 1. The process of developing clinical guidelines, from the assessment of the methodological quality of studies to the assessment of the level of evidence to the formulation of clinical recommendations.

The concepts of “levels of evidence” and “grades of recommendations” were first suggested in 1979 by the Canadian Task Force on the Periodic Health Examination [5]. Since then, numerous systems for assessing the level of evidence and the grade of recommendation have been created and implemented. Apart from large associations for health technology assessment, many specialized medical societies took part in the creation and implementation of new grading systems. In 2002 the AHRQ agency in the United States performed a systematic review and discovered 40 different approaches to the assessment of the level of evidence that were in use at that time [2]. To take this project further, a Canadian task force, COMBUS (Canadian Optimal Medication Prescribing and Utilization Service), added to this list another 10 methods for assessing the level of evidence, which appeared between 2000 and 2005 [6]. Over the years the principles of grading gradually grew more complex. Only 30% of the grading systems (7 out of 23) published before 2000 to some extent took into account both the quality and the quantity of evidence, as well as its consistency, while among the systems published between 2000 and 2002 a full 82% (9 out of 11) took into account all three factors [2]. Besides, while in the early grading systems the quality of evidence depended only on the position of the studies in a fixed hierarchy of designs, at present it is an obligatory component of the assessment to evaluate the methodological quality of each individual study. The consistency of evidence was historically the last criterion to be added to the analysis [2].

Out of the 40 grading systems analyzed in 2002 by the AHRQ, only 12 systems (30%) were created exclusively as tools of evidence-based medicine intended for a systematic analysis of the level of evidence, rather than for writing clinical guidelines. The majority of these systems combined the assessment of levels of evidence and grades of recommendations [2]. The first scale of the grades of recommendations, which was created by the Canadian Task Force on the Periodic Health Examination in 1979, was presented together with grading of evidence and was based primarily on an assessment of the level of evidence, even though the authors noted already then that the grade of recommendation could be lowered depending on “the burden of suffering” caused by the intervention [5].

At present the coexistence of a large number of different scales for grading evidence and recommendations is confusing for both healthcare decision-makers and practicing physicians, and therefore this situation has a negative effect on the quality of health care delivered to the patients. This confusion is aggravated by the fact that different scales use different symbols to indicate the levels: letters (A, B, C, etc), numerals (I, II, III, etc) or a combination of both (Ia, Ib, Ila, etc). For example, when different groups evaluated the effectiveness of antiviral therapy administered to patients with acute hepatitis C in order to achieve clearance of viral RNA, the assigned levels of evidence / grades of recommendation were as follows: I+ and A (SIGN, 2006 [7]), B and I (American Association for the Study of Liver Diseases, 2009 [8]), B and 2 (European Association for the Study of Liver, 2011 [9]). It is quite clear that with the current diversity of systems for grading evidence they are incapable of performing their original function – to provide a prompt and concise summary of the reliability of evidence for the effectiveness of medical technologies and the soundness of recommendations. The need for a unified approach to grading evidence and recommendations is acknowledged by a growing number of international organizations.

In Russia, as early as the late 1990s it was decided that national clinical guidelines should be based on the principles of evidence-based medicine and take into account only the results of methodologically sound studies [23, 24]. However, a large number of modern Russian clinical guidelines include statements that are not based on scientific evidence, and systems for grading evidence and recommendations remain poorly developed and are
not in demand in Russia [17]. The majority of medical societies and associations prefer to rely in their practice on the levels of evidence and grades of recommendations borrowed from foreign clinical guidelines, often forgetting that these must be adapted to the actual Russian conditions. The main reasons why foreign guidelines and the results of clinical trials conducted in other countries cannot be applied directly are the following: population-level differences between the contingents of patients; incommensurate treatment conditions in different health centers; differences in risk factors, severity and outcomes of illnesses; differences in the cost of treatment and the allocation of the healthcare budget; differences in the training of health workers [17]. As evidence-based medicine is gaining ground in Russia, the number of high-quality clinical trials conducted in Russia is increasing and the role of cost-effectiveness analysis is growing under market economy conditions, it is quite certain that the need for perfecting and implementing the tools for grading evidence and recommendations is bound to grow as well.

A DESCRIPTION OF THE SYSTEMS FOR GRADING EVIDENCE AND RECOMMENDATIONS

For the systematic analysis reported in this review we selected the best-known systems for grading evidence and evidence: SIGN, OCEBM, GRADE, NICE, and NHMRC. When analyzing the principles of assessing the level of evidence, we paid attention primarily to three main criteria: quality, quantity, and consistency of evidence. When analyzing the principles of grading recommendations, we took the main criteria to be the following: generalizability of evidence, benefit-to-harm ratio, cost of treatment, values and preferences of patients, and the applicability of recommendations under the actual conditions found in the national healthcare system. Below is a brief description of the selected systems of assessment (the most recent versions available in May 2012)¹.

SIGN (SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK) [25]

The Scottish Intercollegiate Guidelines Network (SIGN) was established in 1993 for the purpose of writing recommendations for the Scottish national healthcare system. Clinical recommendations of the SIGN are intended for a broad range of health workers and cover various clinical fields. The SIGN system as it is used today was adopted in 2000.

The preparation of clinical recommendations by the SIGN begins with an evaluation of the design and methodological quality of studies, and each is assigned a particular level of evidence. The methodological quality is evaluated with various questionnaires, each for a particular type of study design, which are based on the MERGE questionnaires of the Healthcare Committee of New South Wales, Australia. To avoid any possible bias in the evaluation of the methodological quality, each study is assessed by a minimum of two independent experts. Any disagreements are settled through discussion with the entire group of experts or by an external independent expert. The quality of cohort and case-control studies is assessed by experts with experience in the appropriate clinical field. The scale of levels of evidence consists of 8 categories, from 1++ (the most reliable evidence: high-quality systematic reviews of RCTs, RCTs with a very low risk of systematic error) to 4 (the least reliable evidence: expert opinion).

Once each study has been assigned a particular level of evidence, a multidisciplinary expert group begins the task of actually writing the recommendations. This process consists of three stages: first an overall level of evidence is decided upon for all studies combined. To do this, the experts consider the quality and quantity of evidence, its consistency, the generalizability of study results and the applicability of evidence to the target population of patients. At the second stage the experts have to consider and comment on a number of factors related to how the recommendations will be implemented: the potential harm of following the recommendations, the amount of resources required for their implementation, the pros and cons of recommended measures for particular subgroups of patients, and the practical feasibility of recommendations. As a result, based on the overall level of evidence and an analysis of the likely consequences of implementing the recommendations, the expert group assigns one of four grades of recommendation: A, B, C or D. These grades do not reflect the clinical significance of recommendations: instead, they indicate how likely it is that the desired clinical effect will be achieved if the recommendations are followed. Accordingly, at the third stage the expert can choose a key recommendation, which in their opinion is likely to have the greatest impact on the patients’ health and quality of life. Moreover, the task force in charge of writing the recommendations has the right to suggest some so-called “good practice points” – rules that are so obvious that they do not need to be backed up with scientific evidence, i.e. it would be absurd to prove them scientifically.

Even though the task force provides a comprehensive justification for its decision, there are no strict criteria for assigning an overall level of evidence and grade of recommendation in the SIGN system.

An advantage of the SIGN system is the transparency of the process of assessing the methodological quality of studies based on questionnaires and assigning a level of evidence to each study. As a result, levels of evidence assigned to individual studies are highly reproducible, in

¹ A detailed description of all the analyzed systems of assessment may be found in the appendix to this article, which is available on the journal’s web page (www.hta-rus.ru/journal).
contrast to overall levels of evidence and grades of recommendation, for which there are no strict criteria. In 2009 the SIGN decided to switch to another system for grading evidence and recommendations – GRADE. The main principles of GRADE assessment that the SIGN is planning to use in future are described on their web page [26].

**OCEBM (OXFORD CENTER FOR EVIDENCE-BASED MEDICINE) [27-30]**

The mission of the Oxford Center for Evidence-based Medicine (OCEBM) is to promote and develop the principles of evidence-based medicine. The OCEBM scale of levels of evidence was first introduced in 1998 and then revised in 2009 and 2011. The latest version of the scale for assessing **levels of evidence**, just as all previous versions, was intended to be a tool for helping practicing physicians and patients to get their bearings in the world of rapidly accumulating medical evidence. The OCEBM scale of levels of evidence exists in several forms, and the choice of one of them depends on the clinical issue being analyzed, such as the prevalence of a particular medical problem, the effectiveness of a diagnostic test or screening, the outcome of an illness, the benefit or potential risks of treatment. An individual study is assigned a level of evidence based primarily on the study design, but it may be downgraded if the methodological quality of the study is unsatisfactory, the effect size is small, the results are heterogeneous or the evidence indirect; on the other hand, the level of evidence may be upgraded if the effect size is considerable. However, the authors of the OCEBM system do not specify any concrete criteria as to how much and in which cases the level of evidence should be up- or downgraded. The OCEBM scale of levels of evidence consists of 5 categories; for instance, when assessing the therapeutic benefit of an intervention, the level of evidence varies from 1 (the most reliable evidence: systematic reviews of RCTs or “N of 1”2 trials) to 5 (the least reliable evidence: there is only a substantiation of the mechanism of action).

The OCEBM system does not include an assessment of combined level of evidence scores or grades of recommendation. The advantage of this system is that it is straightforward to use and covers practically the whole spectrum of clinical issues that a physician or patient might face in the real-life clinical practice. Its disadvantage is the lack of concrete criteria for evaluating the methodological quality of studies and assigning the final level of evidence. However, the authors themselves note that this system is simply a supplement to the traditional systems for critical evaluation of evidence and may be used by physicians and patients only as a heuristic offering quick answers to clinical questions.

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2 Patients in an “N of 1” trial go through various treatment periods: a period of experimental therapy is followed by a period of standard therapy or placebo. The periods are repeated cyclically.

**GRADE (GRADING OF RECOMMENDATIONS ASSESSMENT, DEVELOPMENT AND EVALUATION) [31-45]**

GRADE is a system for classification and assessment of the quality of recommendations that was created by an international group of experts from several leading organizations for health technology assessment, including NICE, AHRQ, and NHMRC. The GRADE task force was formed in 2000 as an unofficial association of researchers interested in overcoming the shortcomings of the existing systems of assessment. The GRADE system was designed for writing systematic reviews and recommendations about alternative treatment strategies (including no treatment and modern standards of treatment). This grading system is applicable to a broad range of clinical issues, such as diagnostics, screening, prevention, therapeutic treatment, and public health issues.

One of the distinguishing features of the GRADE system is its classification of treatment outcomes according to their significance for the patients with the help of a specially designed scale. This classification includes the following outcomes (in the decreasing order of significance): critical, important, and of limited importance. The reliability of evidence and level of evidence are assessed separately for each critical and important outcome for a combination of studies (Fig. 2). The reason for this outcome-oriented approach is the fact that the reliability of evidence of both an individual study and a group of studies depends on which outcome is assessed. For instance, if a series of RCTs without blinding investigated the severity of pain and overall mortality, it is quite obvious that the results for the former outcome were more affected by the bias arising from the lack of blinding and thus have a lower reliability.

There are 4 levels of evidence in the GRADE system: high, medium, low, and very low. By default, evidence from RCTs is assigned a high level of evidence, while evidence based on the results of observational studies is assigned a low level of evidence. However, there are 5 factors that may lead to downgrading evidence to a lower level and 3 factors that can upgrade evidence to a higher level. Factors leading to downgrading the level of evidence are the following:

1) risk of systematic error;
2) inconsistency of results across studies;
3) indirect evidence;
4) lack of precision in determining the size of effect;
5) publication bias3.

Factors leading to upgrading the level of evidence included the following:

1) a considerable effect size;

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3 Publication bias is a systematic error related to imperfect selection of studies, namely the tendency to publish studies with positive (statistically significant) results.
2) a dose-dependent effect;
3) interfering factors that are not accounted for and that would decrease the size of effect if they were eliminated.

Depending on the extent to which the factors listed above are present, the evidence may be up- or downgraded one or two levels. As the last step of grading the evidence, the final level of evidence and grade of recommendation

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**Fig. 2.** An outline of the process of assessing the level of evidence and the grade of recommendation with the GRADE system (adapted from [36]).
are determined, and they correspond to the lowest levels of evidence assigned to a group of critical outcomes. It should be noted that the GRADE system does not take into account or grade published systematic reviews and meta-analyses. The reason is that even methodologically flawless systematic reviews may be based on both high-quality studies with consistent results and weaker studies with a high risk of bias and inconsistent results, and thus the reliability of the conclusions of such reviews will be poor, despite their high methodological quality. The authors of the GRADE system provide specific criteria and detailed instructions both for assessing each factor that can influence the reliability of evidence and for grading the evidence. To evaluate the methodological quality of studies, the authors use the same criteria for assessing the likelihood of bias that are used by the Cochrane Collaboration.

The grade of recommendation in the GRADE system reflects the certainty that the benefits of an intervention on the whole outweigh its adverse effects. The modality of the recommendation (“for” or “against” an intervention) and its grade are chosen by a group of experts, which is not the same task force that was in charge of the systematic review and assessment of the quality of evidence. There are only two grades of recommendation in this system: a strong recommendation or a weak/conditional recommendation. The expert group chooses the category of “strong recommendation” only when they are entirely convinced that the expected benefits of an intervention outweigh its undesirable effects. The category of “conditional recommendation” is assigned when the expert group is less firmly convinced of a favorable tradeoff between the expected pros and cons of an intervention. The expert group considers four key factors when choosing the appropriate grade of recommendation:

- the reliability of evidence;
- the tradeoff between benefits and adverse effects;
- the values and preferences of patients;
- the cost of treatment.

It is expected that a strong recommendation would be followed by practically every physician and patient with perfect access to information about the intervention; a conditional recommendation would be followed by the majority of physicians and patients with perfect access to information about the intervention, but still a considerable number would make an alternative choice. The status of a conditional recommendation also assumes that physicians should carefully consider the values and preferences of patients and take them into account before recommending the intervention to them.

The main advantages of the GRADE system are its transparency, the clear sequence of steps in the course of the assessment of an intervention, detailed descriptions of the criteria for grading the evidence both for a single outcome and for a combination of outcomes, the requirement for a comprehensive justification for each decision, and the focus on the clinical significance of outcomes. Another advantage of the GRADE system is that it uses symbols and words instead of letters or numbers to indicate the level of evidence and grade of recommendation, making them easier to interpret. However, the authors of the GRADE system suggest that those organizations who wish to continue using letter/number codes may indicate the level of evidence with letters (from A to D) and the grade of recommendation with numbers (1 and 2). Having only two categories of the grade of recommendation (strong or conditional) also makes the recommendations more intuitive and simplifies their implementation in clinical practice.

The main disadvantage of the GRADE system is that it is complex and labor-intensive. Because of this, there is now free software called GRADEpro with an intuitive interface that is intended to simplify the process of grading the evidence and writing recommendations.

**NICE (NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE) [46]**

The British National Institute for Health and Clinical Excellence (NICE) is an independent organization that produces clinical guidelines, recommendations for using medical technologies (the results of health technology assessment), recommendations for implementing interventions, recommendations about public health (prevention of diseases and promotion of a healthy lifestyle). The principles of assessment developed by the NICE were last updated in 2009 and published on the web page of the Institute.

The system of grading evidence developed by NICE uses some of the elements of the GRADE system. For example, the reliability of evidence is assessed separately for each outcome, taking into account all the factors that have an impact on the reliability of evidence and are specified in the GRADE system. However, the NICE system also differs from the GRADE system in several important ways:

1) the methodological quality of studies is assessed with the help of questionnaires developed for each type of study design;

2) the methodological quality of studies is reviewed and assessed using the cost-effectiveness method;

3) combined level of evidence scores and combined grades of recommendations are not assigned;

4) the grades of recommendations are described verbally.

According to the rules of the NICE, the following factors are taken into account when recommendations are prepared: the level of evidence; the clinical significance of outcomes; the tradeoff between the benefits and adverse effects of the intervention; the cost-benefit ratio; a number of additional factors (e.g. the accessibility of the intervention to patients regardless of their gender, nationality, ethnic origin, age, religion, disabilities, etc). To make the transition from the assessment of the level of evidence...
to recommendation writing as transparent as possible, the NICE task force describes each of these factors, substantiating their judgments in an appendix to each report. The NICE system operates with three levels indicating the certainty that an intervention is worth implementing:

- the intervention must or must not be used;
- the intervention should or should not be used;
- the intervention could be used.

A recommendation stating that the intervention “must” be used signifies that it is necessary to use this intervention in all appropriate situations in order to comply with safety requirements and regulations pertaining to the provision of health care. Stating that the intervention “should” be used means that the NICE task force is convinced that the benefit of the intervention is greater than its possible harm for the overwhelming majority of patients and that the intervention will be cost-effective. Finally, if the recommendation states that the intervention “could” be used, it means that the benefit of the intervention is greater than its possible harm for the majority of patients and that the intervention will be cost-effective, but that there are alternative treatments that will also be cost-effective, or that patients may choose less effective but cheaper treatments. In the latter case, the choice of treatment strategy will depend on the values and personal preferences of patients.

Among the advantages of the NICE system we have to emphasize the high reproducibility of the results of assessing the methodological quality of studies (thanks to the use of questionnaires), the focus on the clinical significance of outcomes, and the precision and transparency of the GRADE criteria used to assess the level of evidence. Besides, the authors of the NICE system have completely rejected any codes for grades of recommendations in favor of verbal descriptions. On the one hand, this simplifies practical application of these recommendations, but on the other hand, it may hinder their dissemination among organizations and practicing physicians.

**NHMRC (National Health and Medical Research Council) [47-48]**

The Australian National Health and Medical Research Council (NHMRC) is in charge of writing recommendations in three fields: clinical practice, ethics of medical interventions, and public health. The most recent version of the NHMRC assessment system was developed based on three other systems – SIGN, GRADE and SORT (Strength of Recommendation Taxonomy) – and published in 2009.

The NHMRC system distinguishes five domains that may affect the level of evidence: evidence base, consistency, clinical impact, generalizability of the results to a target population of patients, and their applicability to the Australian health care. Each domain is graded as follows: A (excellent), B (good), C (satisfactory), and D (poor) according to strict criteria presented in a user-friendly table (matrix).

The first domain, “evidence base”, includes the design and methodological quality of studies as well as the amount of evidence (the number of studies and the number of patients in the samples). First each study is assigned an appropriate level in the hierarchy of study designs (the structure of this hierarchy depends on the nature of the clinical issue being investigated: a therapeutic intervention, diagnostic methods, prognosis or etiology of a disease, or screening methods). For example, when assessing therapeutic interventions, the top level in the hierarchy of designs is occupied by systematic reviews of RCTs, while case series occupy the lowest level. Then the methodological quality of each study is assessed, and the developers of recommendations are free to choose the appropriate tool for this task at their discretion. The authors of the NHMRC system offer some guidelines as to which questionnaires are the most appropriate for assessing the methodological quality of studies, depending on their design and the clinical problem (for instance, the GATE questionnaire is recommended for assessing the quality of studies of disease prognosis, while the SIGN or CASP questionnaires are recommended for the assessment of systematic reviews, and so on).

The domain of “clinical impact” includes the assessment of the precision with which the effect is measured, its size and clinical significance for the patients (also compared to alternative treatment strategies), and the tradeoff between the benefit and harm of the intervention. According to the authors of the NHMRC system, the assessment of this domain is particularly subjective and calls for active discussion among all members of the task force in charge of writing the recommendations.

There are no levels of evidence in the NHMRC system, and each recommendation is accompanied by an assessment of each of the 5 domains. The grade of recommendation is calculated as a sum of these assessments (A, B, C or D), and it reflects the reliability of evidence on which the recommendation is based. For instance, recommendations graded A or B are based on evidence that may be seen as reliable in clinical practice, but recommendations graded C or D should be treated with caution and considered in each particular situation. A recommendation may be graded A or B only if the first two domains, “evidence base” and “consistency”, are also graded A or B.

The NHMRC system has a number of advantages: it is possible to see at a glance the contribution of each of the 5 domains to the overall grade of recommendation. Thanks to this approach, different healthcare workers can if necessary make their own decisions, prioritizing this or that domain depending on the nature of the task – and these tasks can vary greatly, from writing recommendations for treating individual patients to making decisions about reimbursement of treatment in an entire country. The main disadvantage of this system is that in it there is no clear distinction between the grading of evidence and the grading of recommendations and no such concept as “the level of evidence”.

Our comparative analysis of the best-established systems of grading evidence and recommendations demonstrated that, despite a number of significant differences, all these systems are based on the same founding principles of assessment (Table 1). When assessing the level of evidence, each of these systems uses three main criteria: quality of evidence (design and methodological quality of studies), quantity or amount of evidence (effect size, the number of studies, the total number of patients), and consistency of evidence. The main difference in grading evidence concerns the object that is graded: in some systems a level of evidence is assigned to each individual study (OCEBM, SIGN) and a group of studies are assigned an overall level of evidence (SIGN); in other systems a level of evidence is assigned to pooled evidence relating to each individual treatment outcome from all studies (GRADE, NICE), while the overall level of evidence corresponds to the lowest level of evidence among all critical and important outcomes (GRADE). Instead of assigning levels of evidence, the Australian NHMRC system assesses pooled evidence in a number of separate domains: “evidence base”, “clinical impact”, “consistency”.

With the exception of OCEBM, all these grading systems are intended for writing clinical guidelines, and their final goal is to assign a grade of recommendation (SIGN, GRADE, NHMRC) or a level of certainty in the desirability of implementing the intervention (NICE). Instead of assigning levels of evidence, the Australian NHMRC system assesses pooled evidence in a number of separate domains. This is the only assessment system among the ones analyzed in this article that lacks a clear distinction between grading of evidence and grading of recommendations.

All these systems (including OCEBM) grade recommendations based primarily on the level of evidence and a
number of more or less the same additional criteria, such as the tradeoffs between the benefit and harm of the intervention, the generalizability of evidence, and the cost of treatment (the latter is not taken into account by the NHMRC system). The authors of the NHMRC system did not include the cost of treatment in the list of criteria for grading recommendations, reasoning that the “willingness to pay” of the end users of recommendations will vary strongly, depending on the circumstances [47]. Besides similar criteria for assessing the level of evidence, the authors of different grading systems also include some additional criteria, such as the applicability of recommendations to the national health care (NICE, NHMRC) and the values and preferences of patients (GRADE).

It should be noted that, despite employing a complex and multi-step process of assessment, none of these systems are capable of completely eliminating the need for judgments (often subjective) on the part of expert members of the task force. To make the grading process as transparent as possible, all the systems discussed above emphasize that every decision about the level of evidence or the grade of recommendation must be documented in detail.

THE PROSPECTS FOR IMPLEMENTING A UNIFIED SYSTEM FOR GRADING EVIDENCE AND RECOMMENDATIONS IN RUSSIA AND IN OTHER COUNTRIES

Given the ongoing proliferation of various clinical recommendations and the growing confusion surrounding their interpretation and practical implementation, it has now become obvious that we need a unified approach to the grading of evidence and recommendations. However, researchers and physicians still have not reached a consensus about whether such a unified system is needed and what it should look like. The most important arguments for establishing a unified system are the following: 1) it would eliminate any confusion about how to interpret and implement clinical guidelines, and 2) it would make it impossible to “go fishing” for a grading system that would assign the highest level of evidence and grade of recommendation to a particular intervention [12]. The only serious argument against a unified grading system is that there is some doubt as to whether it may be possible to have an adequate assessment of the entire range of medical problems, from clinical efficacy of interventions to the effectiveness of the whole healthcare system, within the framework of a single system. Presumably, even if a unified grading system is created, it may turn out to be very complex [12].

Despite the current controversy, a growing number of international organizations are beginning to realize that it is necessary to implement a unified grading system. At present the most common and widely discussed system is probably GRADE, which has already been adapted by over 50 international organizations, such as the WHO, Cochrane Collaboration, SIGN, NICE, AHRQ, Centers for Disease Control and Prevention (CDC) and many European, American and Canadian professional medical associations (http://www.gradeworkinggroup.org/). Compared to other systems, GRADE offers a number of advantages, such as: treatment outcomes are classified according to their importance to the patients; there are detailed criteria for assessing the level of evidence both for separate outcomes and for their combinations; the decision-making process is transparent; the system of designating levels of evidence and grades of recommendations is straightforward; formalized tables are used to present the results of assessment; free software (GRADEpro) is available.

In 2009 Cuello-Garcia et al. [15] addressed international experts who specialize in writing clinical guidelines and suggested that they assess 7 different grading systems (GRADE, NICE, SIGN, OCEBM, SORT, CTFPH, USTFPS) on a 4-point Likert scale based on how easy these systems are to use, how labor- and resource-intensive they are, whether the final grades are unambiguous, and whether the criteria for grading evidence (quality, quantity and consistency of evidence) are comprehensive. The results of this survey demonstrated that the GRADE and NICE systems were preferred by the majority of experts and scored the highest [15]. The results of an RCT that investigated the impact of clinical recommendations on the physicians’ decision to use particular interventions in clinical practice also speak in favor of the GRADE system [16]. This RCT was performed in a sample of pediatricians in Mexico, who were randomly allocated to one of four parallel groups and had to make a choice about prescribing racecadotril to children with diarrhea before and after consulting clinical recommendations. Physicians in different groups were allowed to consult different clinical guidelines, which were based on one of four grading systems (NICE, SIGN, GRADE, OCEBM). The results of this RCT demonstrated that the attitude of physicians towards prescribing racecadotril was most likely to change after they had read clinical recommendations based on the GRADE system. Among the reasons why the impact of these recommendations on practicing physicians was the highest, the authors emphasize that these recommendations are unambiguous (a recommendation can be either strong or weak) and that a complex approach to the process of writing recommendations inspires confidence.

However, we should remember that, despite its growing popularity and a number of advantages, the GRADE system also has some flaws: notably, it is not very user-friendly and very labor-intensive to produce. These disadvantages might limit its general adoption.

To summarize, the time is ripe for the international medical community to adopt a unified system for grading evidence and recommendations, and there is already a tendency to switch to such a system. But this transition is likely to take many years, and it is still not clear whether the GRADE system will emerge as the new standard.
PROSPECTS FOR DEVELOPING A SYSTEM FOR GRADING EVIDENCE AND RECOMMENDATIONS IN RUSSIA

In Russia systems for grading evidence are used primarily in order to prepare the List of Vital and Essential Drugs and a number of national clinical guidelines. In accordance with the most recent version of the “Regulation for Drafting a List of Vital and Essential Drugs” issued by the Ministry of Health and Social Development of the Russian Federation in 2012, the preparation of the List includes clinical evaluation of the pharmaceuticals suggested for inclusion in the List. In the course of this clinical evaluation, senior specialists at the Ministry of Health analyze the quality of each individual clinical trial of each drug, and then the efficacy of this drug is graded in accordance with how convincing the evidence is (which corresponds to levels of evidence), as follows:

A – highly reliable evidence based on the results of several independent clinical trials with consistent results that have been combined in systematic reviews;

B – moderately reliable evidence from several independent randomized clinical trials with similar objectives;

C – limited reliability: the effectiveness data comes from a single clinical trial;

D – stringent scientific evidence is missing, no appropriate clinical trials have been conducted, and the claims of effectiveness are based on expert opinion.

The outcome of clinical evaluation is considered to be positive if the evidence is assigned level A or B. Obviously, this approach to grading the evidence for the effectiveness of pharmaceuticals for the purpose of creating a List of Vital and Essential Drugs is a gross simplification compared to the grading systems discussed in this review, since this process of assigning a level of evidence does not follow closely enough the international principles of grading evidence, namely the quality, quantity and consistency of evidence.

A considerable proportion of Russian clinical guidelines is not based on a systematic analysis of scientific evidence [17]. Even when attempts are made to write recommendations following the principles of evidence-based medicine, the procedure often clashes with international standards. For example, when the Russian Respiratory Society in 2010 published their recommendations called “Outpatient pneumonia among adults: practical recommendations for diagnostics, treatment and prevention”, several “categories of evidence” were specified (Table 2) [49]. The “category of evidence” indicated both the level of evidence and the grade of recommendation. The level of evidence was assessed based on the quality and quantity, but not the consistency, of evidence. The recommendations were written with only one criterion in mind – the level of evidence. None of the additional criteria (benefit-to-harm ratio of the intervention, generalizability of evidence, cost of treatment or values and preferences of patients) were taken into account.

We can thus see that Russia is lagging behind the developed countries when it comes to grading evidence and recommendations. In order to implement such tools of evidence-based medicine as levels of evidence and grades of recommendations, Russian experts should draw on the international experience of well-established organizations and associations for health technology assessment. When choosing the grading system that will be adapted and implemented in Russia, it is important to consider the level of expertise among our experts as well as the costs in terms of time and financial resources that can be borne by the Russian healthcare system. It is also important to consider how well the chosen system will correspond to the actual objectives (preparing formulary lists or writing national guidelines). The GRADE system deserves particular attention when the grading system is chosen, since it is at present one of the most comprehensive, transparent and objective grading systems and the top candidate for the unified international system. It is possible that this system will need some modifications when it is adapted to the conditions characteristic of the Russian clinical practice and health care. However, the authors of the GRADE system are against serious modifications, since this would undermine the project of establishing a unified international grading system.

Whichever grading system gains recognition in Russia, we must realize that the purpose of an effective grading system is not to preclude any personal judgment but

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**Table 2. Categories of evidence and their interpretation in the clinical guideline “Outpatient pneumonia among adults: practical recommendations for diagnostics, treatment and prevention”** [49]

<table>
<thead>
<tr>
<th>Category of evidence</th>
<th>Source of evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Randomized controlled trials</td>
<td>The evidence comes from well–designed randomized trials that included a sufficient number of patients to obtain reliable results. The recommendations are suitable for general application</td>
</tr>
<tr>
<td>B</td>
<td>Randomized controlled trials</td>
<td>The evidence comes from randomized controlled trials, but the number of patients is not sufficient to obtain statistically significant results. The recommendations are suitable for a limited population</td>
</tr>
<tr>
<td>C</td>
<td>Non–randomized clinical trials</td>
<td>The evidence comes from non–randomized clinical trials or studies that included a limited number of patients</td>
</tr>
<tr>
<td>D</td>
<td>Expert opinion</td>
<td>The evidence is based on a consensus opinion about a particular problem reached by a group of experts</td>
</tr>
</tbody>
</table>
rather to make the process of assessing evidence and writing recommendations more transparent and logical. In fact, even though grading is common in evidence-based medicine, the quality and reliability of evidence as well as the soundness of guidelines are continuous characteristics, and their arbitrary division into discrete levels is a simplification of the actual situation. On the other hand, such levels promote optimal decision making in health care as well as implementation and wide adoption of clinical recommendations. Then again, the availability of a hierarchy of levels has the psychological effect of partially taking away the sense of responsibility, freeing people from the need to reason and draw their own conclusions [29]. Levels of evidence and grades of recommendations should never, under any circumstances, be accepted without first deliberating and thoroughly analyzing each particular situation [13, 14].

REFERENCES

47. NHMRC levels of evidence and grade of recommendations. 2009.

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**INTRODUCTION**

The social significance of prostate cancer is determined by the morbidity and mortality from this condition, which has been growing steadily over the last decade, and by the considerable frequency of diagnosing patients at late stages of this disease, when it is no longer possible to apply radical treatment methods. According to the official statistics, in ten years primary morbidity from prostate cancer in Russia grew from 11.58 thousand cases in 2000 to 26.26 thousand cases in 2010 (a 2.26-fold increase), and the number of followed-up patients with prostate cancer grew by 155%. In contrast with the standardized indices of mortality from all malignancies, which decreased considerably between 2000 and 2010, we are witnessing ever higher rates of death from prostate tumors, which grew from 8.23 to 11.61 per 100 000 population – an increase of 41.39% [1-4].

Because of high morbidity and mortality, both early diagnostics of prostate cancer and the choice of an effective treatment strategy are equally important. Considering that more than half of prostate cancer cases are diagnosed at the stage of locally advanced or metastatic cancer (52.5%) [2, 3], there is a need to improve the methods of treating widespread forms of prostate cancer, including an investigation of their economic acceptability and cost-effectiveness [5-9].

One of the effective methods of palliative therapy offered at the most common stages of this disease is hormonal therapy. As far as therapeutic efficacy is concerned, the best method of hormonal therapy is administration of prolonged-action gonadotropin-releasing hormone (GnRH) analogues, which hold an edge over other groups of drugs thanks to their efficacy and considerably better safety. At present this group of drugs is widely used both when prostate cancer is progressing and at earlier stages [7].

**The objective of this study** was to perform a comparative clinical and economic analysis of prostate cancer treatment with various prolonged-action gonadotropin-releasing hormone (GnRH) analogues administered once a month that have been registered in Russia (leuprorelin, goserelin, triptorelin). We demonstrate that in terms of clinical efficacy and safety continuous hormonal monotherapy with GnRH analogue leuprorelin (trade name [TN] Lucrin Depot) for 1 year is identical to therapy with other drugs of this class – goserelin (TN Zoladex) and triptorelin (TN Diphereline). However, leuprorelin is more cost-effective, and its use can reduce the cost of pharmacotherapy.

**KEYWORDS:** prostate cancer, gonadotropin-releasing hormone analogues, leuprorelin, goserelin, triptorelin, cost-minimization analysis.
analogs have identical clinical efficacy. Based on this initial hypothesis, we suggested that prolonged-action leuprorelin may be more cost-effective compared to other representatives of this class of pharmaceutical drugs.

In order to confirm the working hypothesis, we analyzed the existing data on the clinical efficacy and safety of leuprorelin compared with goserelin and triptorelin in the treatment of prostate cancer. The sources of data were the Medline database (U.S. National Library of Medicine, NLM: http://www.ncbi.nlm.nih.gov/pubmed/) and the library of the Cochrane Collaboration (http://www.cochrane.org/). We searched for the results of studies published between 1992 and 2011. In order to select studies with the most reliable results, we assessed the methodological quality of all studies that could potentially be relevant to our review. After the exclusion of duplicates and publications not relevant to hormonal therapy of prostate cancer with GnRH analogues or not meeting the required level of evidence (Ia or Ib), 4 studies were selected and included in the final analysis [16-19]. The selection of studies is presented in Fig. 1.

Even though four GnRH analogues are registered in the Russian Federation (leuprorelin, triptorelin, goserelin, and buserelin), we only compared the profiles of clinical efficacy and safety of leuprorelin, goserelin and triptorelin. The reason is that there are no direct comparative clinical studies confirming that buserelin – a drug produced in Russia – has the same efficacy and safety as the original drugs.

Based on the results of our analysis, we concluded that the clinical efficacy and safety of the drugs included in this study were similar, allowing us to rely on the method of “cost minimization”.

The economic analysis consisted in estimating direct medical costs from the perspective of the Russian healthcare system, including the per-patient cost of androgen deprivation of generalized forms of prostate cancer with prolonged-action GnRH analogues administered as monotherapy. In this study we performed a comparative pharmacoeconomic evaluation of androgen deprivation with prolonged-action GnRH analogues based on a number of assumptions:

- only original GnRH analogues were included in the economic analysis – leuprorelin (TN Lucrin Depot), goserelin (TN Zoladex), and triptorelin (TN Diphereline);
- the costs of pharmacotherapy were calculated based on the dosing regimen described in the instructions for use for each analyzed drug.

Dosing regimens with GnRH analogues were determined based on an analysis of the guidelines of the European Association of Urology and of the regimens of hormonal therapy with prolonged-action GnRH analogues recommended by the P. A. Gertsen Moscow Research Institute of Oncology [7, 8]. Regimens of hormonal therapy and the duration of treatment were determined based on instructions for use of each drug and published data [10-15].

The cost of hormonal therapy for prostate cancer was estimated based on the dosing regimen for each drug (1 injection once per month for Lucrin Depot, 1 injection every 28 days for Zoladex and Diphereline) and the duration of continuous therapy over the period of one year3. Since all the analyzed drugs are included in the List of Vital and Essential Drugs, we used the registered maximum selling prices of the manufacturers of GnRH analogues, taking into account the maximum wholesale markup in Moscow in accordance with the registry of prices for the List of Vital and Essential Drugs at the time when the study was performed (June 2011) [20].

In line with the research hypothesis, which was proven at the first stage, we performed a particular type of cost-effectiveness analysis – “cost minimization” analysis – in order to evaluate the cost-effectiveness of the alternative

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2 The level of evidence of the publications included in our review was determined according to the scale developed by the Agency for Health Care Policy and Research (AHCPR, 1992):

Ia – evidence from meta-analyses of RCTs;
Ib – evidence from at least one RCT.

3 The duration of androgen deprivation varies from 6 months to lifelong therapy, depending on the patient’s condition rather than the chosen drug.
methods of hormonal therapy for prostate cancer. The difference in costs was calculated as follows [21]:
\[ \text{CMD} = DC_1 - DC_2 \]
where
- CMD is the difference in costs,
- \( DC_1 \) is the cost of using the first technology,
- \( DC_2 \) is the cost of using the second technology.

To check how the cost-effectiveness of the evaluated technologies would change with fluctuating values of the original parameters, we performed a single-factor analysis of sensitivity to fluctuations in the price of leuprorelin. We calculated the price range of one package of leuprorelin (TN Lucrin Depot) within which therapy with leuprorelin for prostate cancer still offers better cost-effectiveness compared to therapy with other GnRH analogues included in our analysis.

Moreover, in this study we estimated the number of additional patients that can receive a course of treatment provided that the more cost-effective therapy is used:
\[ N_{add} = \frac{\text{CMD} \times N}{\text{Cost}_L} \]
where
- \( N_{add} \) is the number of additional patients that can receive treatment,
- CMD is the difference in the cost per patient (the difference in the cost of treatment between various regimens containing GnRH analogues),
- \( N \) is the number of patients in one cohort (100 people),
- Cost\(_L\) is the cost of treatment with the cheaper therapeutic regimen per patient.

### RESULTS AND DISCUSSION

The cost-effectiveness of GnRH analogues was demonstrated in a meta-analysis that assessed the 2-year survival of patients treated with GnRH analogues (leuprorelin, buserelin and goserelin) compared to surgical castration based on the results of 10 RCTs [16]. The overall hazard ratio (HR) of death for GnRH versus surgical castration was 1.1262 (95% CI [0.915, 1.386]). The HR of death for each of the evaluated GnRH analogues versus surgical castration was as follows: 1.0994 (95% CI [0.207-5.835]) for leuprorelin; 1.1315 (95% CI [0.533-2.404]) for buserelin; 1.1172 (95% CI [0.898-1.390]) for goserelin.

Our analysis also included three studies which directly compared leuprorelin to other GnRH analogues [17-19] and which were not covered by the meta-analysis. The study by C. C. Abbou et al. [17] did not measure the survival of prostate cancer patients, and two more studies [18, 19] were published after the date of the meta-analysis; besides, one of them was a retrospective study rather than an RCT [19]. These three studies relied on a surrogate measure (castrate levels of testosterone) to compare the clinical efficacy of the evaluated drugs, and the safety criterion was usually the rate of adverse side effects. C. C. Abbou et al. [17] performed a randomized study, in which they assessed the efficacy and safety of leuprorelin 3.75 mg and triptorelin 3.75 mg administered once a month in 68 patients with prostate cancer over 6 months of observation. The proportion of patients achieving castrate levels of testosterone (no more than 0.5 ng/mL), was not significantly different when measured after 1, 3 and 6 months of follow-up. The overall safety of this therapy was considered to be good. The study by N. Tanaka [18] looked at the endocrine response over the first 4 weeks of therapy in patients with prostate cancer stage T2-4, who were given leuprorelin 3.75 mg s/c or goserelin 3.6 mg i/m. The number of patients in this study was small (n=22), indicating a high risk of systematic error. The author reports that the increase in testosterone levels was significantly higher on day 3 of observation in the leuprorelin group. The level of free testosterone on day 3 and day 7 was also higher when the patients were given leuprorelin. The decrease in the concentration of luteinizing hormone on day 28 of observation was more pronounced in the goserelin group. Thus this article reports differences in the endocrine response to therapy with goserelin and leuprorelin. A retrospective non-randomized study by Y. Fujii [19] was conducted to assess testosterone suppression in 232 patients with prostate cancer who received one- or three-month formulations of leuprorelin and goserelin. The highest average testosterone level was: 0.22 ng/mL for 1-month formulation of leuprorelin (40 patients); 0.20 ng/mL for 3-month formulation of leuprorelin (68 patients); 0.19 ng/mL for 1-month formulation of goserelin (50 patients); 0.20 ng/mL for 3-month formulation of goserelin (74 patients). The differences were not statistically significant. The authors conclude that the 1-month and 3-month formulations of goserelin and leuprorelin have a similar, and significant, therapeutic effect and suppress testosterone levels in men with prostate cancer. To summarize, two studies [17, 19] demonstrated that there are no statistically significant differences in the effectiveness of GnRH analogues (leuprorelin 3.75 mg, goserelin, triptorelin) in terms of the castrate levels of testosterone. Judging by the results of this comparative analysis of the clinical efficacy and safety of GnRH analogues, we can conclude that they are equally effective in terms of achieving castrate levels of testosterone and improving the overall survival; there were also no differences in the safety profiles of these drugs. The studies that were included in the final analysis are described in Table 1.

To conclude, our analysis of the available evidence base for the clinical efficacy of GnRH analogues confirmed the research hypothesis of equivalent efficacy of leuprorelin compared to goserelin and triptorelin. These results justify the use of “cost minimization” method to estimate pharmacoeconomic parameters.

Considering the recommended regimens for the treatment of generalized forms of prostate cancer with GnRH analogues, leuprorelin (TN Lucrin Depot) is the cheapest alternative for hormonal therapy in terms of the cost of a course of pharmacotherapy calculated per patient (94,422.60 RUB). Compared to the reference
therapy with leuprorelin, the cost of pharmacotherapy is increased by 13,801.75 RUB per patient per year (108,224.10 RUB) if goserelin (TN Zoladex) is used and by 32,963.49 RUB (127,386.10 RUB) if triptorelin (TN Diphereline) is used. If leuprorelin is prescribed for androgen deprivation instead of the more expensive alternatives, 14 extra patients with prostate cancer can be treated when leuprorelin replaces goserelin and 34 extra patients when leuprorelin replaces triptorelin (calculated per 100 patients; Table 2).

Table 1. Studies included in the analysis of evidence for the clinical efficacy and safety of GnRH analogues

<table>
<thead>
<tr>
<th>First author, year of publication [reference]</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seidenfeld J., 2000 [16]</td>
<td>A meta--analysis of 10 RCTs (1908 patients), the main purpose of which was to compare alternative scenarios of hormonal therapy: surgical castration and hormonal therapy with GnRH analogues (goserelin, buserelin, and leuprorelin*). The primary effectiveness criterion was overall survival rate.</td>
<td>No difference in the 2-year survival of patients after GnRH therapy versus surgical castration. An indirect comparison of survival with goserelin, buserelin and leuprorelin* did not detect any difference, either. There is no reliable evidence that GnRH analogues differ in terms of their efficacy.</td>
</tr>
<tr>
<td>Abbou C. C., 1997 [17]</td>
<td>An RCT performed in order to compare the efficacy and safety of leurorelin* 3.75 mg/month and triptorelin 3.75 mg/month in terms of their ability to reduce the concentration of testosterone in the serum to castrate levels in prostate cancer patients. The duration of this study was 6 months. There were 68 patients in the cohort included in the study.</td>
<td>The proportion of patients who achieved castrate levels of testosterone (not more than 0.5 ng/mL) was not significantly different when measured after 1, 3 and 6 months of follow-up. The overall safety of therapy was considered to be good.</td>
</tr>
<tr>
<td>Tanaka N., 2007 [18]</td>
<td>An RCT performed to assess the endocrine response in the first 4 weeks of therapy with leuprorelin (TN Leuprolide) 3.75 mg s/c once a month versus goserelin 3.6 mg i/m once a month. This study included 22 patients with prostate cancer stage T2–4, Nx, Mx</td>
<td>The study was performed in a very small group of patients (n=22), indicating a high risk of systematic error. Therefore, the results of this study cannot be considered valid.</td>
</tr>
<tr>
<td>Fuji Y., 2008 [19]</td>
<td>A retrospective study that assessed the suppression of serum testosterone by leuprorelin (TN Leuprolide) 3.75 mg and 7.5 mg versus goserelin 3.6 mg and 10.8 mg. The number of patients in the cohort was 232. Mean age = 70. Average testosterone levels before therapy = 4.54 ng/mL. Number of patients without metastasis = 162. Number of patients with metastases = 70.</td>
<td>The highest average testosterone level was: 0.22 ng/mL for 1-month formulation of leuprorelin (40 patients); 0.20 ng/mL for 3–month formulation of leuprorelin (68 patients); 0.19 ng/mL for 1-month formulation of goserelin (50 patients); 0.20 ng/mL for 3–month formulation of goserelin (74 patients). The differences were not statistically significant. Conclusion: 1-month and 3–month formulations of goserelin and leuprorelin have a similar, and significant, therapeutic effect and suppress testosterone levels in men with prostate cancer.</td>
</tr>
</tbody>
</table>

* Leuprorelin microspheres

Table 2. The cost of hormonal therapy with GnRH analogues administered continuously for one year

<table>
<thead>
<tr>
<th>INN</th>
<th>Trade name</th>
<th>Formulation</th>
<th>Maximum selling price with VAT, RUB</th>
<th>Regimen</th>
<th>Cost of treating a cohort of 100 patients for 1 year, RUB</th>
<th>Cost difference, RUB</th>
<th>Number of extra patients who can be treated with more cost-effective therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprorelin Lucrin Depot</td>
<td>Lyophilisate for preparing a suspension for i/m or s/c prolonged–action injection, 3.75 mg. One kit contains: (9 mL ampules) 4.1 mg of lyophilisate N 1 with solvent (2 mL ampules) N 1, a napkin, a syringe and two needles for injections</td>
<td>7,868.55</td>
<td>3.75 mg once per month (12 injections per year)</td>
<td>9,442,260.00</td>
<td>Reference therapy</td>
<td>Reference therapy</td>
<td>14</td>
</tr>
<tr>
<td>Goserelin Zoladex</td>
<td>One capsule for subcutaneous prolonged–action injection, 3.6 mg (1 syringe)</td>
<td>8,324.95</td>
<td>3.6 mg once every 28 days (13 injections per year)</td>
<td>10,822,410.00</td>
<td>1,380,150.00</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Triptorelin Diphereline</td>
<td>Lyophilisate for preparing a suspension for intramuscular prolonged–action injection, 3.75 mg, ampules + solvent: 0.8% solution of mannitol (ampules) 2 mL, 2 disposable syringes and injection needles, cardboard packaging</td>
<td>9,798.93</td>
<td>3.75 mg once every 28 days (13 injections per year)</td>
<td>12,738,610.00</td>
<td>3,296,350.00</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

therapy with leuprorelin, the cost of pharmacotherapy is increased by 13,801.75 RUB per patient per year (108,224.10 RUB) if goserelin (TN Zoladex) is used and by 32,963.49 RUB (127,386.10 RUB) if triptorelin (TN Diphereline) is used. If leuprorelin is prescribed for androgen deprivation instead of the more expensive alternatives, 14 extra patients with prostate cancer can be treated when leuprorelin replaces goserelin and 34 extra patients when leuprorelin replaces triptorelin (calculated per 100 patients; Table 2).
In other words, since all three GnRH analogues are identical in terms of their clinical efficacy and safety, any economic advantages depend on the cost of treatment with each drug. In the context of continuous hormonal therapy with GnRH analogues administered monthly for one year, leuprorelin is more cost-effective than other drugs from this class — goserelin and triptorelin.

A sensitivity analysis demonstrated that hormonal therapy of prostate cancer with leuprorelin (TN Lucrin Depot) remains cost-effective under the following conditions:

- compared with goserelin (TN Zoladex) — as long as the price of one package of leuprorelin remains under 9,017.36 RUB (+14.6% to the current price);
- compared with triptorelin (TN Diphereline) — as long as the price of one package of leuprorelin remains under 10,615.46 RUB (+34.91% to the current price; Table 3).

It should be pointed out that these results agree well with the conclusions of another pharmacoeconomic study performed in 2010 at the Research Institute of Urology of the Ministry of Health and Social Development of the Russian Federation in order to evaluate various prolonged-action GnRH analogues with different dosing regimens in the treatment of prostate cancer in Russia [9]. Among the group of prolonged-action GnRH analogues administered once per month through an injection, the annual costs of androgen deprivation were as follows:

- leuprorelin (TN Lucrin Depot 3.75 mg) — 104,360 RUB per year;
- goserelin (TN Zoladex 3.6 mg) — 111,190 RUB per year;
- triptorelin (TN Diphereline 3.75 mg) — 125,370 RUB per year.

We can thus see that in this study leuprorelin (TN Lucrin Depot 3.75 mg) also turned out to be more cost-effective, while the efficacy of all prolonged-action GnRH analogues administered once per month through an injection was similar.

CONCLUSION

1. A comparative analysis of the results of clinical trials demonstrated that GnRH analogues evaluated in this study — leuprorelin, goserelin and triptorelin — are identical in terms of their clinical efficacy and safety.

2. The cost of a course of pharmacotherapy calculated per patient per year is the lowest when leuprorelin (TN Lucrin Depot) is used — 94,422.60 RUB; alternative strategies of hormonal therapy are more expensive: goserelin — 180,224.10 RUB (difference in cost versus leuprorelin — 13,801.75 RUB), triptorelin — 127,386.10 RUB (difference in cost — 32,963.49 RUB).

3. If leuprorelin is prescribed for androgen deprivation instead of the more expensive alternatives, 14 extra patients with prostate cancer can be treated when leuprorelin replaces goserelin and 34 extra patients when leuprorelin replaces triptorelin (calculated per 100 patients).

4. Monotherapy with leuprorelin (TN Lucrin Depot) remains a cost-effective option for hormonal therapy of prostate cancer even if its price is increased by up to +14.6% from the current level (9,017.36 RUB per package) when compared to goserelin (TN Zoladex) or up to +34.91% (10,615.46 RUB per package) when compared to triptorelin (TN Diphereline).

REFERENCES


Table 3. The results of our sensitivity analysis: the highest wholesale price of leuprorelin at which it is still more cost-effective than other GnRH analogues

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Price of 1 package of leuprorelin (Lucrin Depot), RUB (% of the current price)</th>
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<tbody>
<tr>
<td>Goserelin (Zoladex)</td>
<td>9,017.36 (+ 14.6%)</td>
</tr>
<tr>
<td>Triptorelin (Diphereline)</td>
<td>10,615.46 (+ 34.91%)</td>
</tr>
</tbody>
</table>
9. Apolikhin O. I., Sivkov A. V., Zhernov A. A., Keshishev I. G. Far- 
makoekonomicheskaya otseka analogov LGRG pri lechenii raka 
predstavlyayushchey v Rossii: obosnovanie dlya l'gotnogo obe-
specheniya. Ekperimental'nyi meditsinskiy zhurnal: onkologiya, 2010; 
No. 3. URL: http://www.euro.ru/journal/nomer-3-2010. In Russian 
[O. I. Apolikhin, A. V. Sivkov, A. A. Zhernov, I. G. Keshishev. A 
pharmacoeconomic evaluation of GnRH analogues in the treat-
ment of prostate cancer in Russia: a justification of discounted provision 
of drugs. Experimental and Clinical Urology.]

10. Bukharkin B. V. Sovremennaya medikamentoznaya gormonal'nyaya 
terapiya pervichno vyavlennogo disseminirovannogo raka 
predstavlyayushchey v Rossii. Rossiyskiy meditsinskiy zhurnal: onkologiya, 
2003; t. 11; No. 11. In Russian [B. V. Bukharkin. Modern hormonal 
therapy of newly diagnosed disseminated prostate cancer. The 
Russian Medical Journal: Oncology, 2003; v. 11; No. 11.]

11. Velyeyev E. I. Gormonal'naya terapiya raka predstavlyayushchey v 
Rossii. Prakticheskaya onkologiya, 2008; t. 9; No. 2: 98-103. In Russian [E. 
I. Velyeyev. Hormonal therapy of prostate cancer. Practical Oncology, 
2008; v. 9; No. 2: 98-103.]

12. Rusakov I. G., Alekseyev B. Ya. Gormonoterapiya generalizovan-
nogo RPZh. Oncologiya (zametki klinitsista) RPZh: 8-13. In Rus-
sian [I. G. Rusakov, B. Ya. Alekseyev. Hormonal therapy of gen-
eralized prostate cancer. Oncology (notes of a clinician) of prostate 
cancer: 8-13.]

13. Karelin M. I. Vozmozhnosti palliativnoy i simptomatsicheskoy tera-
pii raka predstavlyayushchey v Rossii. Prakticheskaya onkologiya, 2001; 
and symptomatic treatment of prostate cancer. Practical Oncology.]

14. Dudnichenko A. S. Sovremennye napravleniya gormonoterapii raka 
predstavlyayushchey v Rossii. Oncology (notes of a clinician) of prostate 
cancer. 2003; t. 3; No. 2-3: 110-112. In Russian [A. S. Dudnichenko. Current approaches to hormonal 
therapy of prostate cancer. Oncology (notes of a clinician) of prostate 
cancer: 110-112.]

15. Risner P. I., Pushkar D. Yu., Govorov A. V. Gormonal'naya terapiya 
raka predstavlyayushchey v Rossii. Sovremennaya onkologiya, 2008; 
of the effectiveness of neoadjuvant therapy with bicalutamide and 
goserelin for 3 or 6 months prior to radical prostatectomy. Modern 
Oncology, 2008; v. 10; No. 4: 59-63.]

C., Bennett C. L., Wilt T. J. Single-therapy androgen suppression in 
men with advanced prostate cancer: a systematic review and meta-

17. Abbou C. C., Lucas C., Leblanc V. Tolerance and clinical and 
biological responses during the first 6 months of treatment with 
1-month sustained release LHRH agonists leuprolerin and triptoler-
in in patients with metastatic prostate cancer Prog Urol. 1997; Dec; 
7 (6): 984-95.

18. Tanaka N., Fujimoto K., Hirao Y., Shimizu K., Tsujimoto S., Sama s 
S. Endocrine response to a single injection of goserelin 3.6 mg or 
leuprolide 3.75 mg in men with prostate cancer. Arch Androl. 2007; 

Equivalent and sufficient effects of leuprolide acetate and goserelin 
suf ficiently low to suppress serum testosterone levels in patients with 

20. Informatiya o predel'nykh otpusknyh tsenah proizvoditeley 
in predel'nykh roznichnykh tsenah na zhiznenno neobhodimyie i vazh-
nelyshye lekarstvennye preparaty v Rossiyskoy Federatsii po sos-
toyaniyu na may mesyats 2011 goda. URL: http://www. minzdrav-
soc.ru/medicine. In Russian [Information about the maximum man-
ufacturer’s prices and maximum selling prices of vital and essential 
drugs in the Russian Federation in May 2011.]

diamed; 2008, 778 s. In Russian [Clinical and economic analysis. 

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INTRODUCTION

Medical technologies are methods for diagnostics, treatment, prevention and rehabilitation of patients, including pharmaceuticals and medical devices, medical procedures (such as surgical procedures) as well as any other measures taken to preserve or maintain human health. Medical technologies may be applied to an individual patient (clinical care, individual prevention) or to a population (collective interventions, such as water fluoridation). Population-level medical technologies are almost exclusively preventive measures.

Those medical technologies that are used in clinical practice become subject to rather intensive research, since many national licensing authorities demand evidence of their effectiveness. In contrast, there is much less research into population-level technologies, especially preventive interventions, even though their costs are high.

Prevention is classified into the following two categories:
- Primary prevention – measures that aim to minimize the impact of modifiable risk factors on morbidity.
  - Examples: administration of folic acid to fertile women, measures for restricting the availability of tobacco.
- Secondary prevention – screening of apparently healthy people in order to diagnose certain disorders that may be controlled more effectively if they are discovered at an early (pre-clinical) stage.
  - Examples: screening for cervical cancer, colorectal cancer.

Primary prevention may be arranged at various levels:
- the national level (e.g. iodine-enriched salt, though this may not be a national program);
- the healthcare system (e.g. vaccinations);
- individual companies and industries (e.g. protective masks);
- individual people (e.g. physician’s advice).

Even though primary prevention measures that are organized outside the framework of the healthcare system are not conventionally included in medical technologies, in any case the target is health characteristics (morbidity, fertility, etc), and therefore such measures can also be broadly described as medical technologies. Secondary prevention is almost always organized within the healthcare system. Other types of prevention are sometimes discussed (tertiary, primordial, etc), but this classification is based on an interpretation of the moment of intervention and has nothing to do with the methods of assessing the effectiveness of technologies.

In this article we review methods for the assessment of the effectiveness of medical technologies that are applied at the population level, i.e. for the assessment of population effectiveness, rather than clinical efficacy. Population effectiveness may be assessed in relatively simple studies, such as clinical trials (CTs). A correctly designed CT, i.e. a study with internal validity, measures the effect of a medical technology on participants meeting certain inclusion and exclusion criteria under particular conditions of medical care. The extrapolation of CT results to other people, who are different from the study sample, remains a challenging task. Accordingly, there is a measure of uncertainty in the estimates of the population effectiveness of medical technologies, which depends on the correctness of generalizing from the results of a valid study to a broader category of people.

ESTIMATING THE POPULATION-LEVEL SIGNIFICANCE OF A RISK FACTOR

Risk factors for a disease are signs that predict future manifestation of the disease. Non-modifiable and modifi-
fiable risk factors are distinguished. There is hope that eliminating a modifiable risk factor will reduce the likelihood of developing the illness. Sometimes it is emphasized that a true risk factor must meet the criterion of risk reduction once it is eliminated. Unfortunately, the majority of risk factors that have been identified, e.g. all of the hundreds of risk factors for coronary heart disease, have never been tested to demonstrate the effectiveness of their elimination.

Primary prevention of illnesses is fairly common and may include a diverse arsenal of both social and medical measures, such as:

- promotion of a healthy lifestyle,
- vaccination,
- water chlorination,
- safety belts in cars,
- protective equipment at the workplace (rubber gloves, masks, etc),
- pharmaceutical interventions (aspirin for prevention of acute vascular disorders, folic acid for prevention of embryonic developmental abnormalities, etc).

Primary prevention has traditionally been given priority over secondary prevention, since the attractive concept of primary prevention instills hope that the disease may be eradicated altogether, expressed in the saying that “an ounce of prevention is worth more than a pound of treatment”. The validity of this opinion in this general form has never been proved. We may even go as far as to say that this general statement is incorrect. Nevertheless, in some countries, such as Russia, the precedence given to prevention over treatment is even affirmed in health legislation.

The impact of pharmaceutical methods of primary prevention has been studied extensively, and for some medications there is even a sufficiently large body of evidence. At the same time, many recommendations for lifestyle changes are not based on sound scientific evidence. The main reason is the lack of sound, reliable estimates of the impact of the risk factor itself on morbidity. In this situation we can hardly expect to know the population effectiveness of measures that address this risk factor. For example, for decades there have been attempts to estimate the damage related to increased intake of salt with food and to determine how far it may be helpful to restrict salt intake, and still there are no reliable results. Even so, throughout the world people are trying to reduce the amount of salt in their diet.

According to the concept of risk management, the sequence of steps should be as follows:

1) estimating the risk – comparing the harmful impact of an environmental risk factor on public health with the harm inflicted by other stimuli or social factors and with the benefits of this factor and comparison factors;

2) controlling the exposure – measures that aim to minimize exposure to the risk factor below a certain upper threshold (primary prevention measures as such);

2) monitoring the risk – measuring the new level of risk (the rate of adverse outcomes, which should be lower as a result of controlling the risk factor, and the rate of new adverse effects caused by the medical technology) after the implementation of measures for controlling exposure.

**USING THE RESULTS OF COHORT STUDIES TO ESTIMATE THE IMPACT OF A RISK FACTOR ON MORBIDITY**

In experimental research a risk factor, i.e. a trait (exposure) leading to adverse events, is evaluated through its correlation with an adverse outcome, such as the onset of an illness or another untoward outcome. For example, in cohort studies people exposed to a risk factor may have a higher incidence of an adverse outcome compared to the intact part of the cohort. In controlled studies, it may be demonstrated that participants with an adverse outcome may be more likely to have been exposed to a risk factor in the past.

A cohort study allows the researcher to estimate the impact of exposure to a risk factor on morbidity or some other outcome directly, based on the results of the study. Below is a list of the parameters that are normally estimated (Fig. 1), though the terminology may vary.

![Fig. 1. The relation between attributable risk, relative risk, attributable number, and population attributable risk.](image)

**Note:** The probability of an adverse outcome among those exposed (about 10% of the population) is 90%, and among those not exposed it is 15%. The attributable risk = 90 - 15 = 75%. RR = 90 / 15 = 6. Per million population, 100,000 are exposed, and they experience a total of 90,000 adverse outcomes (100,000 x 0.9), out of which 100,000 x 0.75 = 75,000 is the attributable number (the red small squares in the figure). There are 135,000 outcomes among the 900,000 non-exposed people (900,000 x 0.15; shown as blue small squares in the figure). In total there are 225,000 outcomes per million population (red + yellow + blue squares). Population attributable risk (PAR) = 75,000 / 225,000 = 33%.
1. Attributable risk: the difference in absolute risks (proportions of those with the illness, i.e. probabilities of becoming ill) between those exposed to a risk factor (or having a particular trait – for the sake of brevity we consider a risk factor to be an external stimulus, but everything described below applies equally well to other risk factors, such as features of individual metabolism, behavior, etc) and those who were not exposed to this risk factor. Attributable risk corresponds to the additional (causal) factor, which is a gross simplification.

   Synonyms:
   • risk difference,
   • excess risk,
   • population excess rate.

2. Relative risk (RR): the ratio of the absolute risks (proportions of those with the illness, i.e. probabilities of becoming ill) for those who were and were not exposed to a risk factor. RR is an indirect measure of the impact of a risk factor on the disease. While attributable risk indicates directly how much more likely an adverse outcome becomes, RR only gives us the multiplication factor. For example, the risk may increase from 15% to 30% for people in the high-risk group who were exposed to the risk factor and from 3% to 6% in the low-risk group, but in both cases the RR equals 2. Studies of both preventive and curative interventions often report the more attractive RR, while the small attributable risk remains hidden. Such behavior on the part of researchers should be seen as disinformation.

3. Attributable number (AN): the number of cases that are attributable to exposure to the risk factor. It may be calculated as follows:

   \[ \text{AN} = \text{Ne} \times \text{attributable risk}, \]
   
   where Ne is the number of people exposed in the population.

4. Population attributable risk (PAR): the additional morbidity attributable to the presence of this risk factor, expressed as a share of overall population morbidity [1].

   Synonyms:
   • population attributable fraction (PAF),
   • population attributable risk proportion,
   • population attributable risk percent.

   Taken all together, these parameters, and especially PAR, allow us to compare the relative significance of various risk factors. A risk factor that is dangerous, i.e. related to a high risk of illness, but relatively uncommon may be of little significance to the population health, while a relatively weak but widespread risk factor may be very important, since it creates many new cases of the illness. For instance, smoking is a very common risk factor that is not effectively addressed by current measures, but because this risk factor is so widespread, even a small reduction in the proportion of smokers in a population may be accompanied by a large population-level effect [2].

   It is very tempting to conclude that, given a PAR of 33%, we can prevent 33% of cases if we eliminate this risk factor. But this is a rash conclusion – the size of the actual effect of eliminating a risk factor can only be measured in a prevention experiment. The effect size in such experiments (if any!) tends to be much lower than could be expected based on the PAR.

   Data comparable to the results of a cohort study can be derived from an analysis of the results of clinical trials (CTs). It has become increasingly common to perform this analysis after the completion of a CT. Since clinical trials involve strictly defined categories of participants, the analysis of their results can be very valuable. As a rule, the correlation between a risk factor and the illness estimated from the results of a CT turns out to be weaker than in cohort studies [3].

**USING THE RESULTS OF CASE-CONTROL STUDIES TO ESTIMATE THE IMPACT OF A RISK FACTOR ON MORBIDITY**

If the data on the relation between a risk factor and the illness was collected in a controlled study, the procedure for estimating the impact of the risk factor on population morbidity and its contribution to overall morbidity is not applicable. Firstly, the results of a controlled study do not afford an opportunity to calculate the probability of developing the illness with and without exposure to the risk factor or the relative risk. The only correct measure of the relation between the risk factor and the outcome is then the odds ratio (OR). However, when rare exposure and rare outcomes are studies, the OR may approach the RR. There is no criterion to decide how rare is “rare”, but these are frequencies roughly below 1%. Accordingly, it becomes possible to calculate the approximate PAR as:

\[
\text{PAR} = \left( \frac{\text{Pe}(\text{RR} - 1)}{1 + \text{Pe}(\text{RR} - 1)} \right) \times 100\% ,
\]

where Pe is the proportion of exposed subjects among the controls (those without the illness).

It is worth noting that the proportion of exposed subjects among those with the illness is not found in this formula as such and is also represented by the RR.

An overwhelming majority of reports about the identification of new risk factors of various illnesses are derived from the results of controlled studies. These studies are the most susceptible to systematic errors (biases). Drawing conclusions about the cause of illness or evaluating prevention methods based on such data is a completely pointless exercise.

**ESTIMATING THE POPULATION EFFECTIVENESS OF INTERVENTIONS**

In addition to a correlation between a trait (factor) and the future onset of illness, the traditional definition of a risk factor specifies that eliminating the factor should re-
duce the frequency of this outcome. In other words, once the contribution of a risk factor to morbidity has been established and some measures for eliminating or weakening its impact have been proposed, the effectiveness of this prevention strategy should be assessed in experimental studies. Ideally, such studies should have the design of randomized, blind CTs in which the preventive intervention is administered to the main group, while the control group receives placebo or no intervention (waits for the intervention). Such studies have to demonstrate that morbidity is statistically significantly reduced in the intervention group compared to the control group. This is a perfect equivalent of so-called superiority trials.

While practically all promising pharmaceutical preventive interventions are tested in CTs, there are few studies of non-pharmaceutical preventive interventions. To give one example, let us look at a preventive modification of the diet – reduced intake of salt. Even though salt has always been a valuable product in the history of mankind, the notion that it may be harmful has also been widespread since ancient times – and still remains so. The majority of research supporting this notion comes from controlled studies, ecological studies or, less commonly, cohort studies. It is hard to quantify salt intake, and therefore most studies rely on surrogate measures, such as net per capita salt intake in a country. But there are also a number of CTs that investigated the role of reduced salt intake for prevention of chronic diseases. These studies are summarized in a Cochrane systematic review called “Reduced dietary salt for the prevention of cardiovascular disease” [4]. This analysis of 7 studies with 6489 participants (with elevated or normal blood pressure) and observational period of 7 to 36 months (and in one study the duration of follow-up was 12.7 years after the end of study) demonstrated that there were no differences between the groups of reduced and normal intake of salt in terms of either morbidity or mortality (Fig. 2). On the contrary, limiting salt intake was linked to higher mortality among patients with heart failure (RR = 2.59 [1.04; 6.44]). Unfortunately, the results of CTs indicating the lack of a statistically significant effect of lowering the amount of salt in the diet and the moderate size of effect reported even in those CTs that are the most favorable to this notion fail to convince the proponents of low-salt diets. Based on blind faith and non-systematically pooled results of unconvincing studies, they continue to promote a low-salt diet – a preventive technology with no proven effectiveness, as a part of national preventive programs.

Apart from the lack of evidence for the effectiveness of restricting salt intake, this program is hard to implement. People have a poor capacity for long-term consumption of food that they find distasteful. This technology is doomed to
poor and incomplete implementation. Even if this program did bear fruit, its population effectiveness would still be doubtful. The implementation of such interventions not only fails to deliver the expected benefits, but even wears out the compliance reserve among those people who are willing to devote their time and energy to illness prevention.

Another example is the situation with primary prevention of cardiovascular disorders through complex interventions. Both cohort studies and international comparative studies in the second half of the 20th century identified a considerable number of cardiovascular risk factors. Each of these risk factors was related to a low relative risk and low population attributable risk. Only the selection of a small group of people with extremely high levels of each particular risk factor (very high blood pressure, a very high concentration of cholesterol in the blood) makes it possible to identify individuals with a high relative risk. However, only a very small number of adverse outcomes are explained by this level of the risk factor. Similarly, the selection of people exposed simultaneously to several risk factors leads to the identification of people with a very high risk. But in this case, once again, their illnesses correspond only to a small share of the total number of adverse outcomes (the PAR is low). Even so, simultaneous modification of numerous risk factors appeared to be a very promising approach, and its potential benefits were investigated in a number of CTs. These CTs are summarized in a systematic review [5]. This review is limited to primary prevention, i.e. those CTs that included people without coronary heart disease. The results of 66 such trials ranging from 6 months to 12 years in duration (median follow-up 12 months) were analyzed. According to these results, complex interventions did lower blood pressure, cholesterol levels, and the incidence and intensity of smoking. However, contrary to the expectations, their impact on the risk of being diagnosed with coronary heart disease, morbidity and mortality was minimal. There may be various interpretations of the ineffectiveness of these preventive measures, but the fact speaks for itself: primary prevention based on the modification of risk factors of coronary heart disease is not effective. Even if we assume that there is an effect in some cases, it is so small as to be undetectable. Given the high morbidity and mortality from coronary heart disease, both patients and physicians are very eager to do something in order to reduce the cardiovascular risk. This is why interventions of this type – aiming to modify numerous risk factors at once – are being implemented in a number of countries. However, such programs are a waste of healthcare resources, and besides, they confuse people who are trying to stay healthy.

ESTIMATING THE POPULATION EFFECTIVENESS OF SCREENING

As noted above, screening is the process of diagnosing diseases and conditions for the purpose of intervention aiming to prevent an unfavorable outcome (onset or worsening of an illness, disability or death). A more specific objective of screening is thus to identify medical conditions at an early stage, when few or no symptoms are manifest (i.e. in people who are unaware of having these conditions). A screening program can only be effective if a more effective strategy for treatment or risk reduction exists at these early stages compared to later stages with clinical manifestations that can be detected by traditional methods.

The core component of screening is the diagnostic method per se, which must be highly effective, i.e. have high values of operational parameters (sensitivity and specificity). By definition, screening tests are used when prevalence is low, and therefore the demands towards their sensitivity and specificity are much more stringent than in the case of clinical diagnostics – otherwise the prognostic value of a positive result (i.e. the likelihood of a true positive among all positive results) becomes extremely low. In general, a screening test is not a diagnostic test used for clinical diagnostics, and it has to meet further specific requirements, apart from high sensitivity and specificity. For example, when a very cheap and safe test is available, it may be used even if its specificity is low, provided that additional examinations may be performed to confirm a positive result.

At the same time, screening is certainly not limited to diagnostics of target conditions. Screening is a complex technology, and its efficacy and cost-effectiveness can only be assessed for all its elements considered as a whole. The
most effective screening test may turn out to be of little use for the society if other conditions are not met. A list of these conditions was suggested in 1968 by Wilson and Junger [6] and then adopted by the World Health Organization. Even if a single one among the listed criteria is not met, implementation of the screening program is not justified.

To repeat: the ultimate purpose of screening is not to detect diseases at an early stage but to prevent adverse outcomes – that is what matters to the society. Accordingly, an evaluation of a screening program should demonstrate a reduction in the frequency of outcomes that are undesirable to patients or to the society. For instance, cancer screening should both improve the outcome of the detected cases and achieve the result relevant to the population – reduction of overall mortality.

Assessment of screening programs (their population effectiveness) calls for large-scale, population-level studies ensuring that the experiment is as “pure” as possible, with experimental and control sub-populations, randomizations of participating populations, etc (Fig. 3).

Usually this design cannot be used with individual people or even medical organizations. If individual patients are randomized, different methods of diagnostics and management of patients in the experimental and control groups cannot be followed within the same medical organization. Health workers tend to follow the same routine, and thus patients from the experimental and control groups will be examined and treated in approximately the same way. As a result, any potential difference in outcomes between the two groups will remain undetected. For this reason, it is more common to randomize whole regions, some of which become regions of experimental interventions and some control regions.

Such studies have to demonstrate that screening does produce a positive effect in terms of important outcomes. Thus the main criterion of population effectiveness of screening programs is the reduction of specific mortality and overall mortality. These parameters are measured in matched populations and compared using the same quantitative tools as for clinical interventions, namely:

- RR and the corresponding 95% confidence interval – the ratio of absolute risks in the populations being compared (used in prospective studies),
- OR of the outcome in the compared populations and the corresponding 95% confidence interval (used in retrospective studies).

When assessing the effectiveness of screening programs, it is important to keep in mind that systematic errors are possible.

- **Lead time bias.** The term “lead time” refers to the detection of a disease at screening at an earlier time compared to its diagnostics upon its clinical manifestation. This systematic error may occur if early intervention is not effective, but the prolonged survival after being diagnosed is regarded as increased survival time. To avoid this bias, it is best to analyze age-related mortality rather than lethality or survival time from the moment of the initial diagnosis.

- **Length time bias.** Just as any periodic examination, screening more effectively detects slowly progressing conditions, which are also more favorable in terms of medical prognosis. Rapidly progressing conditions are manifested (and thus diagnosed clinically) in between two examinations, and because of their fast progression, the mortality is high. Accordingly, the mortality among the cases detected at screening is lower than the mortality in the usual clinical practice, but this is caused by the characteristics of detected cases rather than the effectiveness of screening. This bias can be eliminated by an effective randomization when comparing two approaches: “standard health care + screening” vs. “standard health care”.

- **Compliance bias.** People who enroll voluntarily in prevention programs are more likely to comply with the requests of the physician more fully and to be more willing to cooperate. This may lead to a better prognosis compared to those people who are not so eager to enroll in a screening program. This bias is also eliminated by an effective randomization.

A more detailed discussion of systematic errors may be found in [6].

Screening typically relies on cheap tests, but given the large samples and numerous false positives requiring additional examinations and the sharp increase in the number of curative or preventive interventions, the cost of screening programs is very high. It is particularly high when calculated for one identified case or prevented adverse outcome. For instance, even if the test is cheap...
The cost of additional testing becomes 500 thousand roubles per confirmed case. Even with such minimal prices, the resulting costs are catastrophically high. However, they do not even include the cost of treatment or direct and indirect costs for the patients. To conclude, from the point of view of clinical and economic analysis the implementation of screening programs is not justified.

Assessing a screening program, it is important to determine how far this program serves the whole society rather than some particular groups of people who have privileged access to health care. Since an overwhelming majority of people who enroll in a screening program are not sick but suffer the entire range of side effects related to participation in the program, it is very hard to keep every original participant in the program throughout the study period. If the examination involves unpleasant procedures (such as mammography or sigmoidoscopy), the number of participants may drop dramatically over a few years. If the screening gives a lot of false positives, the participants have to undergo traumatic tests such as biopsy and suffer the stress of additional testing. Side effects may be responsible for the lack of expected reduction in the overall mortality – it may be hidden by the increase in mortality caused by the side effects of diagnostic tests and treatment (the disease turns out to be no worse than the intervention).

Such comprehensive studies of the effects of screening are seldom performed, since they are expensive and have

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<th>Preventive measure</th>
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</tr>
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<tbody>
<tr>
<td>Detection of low physical activity and recommendations for optimizing physical activity</td>
<td>Daily physical activity involving all muscle groups. Minimal duration of motor activity for an adult: 30 minutes’ walk at a moderate pace daily</td>
<td>Global Strategy on Diet, Physical Activity and Health. WHA57.17.WHO, 2004</td>
</tr>
<tr>
<td>Detection of carotid stenosis</td>
<td>Not to be performed in people without symptoms of insufficient blood supply to the brain</td>
<td>US Preventive Services Task Force (USPSTF) 2007</td>
</tr>
<tr>
<td>Screening for prostate cancer</td>
<td>Not recommended for people over 75 years of age. For those under 75 the benefit-to-harm ratio is not clear</td>
<td>USPSTF 2011</td>
</tr>
<tr>
<td>Screening for ovarian cancer</td>
<td>Not recommended, including genetic tests (BRCA mutation). Recommended only if these mutations are present in family history</td>
<td>USPSTF 2005</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>All newborn babies should be tested</td>
<td>USPSTF 2008</td>
</tr>
<tr>
<td>Screening for breast cancer in women</td>
<td>After 35 for patients with family history, otherwise from 50 to 74 years of age, with a specially designed X-ray mammograph, once every 2 years. Women must be informed about the potential benefit and harm of screening. Training in self-examination and preventive examinations are not needed</td>
<td>Fight against cancer. EB114/3. WHO, 2004; Cancer prevention and control. WHA 58.22. WHO, 2005; USPSTF 2009</td>
</tr>
<tr>
<td>Screening for cervical cancer (Pap test)</td>
<td>All sexually active women, with negative results – up to 65 years of age</td>
<td>Fight against cancer. EB114/3. WHO, 2004; Cancer prevention and control. WHA 58.22. WHO, 2005; USPSTF 2009</td>
</tr>
<tr>
<td>Screening for colorectal cancer</td>
<td>People of 50–75 years of age, sigmoidoscopy once every 3–5 years or at annual test for hidden blood in the stool</td>
<td>Fight against cancer. EB114/3. WHO, 2004; Cancer prevention and control. WHA 58.22. WHO, 2005; USPSTF 2009</td>
</tr>
<tr>
<td>Screening for depression in adults and children</td>
<td>Should be performed when there is access to specialized care for confirming the diagnosis and providing psychological therapy</td>
<td>USPSTF 2009</td>
</tr>
<tr>
<td>Training in putting infants under 1 year old to sleep</td>
<td>It is not recommended that infants under 1 year old should sleep on their backs because there is a risk of sudden death while asleep</td>
<td>European strategy “Children and Adolescent Health and Development”. Action tool. WHO, 2005</td>
</tr>
<tr>
<td>Assessment of physical development (anthropometry)</td>
<td>In childhood, to detect severe food disorders</td>
<td>Strategic directions for improving the health and development of children and adolescents. WHO/FCH/CAN/02.21</td>
</tr>
<tr>
<td>Detection of scoliosis in children</td>
<td>Screening of symptom–free children is not recommended</td>
<td>USPSTF 2004</td>
</tr>
<tr>
<td>Detection of osteoporosis</td>
<td>Recommended for women over 65 years of age, over 60 for high-risk groups</td>
<td>USPSTF 2002</td>
</tr>
<tr>
<td>Screening for dementia</td>
<td>Benefit–to–harm ratio of screening elderly people is not clear</td>
<td>USPSTF 2003</td>
</tr>
</tbody>
</table>
to include a very large number of participants. Even when such studies have been performed, the situation remains difficult because of the challenge of extrapolating the results of a CT to the population. One example is mammography performed in the context of screening for breast cancer. Even though there have always been some doubts about the effectiveness of screening and the ratio of beneficial and harmful effects, the publication in 2000 of a systematic review of its effects [7] sparked a discussion that has been going on for years and led to a new assessment from the perspective of an individual woman participating in screening and from the perspective of the healthcare system.

Eight clinical studies of screening for breast cancer performed for a total of 600 000 women were analyzed in a Cochrane review [8]. Three studies with an adequate randomization did not detect any reduction in the risk of death from breast cancer over 13 years of follow-up (RR = 0.90 [0.79, 1.02]) or death from all causes (RR = 0.99 [0.95, 1.03]). However, the frequency of performing lumpectomy or mastectomy was elevated in the screening groups (RR = 1.31 [1.22, 1.42]). Screening leads to a 30% rate of over-diagnosing and thus causes unnecessary interventions. This means that for every 2000 women who were screened over 10 years, one woman will have her life prolonged, while 10 more women will be treated and 200 will suffer from psychological stress for many months because of false positives in the screening procedure. The reason for the low effectiveness of the program is the unsatisfactory sensitivity of the screening method (mammography), which produces a considerable number of false positives.

By now the Cochrane Collaboration has published 36 systematic reviews of screening technologies (with the key word “screening” in the heading), and another 22 are being prepared. Some recommendations of Canadian health organizations have been translated into Russian are being prepared. Some recommendations of Canadian health authorities are encouraged to consult sound (http://familymedicine.ru/content/category/4/19/32), and health organizations have been translated into Russian are being prepared. Some recommendations of Canadian health organizations have been translated into Russian are being prepared.

REFERENCES


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We present the main features of PharmEc, an automated system for the evaluation of limited drug lists, and the results of its testing, using as an example the evaluation of a regional reimbursement list. PharmEc makes it possible to perform on-line an interdisciplinary, multi-level, standardized expert evaluation of drug lists at different levels. The process of expert evaluation includes several stages: ABC/VEN (formal)/DDD analysis; expert VEN analysis based on specified evaluation criteria and involving clinical pharmacologists, clinicians, and specialists in evidence-based medicine; analysis of the results and a final coordinated VEN analysis leading to recommendations for optimizing the list. In the course of expert evaluation of a regional reimbursement list consisting of 311 international nonproprietary names (INN) of pharmaceutical drugs, which was conducted with the help of PharmEc and 20 experts in various fields, we performed a comprehensive analysis of drug purchase and suggested a number of recommendations for the optimization of this process. Despite the positive overall impression of drug purchase under the regional reimbursement program, the experts agreed upon a list of medications (49 INNs) that should be taken off the formulary list because of the lack of proven efficacy or availability of alternative treatments with better efficacy and cost-effectiveness. If the experts’ recommendations are followed, the range of reimbursed drugs may be reduced by 15.76%, saving up to 5% of the budget. The principles of assessment described in the article, such as standardization of expert evaluation of formulary lists, involvement of experts from various fields, automatization of the evaluation process, unification of criteria for drug assessment, and strictly scientific decision-making, improve the effectiveness of the process of creating formulary lists at different levels of the health care system.

KEYWORDS: evaluation of drug lists, ABC/VEN/DDD analysis, PharmEc automated system.

RELEVANCE

Drug lists, formularies, lists of essential medicines, limited lists, etc – all these terms with their numerous definitions have been an important component of the Russian system of drug supply for many decades. These lists are created at different levels of the healthcare system, have different functions and vary qualitatively and quantitatively in their contents. These lists are produced by different expert bodies relying on various decision-making rules and criteria of drug evaluation, which are often not even based on any legal documents and are limited to a purely declarative status [1, 2]. Because of the lack of scientific, unified, standardized mechanisms of producing these lists, this system cannot ensure a supply of medications that are truly superior in terms of their efficacy and cost-effectiveness and avoid irrational spending of national resources towards the provision of medications for the population. Twenty years have passed since the first Russian List of Vital and Essential Drugs was approved – a period of time that appears sufficiently long to agree upon and approve unified rules for the inclusion of new drugs in these lists and to standardize (unify) the decision-making process and criteria of expert evaluation.

An important step on the way towards improving the effectiveness of the system responsible for the production of formularies may be their comprehensive clinical and economic assessment. In 2012 an automated system for the evaluation of limited drug lists called “PharmEc” was created in the Research Institute of Clinical and Economic Evaluation and Pharmacoeconomics at the N.I. Pirogov Medical University. PharmEc is a web-based tool for standardized interdisciplinary evaluation of formularies of various levels and functions. The development of this system became the logical continuation of the efforts towards creating an automated system for the compilation and assessment of formulary drug lists at the National Center for HTA, for example PharmCompile software for ABC/VEN/DDD analysis and “Dossier”, an automated system for the compilation of limited lists [3].

A DESCRIPTION OF “PharmEc”, AN AUTOMATED SYSTEM FOR THE EVALUATION OF LIMITED DRUG LISTS

PharmEc is a multi-user web-based tool accessed through a unique user name and password (Fig. 1). The system performs on-line a standardized, multi-level, interdisciplinary assessment of drug lists by a set of specified evaluation criteria.

1 At present the authors of this project are employed at the National Center for Health Technology Assessment and at the Center for Health Technology Assessment of the Russian Presidential Academy of National Economy and Public Administration.
The evaluation of limited lists is a multi-stage process involving an unlimited number of specialists with expertise in various fields: clinical pharmacologists, clinicians, and specialists in evidence-based medicine (Fig. 2). The head evaluator is in charge of maintaining the evaluation process and liaising with the experts. This person has the fullest access to all sections of the system: they perform the primary ABC/VEN (formal)/DDD analysis of the list, add the list to the system, appoint the experts and provide them with access codes, monitor the progress of evaluation, and then analyze the results, writing the final, mutually agreed upon expert report.

When a new list is entered into the system, it has to be presented in a particular format, which in its full form includes the following sections:

- International Non-patented Name (INN);
- Trade Name (TN);
- the results of ABC analysis (the group to which each medication belongs (A, B or C), its cost (RUB) and share in the total expenditure);
- the results of formal VEN analysis performed in accordance with the current List of Vital and Essential Drugs and the list of the Program for the Provision of Essential Medicines;
- the results of DDD analysis, ICD-10 codes for which the drug is indicated.

When necessary, the number of sections in this format may be minimized, e.g. leaving only the drug names (INN and TN). The format including the full range of data to be entered may be prepared using PharmCompile software “ABC/VEN/DDD analysis”.

Following the addition of a new list to the system, the head evaluator appoints clinical pharmacologists (up to 3 specialists) who will be in charge of performing expert VEN analysis of the list. Apart from determining which drugs are vital/essential/non-essential, clinical pharmacologists decide from which medical fields clinicians in future should be enrolled in an additional VEN analysis of the list for particular pharmacotherapeutic groups. A notification inviting the expert to begin the evaluation and providing logins and passwords is sent automatically to the e-mail of the appointed expert.

Both clinical pharmacologists and clinicians should follow certain standardized decision-making criteria when they determine how vital a particular medication is in the course of VEN analysis, supporting the chosen criteria with material evidence, such as standards of...
treatment, Russian and/or international treatment guidelines, the results of clinical or pharmacoeconomic studies, etc. (Fig. 3).

Once clinical pharmacologists and clinicians have completed the expert VEN analysis, the evaluation is taken further by specialists in evidence-based medicine. The head evaluator provides them with a list of medications whose final status is hard to determine because of a significant disagreement among the experts (for example, when the assigned status of vital/essential/non-essential drug varies, or when clinicians and clinical pharmacologists suggest conflicting opinions and arguments about the same drug). In such ambiguous cases a specialist in evidence-based medicine determines the levels of evidence for each medication by means of searching for and analyzing clinical studies, using a special scale, assigning particular levels to the evidence and supporting the final conclusion with the results of actual clinical studies (Fig. 4).

The final stage of expert evaluation is to analyze all the results of VEN analyses (formal and expert) regarding the status of all the drugs on the list as vital/essential/non-essential in order to calculate an integrated final index of vital/essential/non-essential importance of each drug. On average, expert evaluation of one drug list consisting of 300-350 INNs involves 17-20 specialists from different fields, so that there may be from 3 to 6 expert reports for each drug (if the results of formal VEN analysis are included, the number of indices per drug may increase to 8) (Fig. 5).

An important intellectual component of PharmEc is the so-called Compendium of Pharmaceutical Drugs, which at present contains expert reports on approximately 400 drugs (INNs). This book contains the pooled results of expert evaluations of drug lists (the status of vital/essential/non-essential drug and expert reports written by clinical pharmacologists, clinicians, and specialists in evidence-based medicine). Each new list added to PharmEc system is automatically scanned through the “filter” of this compendium, the drugs on the list are compared with those in the compendium, and if some INNs are the same, expert data is exchanged (the data contained in the compendium are automatically appended to the analyzed list). This feature considerably saves the time of experts analyzing new drug lists and thus reduces the number of experts who have to be involved in this process. The information contained in the compendium may be updated as necessary.

At present PharmEc is fully ready for use, and it has been tested: the system was used for expert evaluation of regional formulary drug lists for discounted provision of medicines to outpatients.

A promising direction for future improvement of PharmEc may be the inclusion of various types of reference information, such as standards of treatment, clinical guidelines, and the results of clinical studies that form the basis for expert decision-making. All this will promote further unification and standardization of the evaluation of drug lists and decision-making based on a standard body of high-quality reference data.

Fig. 3. Criteria for decision-making by the experts (clinical pharmacologists and clinicians) in the course of VEN analysis with PharmEc automated system.

Fig. 4. The scale of evidence levels for pharmaceutical drugs used by a specialist in evidence-based medicine with PharmEc automated system.

Fig. 5. The results of VEN analysis of adalimumab performed with the help of PharmEc automated system.

Note: final status “V” signifies that the drug is concluded to be vital. This conclusion is based on the analysis of expert opinions and all the suggested indices of the importance of this medication.
TETING PHARMEC, AN AUTOMATED SYSTEM FOR EXPERT EVALUATION OF LIMITED DRUG LISTS

In 2012 PharmEc was tested in one of the regions of the Russian Federation in the framework of analyzing a regional formulary drug list for discounted provision of medications to outpatients (hereafter referred to as “the regional reimbursement list”). A high level of healthcare funding is characteristic for this region (the per capita standard of funding in the regional program of national guarantees for the provision of free health care exceeded 20 000 RUB in 2012).

The objective of the expert evaluation was to optimize the regional reimbursement list and thus to improve the cost-effectiveness of national drug purchase.

Twenty specialists from various fields took part in the evaluation of the regional reimbursement list, including clinical pharmacologists, clinicians, specialists in evidence-based medicine, and healthcare managers.

The following types of analysis were performed in the course of the evaluation: ABC/VEN (formal)/DDD analysis of the regional reimbursement list, expert VEN analysis of the list by clinical pharmacologists and clinicians from various fields. Furthermore, when there was a considerable degree of disagreement among the experts about certain drugs, evidence of their effectiveness was searched for and analyzed. The outcome of the analysis was the final, mutually agreed upon classification of all medications on the list as vital/essential/non-essential, which was produced by means of integrating the results of the formal and expert VEN analyses. In addition, some suggestions were made for optimizing the regional reimbursement list. Accordingly, the analyzed list passed all 5 stages of expert evaluation with PharmEc system.

The object of expert evaluation was a regional reimbursement list consisting of 311 drugs (INNs). The list contained the following information: INN, trade name, formulation, the number of purchased packages, the price of one package, ICD-10 codes for each indication, and the manufacturer. The format required for adding the list to PharmEc, including the results of ABC/VEN/DDD analysis, was prepared using PharmCompile software “ABC/VEN/DDD analysis”.

The results of ABC-analysis of the regional reimbursement list are presented in Table 1.

As the data above shows, 49 (15.76%) of the drugs included in the list make up group A of the most costly medications (80.39% of the total expenditure), 61 (19.61%) drugs make up group B (15.06% of expenditure), and 201 (64.63%) drugs make up group C (4.55% of expenditure). The first 10 costliest medications are listed in Table 2.

DDD analysis of the regional reimbursement list revealed the consumption structure for 248 (79.7%) drugs on the list, while DDD data is so far absent for 63 drugs. This analysis demonstrated that 16 medications make up group A with 80% of consumed DDDs. The largest share of the total consumption belongs to cardiovascular (lisinopril, perindopril, enalapril, amlodipine, indapamide, etc) and endocrine (metformin, glibenclamide, gliclazide, glimepiride, etc) drugs. The first 10 medications with the highest rate of consumption are listed in Table 3.

Metformin had the highest consumption rate of all the drugs on the list – 85.3 DDDs per 1000 reimbursed patients per day (i.e. 8.5% of reimbursed patients were receiving 2 g of metformin daily for a year). Metfor-

<table>
<thead>
<tr>
<th>#</th>
<th>INN</th>
<th>Share in the total expenditure, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trastuzumab</td>
<td>9.04</td>
</tr>
<tr>
<td>2</td>
<td>Insulin glargine</td>
<td>6.40</td>
</tr>
<tr>
<td>3</td>
<td>Perindopril</td>
<td>4.11</td>
</tr>
<tr>
<td>4</td>
<td>Insulin isophane</td>
<td>2.78</td>
</tr>
<tr>
<td>5</td>
<td>Metformin</td>
<td>2.62</td>
</tr>
<tr>
<td>6</td>
<td>Dasatinib</td>
<td>2.26</td>
</tr>
<tr>
<td>7</td>
<td>Temozolomide</td>
<td>2.18</td>
</tr>
<tr>
<td>8</td>
<td>Budesonide+formoterol</td>
<td>2.10</td>
</tr>
<tr>
<td>9</td>
<td>Lipoic acid</td>
<td>2.10</td>
</tr>
<tr>
<td>10</td>
<td>Valproic acid</td>
<td>1.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>INN</th>
<th>DDD per 1000 reimbursed patients per day</th>
<th>DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metformin</td>
<td>85.3</td>
<td>2.00 g</td>
</tr>
<tr>
<td>2</td>
<td>Lisinopril</td>
<td>79.6</td>
<td>10.00 mg</td>
</tr>
<tr>
<td>3</td>
<td>Perindopril</td>
<td>79.0</td>
<td>4.00 mg</td>
</tr>
<tr>
<td>4</td>
<td>Amlodipine</td>
<td>63.5</td>
<td>5.00 mg</td>
</tr>
<tr>
<td>5</td>
<td>Enalapril</td>
<td>53.9</td>
<td>10.00 mg</td>
</tr>
<tr>
<td>6</td>
<td>Indapamide</td>
<td>49.9</td>
<td>2.50 mg</td>
</tr>
<tr>
<td>7</td>
<td>Glibenclamide</td>
<td>36.0</td>
<td>10.00 mg</td>
</tr>
<tr>
<td>8</td>
<td>Gliclazide</td>
<td>35.4</td>
<td>60.00 mg</td>
</tr>
<tr>
<td>9</td>
<td>Lipoic acid</td>
<td>33.1</td>
<td>0.20 g</td>
</tr>
<tr>
<td>10</td>
<td>Bisoprolol</td>
<td>31.4</td>
<td>10.00 mg</td>
</tr>
</tbody>
</table>
The majority of drugs assigned index “N” were found in the least costly group C, and only a small number of them were found in group A, regardless of whether the List of Vital and Essential Drugs or the list of the Program for the Provision of Essential Medicines was used as a reference. Thus this formal analysis of the vital importance of drugs on the regional reimbursement list revealed that over 70% of these drugs and over 80% of the funding corresponded to the supply of vital medications.

The results of ABC and expert VEN analysis are presented in Table 5.

According to the opinion of experts regarding the status of drugs on the list as vital/essential/non-essential, the majority of non-essential drugs (N) were found in the least costly group C (6.47% to 26.87%), and only a small number of them were found in group A (0% to 16.33%). If we summarize the opinion of experts for all three groups (A, B and C), the share of non-essential (N) drugs varies in the range of 5.47% to 23.47%, and their share of the total expenditure lies between 0.63% and 11.13%.

Those drugs that caused a considerable disagreement among the experts were analyzed by specialists in evidence-based medicine. No solid evidence proving the effectiveness of such drugs as hopantenic acid, cinnarizine, piracetam, clonidine, etc was found, and therefore their purchase under the regional reimbursement program appears to be unjustified.

The final analysis of all expert reports and the results of formal VEN analysis performed at the concluding stage of the evaluation demonstrated that 66.56% of all drugs on the regional reimbursement list (89.93% of expenditure) were of vital importance, 17.68% (5.37% of expenditure) were essential, and 15.76% (4.69% of expenditure) were non-essential. These estimates correlate most closely with the opinion of clinicians (Fig. 6). It is worth noting that only 3 non-essential drugs were found in the costliest group A (lenograstim, ademetionine and clodronic acid), and they corresponded to less than 3% of the total cost of medications purchased in one year.

According to the pooled opinion of experts, the share of vital and essential drugs on the regional reimbursement list thus amounted to 84.24%, corresponding to 95.31% of the total expenditure.

<table>
<thead>
<tr>
<th>Group</th>
<th>The share of medications from each category, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>List of Vital and Essential Drugs*</td>
<td>List of the Program for the Provision of Essential Medicines*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>N</td>
<td>V</td>
</tr>
<tr>
<td>A</td>
<td>81.63</td>
<td>18.37</td>
<td>79.59</td>
</tr>
<tr>
<td>B</td>
<td>73.77</td>
<td>26.23</td>
<td>78.69</td>
</tr>
<tr>
<td>C</td>
<td>72.64</td>
<td>27.36</td>
<td>77.61</td>
</tr>
<tr>
<td>Total</td>
<td>74.28</td>
<td>25.72</td>
<td>78.14</td>
</tr>
</tbody>
</table>
Despite the positive overall impression of drug purchase under the regional reimbursement program, the experts agreed upon a list of 49 medications that should be taken off the formulary, with or without replacement. The first ten costliest drugs that are recommended for exclusion are listed in Table 6.

The exclusion of these drugs from the regional reimbursement list, with or without replacement, was suggested for a variety of reasons. For some of them, there is no solid evidence of clinical efficacy (ademetionine, clodronic acid, silibinin, hylak forte, cerebrolysin, etc), while others are not cost-effective enough (lenograstim), since there are more cost-effective alternatives on the market. Some drugs could be replaced by safer and more effective (e.g. zoledronate or ibandronate could be substituted for clodronic acid) or more cost-effective therapeutic alternatives (e.g. lenograstim could be replaced with filgrastim), while others were recommended to be taken off the list without replacement.

The overall share of non-essential drugs in the list amounted to 15.76% (4.69% of expenses). Canceling the orders for these drugs or replacing them with therapeutic alternatives with better efficacy and cost-effectiveness may save financial resources.

CONCLUSION

The approach to evaluating formulary drug lists reviewed in this article consists in standardizing the process of expert evaluation, involving specialists from various fields, automating the evaluation process, and unifying the criteria of drug evaluation and decision-making. This makes the compilation of formularies at different levels of the healthcare system more effective. A scientifically sound evaluation of the already existing formulary drug lists coupled with increased transparency of decision-making that is afforded by automated systems will lead to the identification of the optimal configuration of each list from the clinical and economic point of view, thus saving budget resources and at the same time improving the quality of medical care provided to the population.

REFERENCES


2. Sura M. V., Omelyanovsky V. V. Evolutsiya sistemy expertizy pri formirovanii Perechnya zhiznenno neobhodimykh i vazhneyshih lekarstvennyh preparatov. Meditsinskiye tehnologii. Otsenka i vybor 2011; No.3(5): 30 – 33. In Russian [Sura M. V., Omelyanovsky V. V.
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Pharmacoeconomic Analysis of Antiplatelet Therapy with Ticagrelor and Clopidogrel for Prevention of Vascular Events and Death in Patients with Acute Coronary Syndrome

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Introduction. Ticagrelor demonstrated its superior efficacy compared to clopidogrel without a marked increase in the frequency of significant bleeding in the PLATO randomized controlled trial (NCT00391872).

Objective. To perform a comparative analysis of the costs of two alternative regimens of antiplatelet therapy (ticagrelor + acetylsalicylic acid (ASA) versus clopidogrel + ASA) administered for 12 months to patients with acute coronary syndrome, from the societal perspective.

Methods. We used the rate of adverse cardiovascular events registered in the PLATO study (NCT00391872) to calculate the difference in direct and indirect costs under the actual conditions of Russian health care. The calculations were performed in a model created using Excel software. We estimated the differences in the cost of antiplatelet therapy, medical care provided to patients with myocardial infarction, and death from various causes. The costs were calculated for a period of one year, including the cost of administering pharmacotherapy and managing cardiovascular events occurring within one year from the primary event in ACS patients.

Results. As a component of antiplatelet therapy in combination with ASA, ticagrelor saves about 2,749.97 RUB per person per year compared with clopidogrel. As long as the price of one package of ticagrelor (56 tablets) is below 3,520.94 RUB (including 10 % VAT and 22 % markup) and other parameters are unchanged, it remains the preferred choice over clopidogrel.

Conclusion. Administration of ticagrelor to patients with ACS is less costly compared to therapy with the original clopidogrel.

KEYWORDS: ticagrelor, clopidogrel, acute coronary syndrome (ACS), myocardial infarction (MI), cost-effectiveness analysis.

Acute coronary syndrome (ACS) is a group of clinical signs and symptoms of coronary heart disease (CAD) that indicate a developing acute myocardial infarction (MI) or unstable angina – conditions caused by the same underlying pathological process, namely thrombosis of variable severity that forms above a rupture in an atherosclerotic plaque or a lesion (erosion) in the endothelium [1].

Early pharmacotherapy of ACS aims to prevent an MI with the help of antiplatelet drugs (antiaggregants) and anticoagulants. The following antiplatelet drugs are currently used: cyclooxygenase inhibitors (acetylsalicylic acid, ASA), inhibitors of adenosine diphosphate-dependent platelet aggregation (clopidogrel, prasugrel¹, ticagrelor), and glycoprotein IIb/IIIa inhibitors (tirofiban¹, abciximab, etc) [2]. Combination treatment with ASA and clopidogrel is recommended by a number of clinical guidelines as standard antiplatelet therapy in ACS patients. Some European guidelines currently recommend ASA in combination with ticagrelor – a reversible direct inhibitor of P2Y12 adenosine diphosphate receptors that acts more rapidly and powerfully [3, 4] than clopidogrel and reduces the risk of MI as well as cardiovascular mortality [8].

At present there is no pharmacoeconomic data on ticagrelor compared to other antiplatelet drugs in the Russian health care. The goal of our study was to perform a comparative analysis of the costs of alternative regimens of antiplatelet therapy with ticagrelor or clopidogrel in combination with ASA in patients with ACS.

To achieve this goal, we performed the following sequence of tasks:

1. Analyzed the results of studies of clinical efficacy and safety of ticagrelor and clopidogrel in combination with ASA in terms of reducing the risk of vascular events and death in ACS patients; we also analyzed the methodological quality of these studies and their level of evidence.

2. Estimated the differences in direct medical, direct non-medical and indirect costs of treatment of ACS patients with ticagrelor and clopidogrel for one year, taking into account the effectiveness of each treatment (prevention of cardiovascular complications).

RESEARCH HYPOTHESIS

Treatment of ACS patients with the combination of ticagrelor + ASA is more cost-effective than the combination of clopidogrel + ASA thanks to a lower rate of cardiovascular events (MI and cardiovascular mortality) and lower overall costs of treatment.

¹ Not currently registered in Russia.
MATERIALS AND METHODS

In this study we estimated the costs of treatment with ticagrelor versus clopidogrel (both in combination with ASA). Clopidogrel was the chosen comparator drug, since, as mentioned above, its combination with ASA is considered to be the standard treatment for ACS. In Russia clopidogrel is included in the standards of inpatient and outpatient care for patients with acute MI [5, 6] as well as in the List of Vital and Essential Drugs [7].

To assess the clinical efficacy and safety of ticagrelor, we searched for clinical studies in the databases of Cochrane Library (in the registry of systematic reviews and the registry of controlled clinical trials) and Medline for the period from 2000 to 2011 (Fig. 1). We searched for the following keywords in the title, abstract or keywords of articles: ticagrelor, clopidogrel, acute coronary syndrome. A total of 32 publications were identified by these keywords. There were no systematic reviews or meta-analyses of this topic; only randomized controlled trials (RCTs) of direct relevance to ACS treatment were selected. In terms of their contents, publications that directly compared ticagrelor with clopidogrel in the treatment of ACS patients were given priority.

Creating the model

Based on the results of the PLATO RCT [8, 9], a direct comparative study of the efficacy and safety of ticagrelor + ASA versus clopidogrel + ASA, we analyzed the costs of these two combination treatments.

The model included an estimation of direct medical, direct non-medical, and indirect costs of treating ACS patients for one year with ticagrelor or clopidogrel (both in combination with ASA), taking into account the effectiveness of therapy (prevention of cardiovascular events, such as MI, death from cardiovascular and other causes). The structure of this model is presented in Fig. 2.

Data on the risk of non-fatal MI and death was obtained from the PLATO study report containing a detailed description of outcomes, which was provided by the manufacturer of ticagrelor to the British National Institute for Health and Clinical Excellence (NICE) [9]. All relative frequencies were estimated with Weibull regression based on the total number of patients included in the PLATO study.

The model estimates the following costs:
- direct medical costs of treatment with ticagrelor and clopidogrel, management of patients with non-fatal acute MI, and medical care provided to patients who died from vascular and non-vascular causes;
- direct non-medical costs: expenditures related to the payment of temporary disability benefits and pensions for permanently incapacitated patients with MI;
- indirect costs: economic losses (lost GDP) related to death and temporary or permanent disability caused by MI.

The cost of medical care provided to patients with MI included the cost of emergency, inpatient and outpatient care (the latter – within 6 months of the MI). When estimating the costs, we took into account the fact that some patients with acute MI require endovascular surgical interventions that are more expensive than routine inpatient care and that may have a considerable impact on the overall cost of MI treatment. In the PLATO study, 72% of patients underwent percutaneous coronary interventions (PCI), but this frequency does not correspond to the typical practice in the Russian health care. Accordingly, in our model the frequency of PCI was taken from the official Russian statistics (Form No.14 of National Statistics) and equaled 7.87%.

In order to estimate the cost of medical care provided to those patients who died from cardiovascular causes, we surveyed 6 experts – cardiologists and emergency cardiologists – about the frequency of death at home, in the ambulance and in the hospital, as well as the distribution of the duration of hospitalization among the deceased. Since there is no data on the distribution of patients by cause of death in the PLATO RCT, we assumed that the cost of any death from cardiovascular causes was equivalent to the cost of

Fig. 1. The method of selecting studies to assess the evidence for the efficacy and safety of ticagrelor and clopidogrel in combination with ASA in patients with ACS.

2 Only the costs of ticagrelor (Brilinta) and clopidogrel (Plavix) were considered; the cost of ASA was not included in the calculations, since patients in the PLATO study were receiving ASA in the same dose in combination with either ticagrelor or clopidogrel, and therefore the cost of ASA could not affect the difference in the overall cost of treatment.
death from MI and its complications. The cost of medical care provided to those patients who died from other (non-cardiovascular) causes was assumed to be equal to the cost of an ambulance ride. It was not possible to take other costs into account, since the exact causes of death were not specified in the published results of the PLATO study.

Table 2. Data for estimating direct medical costs

<table>
<thead>
<tr>
<th>Healthcare resources</th>
<th>Data used for estimating the costs</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic therapy</td>
<td>The loading dose of clopidogrel</td>
<td>Registry of acute coronary syndromes “Record” [10]</td>
</tr>
<tr>
<td></td>
<td>The daily dose of clopidogrel and ticagrelor</td>
<td>PLATO RCT [8]</td>
</tr>
<tr>
<td></td>
<td>The price of one package of clopidogrel</td>
<td>Maximum selling prices, maximum wholesale markups and VAT for medicines included in the List of Vital and Essential Drugs in Moscow [11]. Data from IMS Health database on the sales of clopidogrel (Plavix) in various packages in 2011.</td>
</tr>
<tr>
<td></td>
<td>The price of one package of ticagrelor</td>
<td>Approximate selling prices of the manufacturer and the average markup in the wholesale branch in Moscow for medicines not included in the List of Vital and Essential Drugs, based on the results of a marketing study by Sezhedim Ltd in 2011.</td>
</tr>
<tr>
<td>Treatment of non-fatal MI (including ambulance service, emergency care, inpatient care, high-technological medical care and outpatient care)</td>
<td>The likelihood of MI with clopidogrel</td>
<td>The results of the PLATO study. The values of parameters were taken from the report presented to NICE (the likelihood of experiencing an MI was estimated using Weibull regression analysis for one year)</td>
</tr>
<tr>
<td></td>
<td>The likelihood of MI with ticagrelor</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>The cost of an ambulance</td>
<td>Standards of financial costs in the regional program of state guarantees in Moscow [12]</td>
</tr>
<tr>
<td></td>
<td>The cost of resuscitation</td>
<td>Current tariffs for staying at the intensive care unit under the program of obligatory medical insurance (OMI) in Moscow in 2011, with a correction coefficient of 2.7 corresponding to the share of OMI funding in healthcare expenditures</td>
</tr>
<tr>
<td></td>
<td>The cost of a complete course of inpatient treatment</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>The frequency of performing PCI</td>
<td>Data from Report Form No.14 of National Healthcare Statistics for 2010</td>
</tr>
<tr>
<td></td>
<td>The quota of high-technological medical care in the field of cardiovascular surgery</td>
<td>Standards of financial costs for high-technological medical care in the field of cardiovascular surgery [13]</td>
</tr>
<tr>
<td></td>
<td>The cost of rehabilitation and pharmacotherapy for 6 months after discharge from hospital</td>
<td>Standard of medical care provided to patients with acute myocardial infarction [14], OMI tariffs with a correction coefficient, national registry of prices of medicines included in the List of Vital and Essential Drugs</td>
</tr>
</tbody>
</table>
Table 3. Data used for estimating direct non-medical costs and indirect costs related to MI and death

<table>
<thead>
<tr>
<th>Expenditures</th>
<th>Data used for the calculations</th>
<th>Source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>General data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>–</td>
<td>The proportion of working pensioners</td>
<td>Data from the Federal State Statistics Service of Russia for 2010</td>
</tr>
<tr>
<td>Temporary disability benefits</td>
<td>The average monthly salary</td>
<td>Data from the Federal State Statistics Service of Russia for 2010</td>
</tr>
<tr>
<td>–</td>
<td>The duration of temporary disability after an MI</td>
<td>Published data [16]</td>
</tr>
<tr>
<td>Permanent incapacitation benefits</td>
<td>The average pension for disability</td>
<td>The Pension Fund of the Russian Federation (official site: <a href="http://www.pfrf.ru/pensionres/">http://www.pfrf.ru/pensionres/</a>)</td>
</tr>
<tr>
<td>–</td>
<td>The number of working–age people newly classified as permanently disabled because of CAD</td>
<td>Statistical compilation “The main indicators of primary incapacitation of adults in the Russian Federation in 2010” [17]</td>
</tr>
<tr>
<td>–</td>
<td>The duration of the payment of benefits</td>
<td>An estimate*</td>
</tr>
<tr>
<td>Loss of GDP because of temporary disability</td>
<td>The number of economically active Russian citizens in 2011</td>
<td>Data from the Federal State Statistics Service of Russia [15]</td>
</tr>
<tr>
<td>–</td>
<td>The duration of temporary disability</td>
<td>Published data [16]</td>
</tr>
<tr>
<td>Loss of GDP because of permanent incapacitation</td>
<td>The number of economically active Russian citizens in 2011</td>
<td>Data from the Federal State Statistics Service of Russia [15]</td>
</tr>
<tr>
<td>–</td>
<td>The number of days of permanent incapacitation</td>
<td>Estimate*</td>
</tr>
<tr>
<td>Loss of GDP because of early death</td>
<td>The number of economically active Russian citizens in 2011</td>
<td>Data from the Federal State Statistics Service of Russia [15]</td>
</tr>
<tr>
<td>–</td>
<td>The proportion of patients who die of MI (including working–age individuals and pensioners)</td>
<td>Report Form No.14 of National Healthcare Statistics for 2010</td>
</tr>
<tr>
<td>–</td>
<td>The duration of underproduction of GDP</td>
<td>Estimate*</td>
</tr>
</tbody>
</table>

* In case the patient died at home or during emergency care and in cases of sudden death or death from an unknown cause, the cost of provided medical care was assumed to be equal to the cost of sending one ambulance. In all other cases the cost of emergency care was added to the cost of inpatient care.
The costs of medical care were calculated based on the tariffs on medical services and financial standards in the healthcare system in Moscow in 2010-2011. The sources of data on direct medical costs are listed in Table 2.

When estimating direct non-medical costs and indirect costs of MI and death, we took into account the proportion of patients with MI who were of working age or who had reached the age of retirement but continued working. The proportion of working-age patients with MI in our model was assumed to be equal to that reported in the National Statistics of the Russian Federation, and the proportion of working pensioners was taken from the Pension Fund of the Russian Federation. According to the branch-specific standard “Clinical and Economic Studies: a General Description”, direct medical costs correspond to the actual monetary payments, such as temporary disability benefits and pensions for permanently incapacitated individuals, which are caused by a temporary or permanent loss of the ability to work. Indirect costs include estimated economic losses related to the reduction in the GDP caused by temporary disability, permanent incapacitation or early death of patients with ACS who have survived an acute MI. The parameters used for estimating direct non-medical and indirect costs and the corresponding sources of data are presented in Table 3. Because some statistical details are missing for 2011, we calculated some parameters based on the data for 2010.

At the final stage we analyzed the sensitivity of our model to fluctuating values of some parameters. Among the potentially variable parameters (the price of clopidogrel and ticagrelor, the differences in their clinical efficacy, etc) we have chosen the price of ticagrelor to include in single-factor sensitivity analysis, since (in contrast to the original clopidogrel) its price is not yet registered in the National Registry of Maximum Selling Prices and appears to be crucial to the outcome of our modeling.

We calculated the costs in the model to determine the break-even point for ticagrelor, i.e. the highest price per package at which this drug will still be the preferred choice. Furthermore, according to one study [8], compliance with antiplatelet therapy was less than 100%, and therefore we looked at the impact of lower compliance on the overall costs.

In addition, we performed a single-factor sensitivity analysis for fluctuations of the price of clopidogrel within ±10% of the original price.

The modeling and all calculations were performed using Microsoft Excel 2007 software.

RESULTS

Our search for studies of the efficacy and safety of ticagrelor and clopidogrel revealed a single direct comparative RCT – PLATO (Wallentin L., et al. [8]). This multicenter, randomized, double-blind study included 18 624 patients with ACS who were hospitalized within 24 hours of the onset of symptoms and received anti-aggregation therapy with ticagrelor (180 mg once, then 90 mg twice per day) or clopidogrel (300 mg once, then 75 mg/day). All patients also received aspirin (75-100 mg/day). Those patients who underwent bypass surgery could be given 325 mg of ASA for 6 months, at the discretion of the operating surgeon. The primary endpoint was a combination of death from all causes – vascular complications, MI, and stroke [8].

The results of the PLATO study [8] demonstrated that the risk of MI was lower among patients who were receiving ticagrelor compared to patients who were receiving clopidogrel – 5.8% and 6.9%, respectively. The risk of death from cardiovascular causes was also lower in the ticagrelor group: 4.0% and 5.1%, respectively. However, the rate of severe bleeding was not significantly different in the groups of ticagrelor and clopidogrel: 11.6% versus 11.2%, respectively. The risk of stroke was not significantly different, either: 1.5% with ticagrelor and 1.3% with clopidogrel. In our model we estimated the cost of only those events the rate of which was significantly different in the two groups, namely MI and death.

We calculated the frequencies of MI and death for patients with ACS receiving a combination therapy with ticagrelor + ASA or clopidogrel + ASA over the period of one year, based on the original data on the rate of adverse events reported in the PLATO RCT (Table 4).

The costs of ticagrelor and clopidogrel are presented in Table 5. Therapy with ticagrelor 180 mg/day costs 118.21 RUB and clopidogrel 75 mg/day costs 116.60 RUB per day. A loading dose of ticagrelor costs 118.21 RUB. The distribution of the loading doses of clopidogrel in the real-life clinical setting based on the data in the National Registry of ACS “Record” can be found in Table 6. The weighted average cost of a loading dose of clopidogrel is 439.94 RUB. The cost of antiplatelet therapy with ticagrelor and clopidogrel per patient per year was thus 43,148.08 and 42,883.61 RUB, respectively.

Table 4. The risk of adverse events in patients with ACS receiving a combination of ticagrelor + ASA or clopidogrel + ASA for one year

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel + ASA</th>
<th>Ticagrelor + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non–fatal MI</td>
<td>0.0582</td>
<td>0.0505</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>0.0514</td>
<td>0.0411</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>0.0081</td>
<td>0.0058</td>
</tr>
<tr>
<td>Significant bleeding</td>
<td>0.1200</td>
<td>0.1244</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.0100</td>
<td>0.0102</td>
</tr>
</tbody>
</table>

Note: the probabilities were calculated using Weibull regression analysis based on the original results of the PLATO study.
The weighted average cost of treating one patient with non-fatal MI in this model was 115,560.55 RUB, including the following:

- emergency medical care – 5,136.78 RUB;
- inpatient care – 98,403.15 RUB, consisting of: 82,388.27 RUB for specialized care (resuscitation + hospitalization), 16,014.88 RUB for high-technological medical care and PCI;
- outpatient care for 6 months – 12,020.62 RUB, consisting of: 10,399.83 RUB for medical services and 1,620.79 RUB for medications.

The structure of weighted average costs of treating one patient with MI is presented in Fig. 3.

Table 7 summarizes the results of our survey of experts about the real-life practice of treating patients who die of MI. Based on this data, we calculated the cost of death from cardiovascular causes in our model – 23,189 57 RUB. As described in the section on methodology, the cost of death from other causes was assumed to equal the cost of an ambulance, which is 5,136.78 RUB.

The weighted average direct costs of medical care provided to one patient treated with clopidogrel or ticagrelor were calculated in our model as follows:

- MI – 6,700 RUB and 5,800 RUB, respectively;
- death from cardiovascular causes – 1,200 RUB and 900 RUB, respectively;
- death from other causes – 42 and 30 RUB, respectively (Table 8).

![Fig. 3. The structure of weighted average costs of treating one patient with MI, RUB.](image)
A lower risk of MI and death associated with ticagrelor thus decreases the cost of medical care by 1,140.48 RUB per year per patient.

The direct non-medical and indirect costs of MI in working-age patients are presented in Table 9.

The overall costs considering the risk of MI and death as well as the differences in the cost of antiplatelet therapy with ticagrelor and clopidogrel in combination with ASA per year per patient with ACS are summarized in Table 10. Ticagrelor appears to be more cost-effective: it saves the healthcare system 2,759.97 RUB per year per patient. The price of ticagrelor is higher than the price of clopidogrel (the former costs 264.46 RUB more per patient), but this difference in price is offset by other direct medical costs, which are lower (1,140.48 RUB), as well as direct non-medical and indirect costs (1,873.94 RUB). The greatest saving is due to the differences in the cost of managing MI and in indirect costs.

To summarize, under the conditions assumed in this model ticagrelor is the preferred choice, being both a more effective and a more cost-effective antiplatelet agent than the original clopidogrel.

Sensitivity analysis demonstrated that, as long as the price of one package of ticagrelor (56 tablets) is below 3,520.94 RUB. (including 10 % VAT and 22 % markup in Moscow) and other parameters are unchanged, it remains the preferred choice over clopidogrel.

If the costs in our model are re-calculated to account for imperfect compliance reported in the study (82.8%) [8], the difference in the cost of antiplatelet therapy with clopidogrel and ticagrelor diminishes, but clopidogrel still has an advantage (Table 11). However, ticagrelor is still better in terms of the overall costs, saving 2,795.46 RUB per patient with ACS per year.
Our analysis of the sensitivity of the model to fluctuations in the price of clopidogrel demonstrated that ticagrelor would save 7,038.33 RUB of the overall costs if the price of one package of clopidogrel went up 10%, while a 10% drop in the price of clopidogrel would make it the better option, since treatment with ticagrelor would then cost 1,538.39 RUB more per patient with ACS per year.

DISCUSSION

The results of our study suggest that ticagrelor should be administered to patients with ACS in Russia, but with some caveats. Because of the lack of official statistics and data on the amount of health care provided to patients in the real-world clinical practice, at present it is impossible to estimate comprehensively the cost of treating ACS in the Russian Federation. There are also certain problems with the methodology of estimating direct and indirect costs that are related to some particular features of the funding of the Russian healthcare and of Russian economy as a whole [18].

Clinical advantages of ticagrelor over clopidogrel have been proved in an RCT and consist in the lower risk of MI and death without any increase in the risk of major bleeding – potentially a serious side effect of antiplatelet therapy. Accordingly, the economic advantages of ticagrelor are related to lower costs of treating patients who survived an MI and died within one year of the onset of ACS. The costs of treating MI patients vary depending on the particular medical center and region of the Russian Federation, and therefore the outcome of pharmacoeconomic analysis may be different if it is performed from the perspective of the healthcare system in a particular region of the Russian Federation (the advantages of ticagrelor may not be manifest when the tariffs on medical care provided to MI patients are low, or when it is compared to clopidogrel generics). However, in our analysis the cost of managing one MI patient was 115,560.55 RUB per year, which does not appear to be an inflated estimate.

The cost of treating those patients who died from cardiovascular causes are also estimated to be rather low – 23,189.57 RUB; these estimates should be verified in dedicated studies. When estimating the cost of treating patients who died from other causes, we considered the “minimal” scenario (only the cost of an ambulance), and therefore in this case the costs are more likely to be underestimated rather than overestimated.

Dwinding investments in the treatment of patients with cardiovascular disorders under programs for modernizing health care and a growing number of myocardial revascularization procedures performed in patients with ACS make the economic advantages of using ticagrelor for antiplatelet therapy more pronounced, since the difference in the costs of managing MI is increasing.

One limitation of our study is the fact that we only considered the cost of the original clopidogrel. When reproduced drugs (generics) are used, the difference in the cost of antiplatelet therapy becomes more significant. On the other hand, in this case the question of therapeutic equivalence of generics and the original drug remains open.

Pharmacoeconomic studies of the cost-effectiveness of ticagrelor compared to clopidogrel conducted in other countries concluded that ticagrelor was a more cost-effective alternative thanks to its low incremental costs [19]. For instance, the results of a cost-effectiveness analysis for England and Wales presented on the official site of the British National Institute for Health and Clinical Excellence (NICE) demonstrate that combination treatment with ticagrelor + ASA is more cost-effective compared to clopidogrel + ASA. The additional cost is £3,521 per quality-adjusted life year (QALY), and the likelihood that ticagrelor will remain more cost-effective if the cost increases to £5,000 and £20,000 per QALY is 76.6% and 99.9%, respectively [19].

D. J. Crespin et al. [20] studied the administration of ticagrelor to patients with genetically lower sensitivity to clopidogrel for secondary prevention after the onset of ACS. Their cost-effectiveness analysis demonstrated that ticagrelor was more cost-effective than clopidogrel, and the additional cost per QALY was $10,059. According to a probabilistic sensitivity analysis, the incremental costs will be less than $50,000 per QALY in 97% of cases.

To summarize, the results of our pharmacoeconomic analysis demonstrate that, despite some limitations due to objective problems with the estimation of costs, ticagrelor may be considered a good alternative to clopidogrel for patients with ACS in terms of its clinical efficacy and cost-effectiveness.

CONCLUSION

1. Ticagrelor in combination with ASA statistically significantly reduces the risk of acute MI and death from cardiovascular causes in patients with ACS compared to clopidogrel in combination with ASA, without increasing the risk of serious adverse events, such as major bleedings.

2. A model created on the basis of the results of the PLATO RCT shows that ticagrelor as a component of antiplatelet therapy is superior to clopidogrel under the conditions of the Russian health care. It is a cheaper and more effective alternative that saves the healthcare system on average 27,499.97 RUB per patient per year due to lower direct and indirect costs of MI and lower direct medical costs of treating patients who die from cardiovascular causes.

Table 11. The overall cost of antiplatelet therapy of one patient with ACS in the primary analysis and in the sensitivity analysis taking into account compliance with treatment, per patient per year, RUB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary analysis</th>
<th>Sensitivity analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>42,883.61</td>
<td>35,507.63</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>43,148.08</td>
<td>35,726.61</td>
</tr>
<tr>
<td>Difference</td>
<td>~ 264.46</td>
<td>~ 218.98</td>
</tr>
</tbody>
</table>
3. Ticagrelor will remain the preferred choice over clopidogrel, as long as the price of one package of ticagrelor (56 tablets) is below 3,520.94 RUB (including 10% VAT and 22% wholesale markup) and other parameters are unchanged.

REFERENCES


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Analytical Report on Recent Trials Evaluating Technologies in Abdominal Surgery

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Abdominal surgery is among the most significant fields of medicine. We present an analytical report on recent trials evaluating technologies such as laparoscopic surgery, robot-assisted surgery, organ transplantation and other modern approaches to the treatment of patients with chronic abdominal diseases that are now being investigated all over the world.

**KEYWORDS:** evidence-based medicine, abdominal surgery, analytical report, modern technologies, recent studies, recent trials, laparoscopic surgery, robot-assisted surgery, organ transplantation.

Health technology assessment relying on the principles of evidence-based medicine is of particular relevance in the field of surgery. Unfortunately, a common approach is to evaluate the results of a clinical trial based on the surgeon’s own (“expert”) opinion, rather than the results of meta-analyses, clinical trials or randomized controlled trials (RCTs). Nevertheless, there have been some positive changes, and the surgery is now becoming more open to decision-making that relies on the principles of evidence-based medicine.

Abdominal surgery remains one of the key fields among all other specializations within surgery. Suffice it to say that 13.7% of over 9 million surgical interventions performed in Russian hospitals in 2011 were operations on the organs in the abdominal cavity. One reason why abdominal surgery has been developing so actively over the last few years is the introduction of new technologies that make the treatment of various abdominal diseases more effective.

In view of this, we found it worthwhile to present an analytical report on studies conducted between 2010 and 2013 that reflect the main recent trends in the surgery of various organs of the abdominal cavity.

**The purpose of this review** is to investigate current trends in the recent studies of technologies in abdominal surgery.

**Methodology of the report.** We included both completed and ongoing studies in this report, especially studies of the key technologies, such as laparoscopic surgery, robot-assisted surgery and organ transplantation, but also other approaches to the treatment of patients with various diseases of internal organs (Table 1).

We mainly searched for studies conducted in the leading medical centers of the United States, Western Europe, Japan, China, and South Korea. The sources of information included web pages of medical centers and the Medline database of abstracts. The following search terms were used: “laparoscopic” + “surgery”, “laparoscopy”, “robot-assisted”, “transplantation”, “graft” + “surgery” (formulated after a discussion with experts surgeons).

This analysis included the leading medical research centers in North America and Western Europe, as well as the leading researches in the field of abdominal surgery who are now widely cited by the surgical community (Tables 2 and 3).

We searched for studies and evaluated their methodological quality in accordance with the standard operational procedures of the autonomous non-commercial organization “National center for health technology assessment”. The levels of evidence for each type of study design are listed in Table 4.

<table>
<thead>
<tr>
<th>Table 1. The main diseases included in the analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affected organ</strong></td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Biliary tract</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Colon and rectum</td>
</tr>
<tr>
<td>Adrenals</td>
</tr>
<tr>
<td>Retroperitoneal space</td>
</tr>
</tbody>
</table>

¹ Data from the joint annual report of the territories of the Russian Federation presented in Form 14 of the National Statistical Survey.
Table 2. Medical centers in North America and Western Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Medical research center</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Mayo Clinic, John Hopkins University, MD Anderson Center, Memorial Sloan–Kettering Cancer Center</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Liverpool Cancer Centre</td>
</tr>
<tr>
<td>France</td>
<td>Clinique Ambroise Pare, L’Hôpital Paul Brousse, Beaujon Hospital</td>
</tr>
<tr>
<td>Germany</td>
<td>Hannover Medizinische Hochschule</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Academic Medical Center (Amsterdam)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>University Hospital of Zurich</td>
</tr>
</tbody>
</table>

Table 3. The world’s leading researchers in abdominal surgery

<table>
<thead>
<tr>
<th>Country</th>
<th>Researches</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>W. Pinson</td>
</tr>
<tr>
<td>Italy</td>
<td>C. Bassi, L. Capussotti</td>
</tr>
<tr>
<td>Germany</td>
<td>P. Andreas</td>
</tr>
<tr>
<td>Argentina</td>
<td>E. de Santibannes</td>
</tr>
<tr>
<td>Australia</td>
<td>C. Christolphi, R. Padbury</td>
</tr>
</tbody>
</table>

Table 4. Levels of evidence in accordance with the study design

<table>
<thead>
<tr>
<th>Study design</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review, meta–analysis</td>
<td>I</td>
</tr>
<tr>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td>Observational study (case–control, case series, cohort study)</td>
<td>III</td>
</tr>
</tbody>
</table>

Fig. 1. The results of our search for publications grouped by study design.

Table 5. The number of identified studies by the type of technology

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Number of identified studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic surgery</td>
<td>26</td>
</tr>
<tr>
<td>Manually assisted laparoscopic surgery*</td>
<td>6</td>
</tr>
<tr>
<td>Laparoscopically assisted surgery**</td>
<td>6</td>
</tr>
<tr>
<td>Single–port laparoscopy</td>
<td>5</td>
</tr>
<tr>
<td>Laparoscopic simulation</td>
<td>3</td>
</tr>
<tr>
<td>Robot–assisted surgery</td>
<td>14</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>7</td>
</tr>
<tr>
<td>Postoperative care and therapy following abdominal cavity interventions</td>
<td>6</td>
</tr>
</tbody>
</table>

Notes:
* A minimally invasive method: the non-dominant hand of the surgeon is inserted with a device allowing access for the hand through a special incision, leaving the pneumoperitoneum intact.
** A method combining open access and laparoscopy: for example, laparoscopy is used at the stage of organ mobilization, and then the main stage (resection, etc) is performed with minimal access (openly, without pneumoperitoneum).
STUDY RESULTS

The total of 73 publications (6 systematic reviews, 22 RCTs, and 45 observational studies) were found, of which 67 have been completed and 6 are still going on (Fig. 1). The outcome of our search is presented in Table 5, including the number of identified studies that evaluated modern surgical technologies and the changes for the period from 2010 to the present (Fig. 2).

Our search identified 26 recent publications that evaluated the use of laparoscopic surgery in the abdominal cavity, including two systematic reviews [1, 2], five RCTs [3-7], and nineteen observational studies [8-26]. The authors of two systematic reviews [1, 2], four RCTs [3, 5-7] and seventeen observational studies [8-10, 12-20, 22-26] concluded unambiguously that laparoscopic surgery is an effective and safe method for abdominal interventions. One of the observational studies [11] reported that laparoscopic surgery plays only a minor role in locating disseminated lesions in patients with incidental gallbladder cancer, but there were few such patients in this study. The correspondence of real-life practice (including laparoscopic interventions) to the existing standards of surgical treatment of acute pancreatitis in Italy was judged to be poor in one publication [21].

We also discovered one ongoing RCT [4] that compares laparoscopic distal resection with open intervention in patients with operable stomach cancer following neoadjuvant therapy. The results of this study are expected in 2014.

Manually assisted laparoscopic surgery (laparoscopic surgery with a “helping hand”, hand-assisted surgery) was investigated in six publications [27-32], including one systematic review [27], two RCTs [28, 29], and three observational studies [30-32]. According to the results of the systematic review [27] and two observational studies [30, 32], manually assisted laparoscopic surgery shortens the duration of colorectal surgical procedures. Moreover, the results of two RCTs [28, 29] demonstrated that manually assisted laparoscopic surgery is a practically feasible and safe method for right colectomy. However, one of these publications [29] does not recommend routine use of this method for this type of surgical interventions, since it failed to demonstrate a statistically significant advantage in terms of shortening the duration of the procedure compared to total laparoscopy. In one of the observational studies [31] it was concluded that manually assisted laparoscopic surgery is a feasible method that may be used for liver transplantation from a living donor.

In addition, we discovered six studies [33-38] that evaluated laparoscopically assisted surgical interventions (laparoscopically-assisted surgery) in the abdominal cavity: four RCTs [33-36] and two observational studies [37, 38]. This surgical method was considered to be feasible and safe in patients with disseminated stomach cancer in one of the RCTs [33]. The authors of another RCT [34] discovered that laparoscopically assisted surgery reduced rehabilitation time after right resection in patients with colorectal cancer, while the duration of the operation itself increased. Two observational studies [37, 38] demonstrated that the method of laparoscopically assisted surgery is associated with an increased number of complications.
cally assisted surgery is practically feasible in patients with early-stage stomach cancer. Two RCTs are now being performed in the United States [35, 36] to compare this technology with open surgical intervention in patients with colorectal cancer.

The method of single-port (single-incision) laparoscopic surgery used for interventions in the abdominal cavity was evaluated in five publications, including one systematic review [39], three RCTs [40-42], and one observational study [43]. The conclusions of these studies [39-43] are quite consistent: single-port laparoscopy is a safer, and thus a preferable, method compared to standard (multiple-incision) laparoscopic abdominal surgery.

We discovered three publications that discuss laparoscopic simulations in abdominal surgery: one systematic review [44], one RCT [45], and one observational study [46]. According to the results of the systematic review [44] and the RCT [45], laparoscopic simulation is an effective method for training in abdominal laparoscopic surgery. The observational study [46] discusses the issues of calibrating (setting up) Simbionix virtual reality simulator for the purpose of training novice surgeons in the technique of laparoscopic intervention.

The use of robot-assisted surgical interventions (robot-assisted surgery) was evaluated in a total of fourteen studies, including one systematic review [47], one RCT [48], and twelve observational studies [49-60]. In all these studies [47-60] it was concluded that robot-assisted surgery is a practically feasible and safe method of abdominal surgery. However, it is claimed in one RCT [48] that this method is not superior to standard laparoscopy for right colectomy in terms of its cost-effectiveness. Other surgeons in one of the observational studies [49] note in their conclusions the increased duration of operation for patients undergoing pancreatectomy with robot-assisted “Da Vinci” system compared to the standard laparoscopic intervention, but they still conclude that this technology is likely to become generally adopted for this surgical procedure in the near future.

As for organ transplantation, seven publications were identified: one RCT [61] and six observational studies [62-67]. The results of the RCT [61] demonstrate that perioperative therapy with synbiotics reduces the rate of infectious complications after liver transplantation from a living donor. According to the results of one of the observational studies [62], neoadjuvant chemotherapy followed by liver transplantation improves the quality of life of patients with proximal cholangiocarcinoma. Another study [63] demonstrated that liver transplantation improves the survival rate of patients with hepatocellular carcinoma. It is claimed in another publication [64] that endoscopic retrograde cholangiography with balloon dilation and stenting leads to the best results in terms of disintegration of anastomotic biliary strictures following liver transplantation from a living donor, thus avoiding surgical interven-

tion and re-transplantation. The authors of one observational study [65] conclude that transplanting the liver in smaller grafts is an alternative approach to performing this surgery in children with body weight under 10 kg. Another publication [66] discusses the observed reduction in the rate of liver transplantation among the patients with bile duct lesions in Argentina. Furthermore, a study is now under way in the United States which evaluates the use of endotracheal cardiac output monitor during surgical procedures of liver transplantation [67].

The issues of postoperative care and pharmacotherapy of patients who undergo abdominal surgery were discussed in six publications [68-73], including five RCTs [68-72] and one observational study [73]. A multi-factor analysis performed in one RCT [68] demonstrated that the administration of fluoride-uracil in combination with folic acid or gemcitabine statistically significantly improved the survival of patients with periamplullary adenocarcinoma following the resection of pancreas compared to observation without treatment. Another RCT [69] evaluated adjuvant chemotherapy with gemcitabine versus fluoride-uracil in combination with folic acid in patients with pancreatic cancer following tumor resection. In this study gemcitabine showed no advantage in terms of overall survival. The combination of fluoride-uracil, cisplatin and interferon alpha-2b was compared to monotherapy with fluoride-uracil in patients with resected pancreatic adenocarcinoma in another RCT [70], but no advantage of the former regimen was discovered in terms of survival. An RCT conducted in Japan [71] demonstrated that Japanese medicinal herbs suppressed the inflammatory reaction after a laparoscopic surgical intervention in patients with colorectal cancer. At present two protocols are being investigated in the Netherlands [72, 73], one of which concerns the efficacy and safety of a new method for peri- and postoperative ileostomy care called “I-aid” [72], while the other focuses on molecular strategies for treating Barrett’s esophagus [73]. Both of these studies are expected to be completed in 2014.

The analytical report presented in this article demonstrates the broad scope of modern studies of technologies in abdominal surgery. Predictably, the majority of publications evaluate laparoscopic surgery, but studies of robot-assisted abdominal surgery already fill a significant niche. This indicates that the demand for this method may be expected to grow in the near future. Furthermore, it is worth noting that the majority of identified studies that evaluated robot-assisted surgical interventions were conducted in China, Japan and South Korea. We also have to note that researchers are interested in such technologies as single-port laparoscopic surgery and laparoscopic simulation. Overall, in spite of the specific features and conservative nature of abdominal surgery, the number and diversity of studies identified in this review certainly justify the conclusion that there is a growing trend among
the surgeons in many countries to consider clinical problems and evaluate technologies from the perspective of evidence-based medicine.

REFERENCES


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Clinical and Economic Aspects of Early Diagnostics and Radical Treatment of Prostate Cancer

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We analyze the cost-effectiveness of the following program implemented in Moscow: “Targeted Screening of Males for Prostate Disorders”. We have analyzed the rate at which various services (diagnostic procedures and radical treatment) are provided in this program and estimated the labor costs of identifying patients with prostate cancer who need radical treatment, depending on the stage of the disease. Overall, the cost of identifying a single patient in need of radical treatment in this program is high and comparable to the labor costs of the actual specialized urological care that is provided to these patients.

The article is supplemented with an analysis of some potential methods of cost optimization.

KEYWORDS: prostate cancer, early diagnostic procedures, radical treatment of prostate cancer, clinical and economic analysis.

INTRODUCTION

A program called “Targeted Screening of Muscovites” was initiated in 2002 by order No.50 of the Healthcare Committee of Moscow. The goal of this program is to ensure early diagnostics of socially significant illnesses, and one of its branches is the sub-project called “Targeted Screening of Males for Prostate Disorders”. The objective of this sub-project (hereafter referred to as “the Program”) was early diagnostics of pathologies affecting the prostate gland, primarily prostate cancer – the most socially significant disorder affecting men over 50 years of age [1, 2]. However, diagnostics, even early diagnostics, is not self-sufficient – it provides an opportunity for administering a specific treatment, the effectiveness of which may be improved if the illness is discovered at an early stage. In the case of prostate cancer the benefits of early diagnostics are obvious – it offers a chance of conditional cure from a malignant tumor, which is only possible if the patient is given radical treatment at an early stage. The cure is regarded as “conditional”, since a recurrence of prostate cancer is possible even after a very long time has passed since the surgery or radiation therapy.

An additional, but very important, consideration is the social factor, namely a chance to achieve complete rehabilitation and return the patient to productive work, which in most cases is only possible when prostate cancer is treated actively at an early stage [3]. Therefore, when looking at the economic aspect of the Program, it may be important both to calculate the cost of identifying a typical patient suffering from prostate cancer and to estimate the cost-effectiveness of the search for potentially curable patients.

MATERIALS AND METHODS

At the first stage of this study we analyzed the results of an integrated evaluation performed in the framework of the program “Targeted Screening of Muscovites” [4]. At the second stage we assessed the real-life clinical practice, looking at the provision of specialized urological (oncourological) services to prostate cancer patients in 2009-2011 based on the data collected by the Department of Health of Moscow and City Clinical Urological Hospital No.47 (a total of 3524 patients).

Examination procedure in the Program

To standardize the sequence and number of examinations, a particular diagnostic procedure was created for the Program, which took into account both the fact that city hospitals were understaffed with urologists specializing in ambulatory practice and the limited material and technological base of city outpatient centers and hospitals. The key study using this procedure was performed in order to measure total prostate-specific antigen (PSA) in men over 50 years of age seeking ambulatory medical care in an outpatient center. Following the measurement of this oncological marker, each patient was seen by an urologist, who decided whether further diagnostic procedures were necessary and how extensive they needed to
be. Patients with normal levels of PSA were examined further only if they presented with complaints typical for prostate disorders. If there were no complaints, the urologist reported that “no prostate disorders were discovered”.

If the patient had complaints, the examination aimed primarily to detect infravesical obstruction and included an obligatory rectal palpation, a survey using the IPSS questionnaire, and an ultrasound scan of the bladder and prostate. When necessary, the following laboratory tests were requested: general urinalysis, analysis of the prostate secretions, followed by a test for the sensitivity of microflora to antibacterial drugs. The outcome of this complete examination was either a diagnosis (prostate adenoma, prostatitis) or the conclusion that “no prostate disorders were discovered”.

When the level of PSA was elevated (> 4 ng/mL), thus indicating the risk of prostate cancer, the patient was advised to undergo multifocal biopsy of the prostate gland. The results of this biopsy lead to one of 3 principle diagnoses: prostate cancer, prostate adenoma, or prostatitis.

Those patients who were not diagnosed with cancer based on the biopsy results were included in the high-risk group. They were re-examined after 6 months, including rectal palpation, total and free PSA levels, and transrectal ultrasound. In case of elevated PSA and abnormalities discovered in one of the tests, a multifocal biopsy of the prostate was repeated.

**Frequency analysis**

Apart from a description of the methodology, data on the frequency of using particular tests and treatment strategies is needed for the task of evaluating the cost-effectiveness of this diagnostic procedure.

We performed a frequency analysis, looking at the frequency with which the methods described above, as well as radical treatment of prostate cancer, were used in Moscow between 2009 and 2011. The sources of our data included the following: annual economic reports of the Moscow urological service, annual reports about the screening of males for early diagnostics of prostate disorders, and the materials prepared by the Collegium of the Department of Health of Moscow for an overall review of the Moscow urological service in 2009-2011 and the measures taken for its improvement [5].

**Assessment of cost-effectiveness**

Since the prices of medical services changed repeatedly during the time when the Program was in progress, we assessed its cost-effectiveness using conventional units of labor costs (CULCs).

The costs were expressed in CULCs and calculated based on the Registry of Medical Services Specifying Conventional Units of Labor Costs (an actualized draft from 2007 of Appendix 1 to the Nomenclature of Tasks and Services in Health Care, http://www.rspor.ru).

The following codes of services and CULCs were used for the calculations.

- **Examination by a urologist** (B01.053.01): 0.8 CULCs for the physician, 0.8 for the nurse.
- **Prostate biopsy** (A11.21.005): 6.0 CULCs for the physician, 15.0 for the nurse.
- **Histological study of the biopsecte** (A08.31.015 – histological study of a tumor extract or tumor-like formations in soft tissues): 3.0 CULCs for the physician, 2.0 for the nurse.
- **Measurement of the level of prostate-specific antigen** (PSA) (A09.05.135): 3.5 CULCs for the physician, 12.0 for the nurse.
- **Ultrasound scan of the prostate** (A04.21.001): 2.0 CULCs for the physician, 2.0 for the nurse.
- **Hematology** (B03.016.03 – general (clinical) hematological analysis, complete): 1.2 CULCs for the physician, 1.4 for the nurse.
- **Blood biochemistry** (in urological clinical practice, the following parameters are required: creatinine, urea, potassium, sodium), B03.016.04 in the Registry – biochemical hematological analysis, general therapeutic: 0.3 CULCs for the physician, 2.1 for the nurse.
- **Coagulogram** (B03.005.06): 1.0 CULCs for the physician, 0.3 for the nurse.
- **General urinalysis** (B03.016.06 – general urine analysis): 0.8 CULCs for the physician, 0.8 for the nurse.
- **Wassermann reaction** (A12.06.011): 0.1 CULCs for the physician, 1.1 for the nurse.
- **HIV blood test** (B03.014.01 – a series of tests for suspected infection with human immunodeficiency virus): 3.0 CULCs for the physician, 3.0 for the nurse.
- **Blood test for viral hepatitis** (B03.016.08 – a series of tests for hepatic cellular damage): 0.5 CULCs for the physician, 0.8 for the nurse.

The purpose of this study is to assess the labor costs of identifying one potentially curable patient suffering from prostate cancer (cost-effectiveness analysis). The calculations were based on the Registry described above and the known frequency of using each particular test and radical treatment of prostate cancer (see section “Frequency analysis”).

Cost/effectiveness ratio (CER) was calculated as follows:

\[ CER = \frac{C}{Ef} \]

“C” is the labor cost of identifying in the framework of the Program one patient suffering from prostate cancer (regardless of the stage of the condition, its operability, etc). This cost was 578.9 CULCs for the physician and 1526.3 CULCs for the nurse [4];

“Ef” is the likelihood of achieving the goal of the Program based on various criteria (diagnostics of cancer at a particular stage, administration of radical treatment, five-year survival rate with the use of these methods).

**RESULTS**

First we have to consider the distribution of patients with prostate cancer, regardless of the stage of its pro-
The presence of prostate cancer was histologically confirmed in all patients included in the analysis. The smallest proportion of patients, 13%, were diagnosed at stage I (Fig. 1). The proportions of patients whose prostate cancer was diagnosed at stages II and IV were comparable – 26% and 22%, respectively. Patients with stage III prostate cancer were the most common (39%).

Based on these results and the average labor costs of identifying one case of prostate cancer (578.9 CULCs for the physician and 1,526.3 CULCs for the nurse), it is possible to estimate the labor costs of finding one patient at a given stage of the disease (Table 1). The search for one patient with stage I prostate cancer requires 4,453.1 CULCs for the physician and 11,740.1 CULCs for the nurse. The labor costs of identifying patients at stages II and IV for the physician/nurse are 2,226.5/5,870.4 CULCs and 2,631.4/6,937.7 CULCs, respectively. Finally, 1,484.4 CULCs for the physician and 3,913.6 CULCs for the nurse are required to identify a single patient with stage III prostate cancer.

In view of the original goal, namely the identification of patients who need radical treatment, it is worth estimating the labor costs of diagnosing prostate cancer at stages I and II. Radical treatment is indicated only in some exceptional cases at later stages of the disease, and even then it is often doubtful how “radical” surgery or radiation therapy may be. Accordingly, we may provisionally equate the search for patients with prostate cancer at stage I or II with the search for patients who need radical treatment.

The probability of finding a patient with stage III prostate cancer is equal to the frequency of this stage (39%) and requires 1,484.4 CULCs for the physician and 3,913.6 CULCs for the nurse, which is 2.6 times higher than the average labor costs of identifying a prostate cancer patient regardless of the stage of the disease.

At the second stage of this study we concluded that the availability of radical treatment methods to prostate cancer patients residing in Moscow is at present quite satisfactory. Accordingly, we presumed that patients to whom radical treatment was medically indicated could either obtain such treatment or refuse it in writing. Not surprisingly, such refusals are extremely rare – about 1 out of 150 cases, according to expert estimates [5]; thus any bias caused by ignoring this patient group is likely to be negligible.

The following radical treatment methods are currently offered to prostate cancer patients in the real-life clinical setting: radical prostatectomy, brachytherapy, and radical radiation therapy [5, 6]. Each of these methods has its pros and cons, but overall they are comparable in terms of both their effectiveness and the rate of adverse effects.

New methods of radical treatment of prostate cancer are being developed and implemented, such as HIFU therapy, which uses the effects of high-frequency ultrasound. However, the majority of these techniques are only being tested in research centers, and their position in the structure of clinical treatment of prostate cancer is yet to be determined.

According to the available evidence, 92% of patients with stage I prostate cancer have received radical treatment: radical prostatectomy (65%), brachytherapy (20%) or radical radiation therapy (7%; see Table 2).

The remaining 8% of patients either had significant comorbidities that made these treatment methods excessively risky or refused radical treatment for personal, non-medical reasons. This group of patients received a conservative treatment, such as monotherapy or combination therapy with antiandrogens and gonadotropin-releasing hormone agonists. Pharmacotherapy of prostate cancer is fairly effective in terms of survival rate and is well tolerated, since in therapeutic doses these drugs have no intrinsic

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**Table 1. Labor costs of identifying patients with particular stages of prostate cancer**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stages I and II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Average (regardless of the stage and other disease characteristics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rate of identifying patients at this stage</td>
<td>13.0</td>
<td>26.0</td>
<td>39.0</td>
<td>39.0</td>
<td>22.0</td>
<td>-</td>
</tr>
<tr>
<td>Physician CULCs per patient</td>
<td>4,453.1</td>
<td>2,226.5</td>
<td>1,484.4</td>
<td>1,484.4</td>
<td>2,631.4</td>
<td>578.9</td>
</tr>
<tr>
<td>Nurse CULCs per patient</td>
<td>11,740.8</td>
<td>5,870.4</td>
<td>3,913.6</td>
<td>3,913.6</td>
<td>6,937.7</td>
<td>1,526.3</td>
</tr>
</tbody>
</table>

---

1. Brachytherapy is synonymous with interstitial radiation therapy. Grains of radioactive material are implanted in the parenchymatous tissue of the prostate affected by malignant growth. One of the isotopes of cobalt is normally used. The radioactive grains are implanted through surgery, and the gamma rays they produce are responsible for the therapeutic effect.
cytotoxicity, in contrast to cytostatics and antimetabolites. However, pharmacotherapy can only slow down the progression of prostate cancer, though in some cases it leads to a partial tumor regression. There is nothing “radical” about this treatment, and therefore this group of patients is not included in our economic analysis.

The effectiveness of radical treatment methods, in this context understood as five-year recurrence-free survival rate, varied from 85% to 88% for stage I cancer, without any significant differences.

Eighty nine percent of patients with stage II prostate cancer received radical treatment: 64% underwent radical prostatectomy, 18% brachytherapy, and 7% radical radiation therapy. Eleven percent of patients could not be operated on because of the risks related to surgery and anesthesia or refused radical treatment for personal reasons. The effectiveness of radical prostatectomy was 78%, brachytherapy 73%, and radical radiation therapy 67%. Statistically significant differences were discovered only between groups of patients who were at different stages of the disease but received the same treatment (p < 0.05).

Twenty eight percent of patients with stage III prostate cancer received radical treatment. Nine percent underwent radical prostatectomy, and the remaining 19% - radical radiation therapy. Brachytherapy is not indicated at stage III, since radical effect is not possible and the risk of post-operative complications is high. However, 10% of patients underwent endoscopic surgery, which is a palliative measure taken to improve the quality of urination: 3% underwent transurethral prostate resection and 7% prostate incision. A considerable proportion of patients at stage III (62%) received only pharmacotherapy.

In contrast to stage II, at this stage the effectiveness of radical prostatectomy is reduced to 57% and that of radical radiation therapy to 51%. The differences are statistically significant (p < 0.05).

At stage IV of prostate cancer radical treatment is offered only to a few patients (8%). Prostatectomy is then no longer technically feasible. A radical effect can only be expected with radiation therapy, but the results of such treatment are modest – the five-year recurrence-free survival rate does not exceed 40%. Practically all these patients were given pharmacotherapy (92%), and some underwent palliative surgery (in total 24%).

On average, 47.8% of patients with histologically confirmed prostate cancer received radical treatment.

Now it is time to discuss the labor costs of identifying patients with prostate cancer amenable to radical treatment, separately for each stage of the disease (Table 3). For stage I prostate cancer, the labor costs of identifying one patient to whom radical treatment is indicated are 4,840.3 CULCs for the physician and 12,761.7 CULCs for the nurse, while for stage II prostate cancer these figures are 2,501.7 CULCs and 6,595.94 CULCs, respectively. At later stages the likelihood of finding a patient who could benefit from radical treatment is relatively low, and the labor costs of identifying such patients increase accordingly: 5,301.2 CULCs for the physician and 13,977.1 CULCs for the nurse at stage III and 32,892.1 CULCs for the physician and 8,6721.6 CULCs for the nurse at stage IV.

### Table 2. The frequency of using different treatment methods of prostate cancer and their effectiveness depending on the stage of the disease, %

<table>
<thead>
<tr>
<th>Treatment method</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Effective-ness</td>
<td>Frequency</td>
<td>Effective-ness</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>65</td>
<td>87</td>
<td>64</td>
<td>78</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>20</td>
<td>85</td>
<td>18</td>
<td>73</td>
</tr>
<tr>
<td>Radical radiation therapy</td>
<td>7</td>
<td>88</td>
<td>7</td>
<td>67</td>
</tr>
<tr>
<td>Conservative therapy</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conservative therapy + palliative TURP</td>
<td>0</td>
<td>-</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Conservative therapy + prostate incision</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>

Note: *TURP = transurethral resection of the prostate*

### Table 3. Labor costs of identifying one patient to whom radical treatment is indicated, depending on the stage of prostate cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rate of administering radical treatment</td>
<td>92.0</td>
<td>89.0</td>
<td>26.0</td>
<td>8.0</td>
</tr>
<tr>
<td>CULCs per patient to whom radical treatment is indicated: physician nurse</td>
<td>4,840.30</td>
<td>2,501.73</td>
<td>5,301.28</td>
<td>32,892.05</td>
</tr>
<tr>
<td></td>
<td>12,761.71</td>
<td>6,595.94</td>
<td>13,977.11</td>
<td>86,721.59</td>
</tr>
</tbody>
</table>
On average, it takes 1,211.1 CULCs for the physician and 3,193.1 CULCs for the nurse to identify one candidate for radical treatment of prostate cancer.

The performance of prostatectomy, brachytherapy or radical radiation therapy does not guarantee that the patient will be cured. There is always a risk of recurrence or death from complications, even at a much later time. The risk of unsuccessful radical treatment increases with disease progression, and according to our data it is 13.3%, 27.8%, 46% and 60% for stages I, II, III and IV of prostate cancer, respectively. Based on these figures, we can estimate the labor costs of identifying patients who will achieve the endpoint, i.e. a conditional cure (no recurrence for five years). A recurrence of prostate cancer is possible even later, but according to expert estimates its likelihood does not exceed 10%. As a result, the cure is considered “conditional”, and the patient is followed up. If no complaints occur, after five years the follow-up is restricted to an annual measurement of PSA level.

Modern oncological (and oncourological) literature contains various criteria for evaluating the effectiveness of radical treatment of prostate cancer, such as general and “tumor-specific” 5- or 10-year survival rates. Even 15-year survival rate is discussed in scientific publications [6]. In this study we chose to use the “tumor-specific” five-year survival rate as the easiest parameter to control.

The labor costs of identifying one patient with stage I prostate cancer who will in future be conditionally cured from this disease are 5,582.8 CULCs for the physician and 14,719.4 CULCs for the nurse (Table 4). The corresponding figures for stage II prostate cancer are 3,441.2 and 9,072.8 CULCs. The effectiveness of radical treatment is much lower at later stages of the disease. The number of patients with recurrence-free five-year survival is proportionally lower as well. As a result, the labor costs of identifying such patients is considerably higher: 9,817.2 / 25,883.5 CULCs for the physician/nurse at stage III and 82,230.1/216,804.0 CULCs for the physician/nurse at stage IV.

The tendency of growing labor costs of identifying a single patient who could, and in fact did, benefit from radical treatment at later stages of the disease is clearly seen in Figure 2.

The overall estimate (regardless of the stage of prostate cancer) of the likelihood of identifying one patient who can be completely cured of prostate cancer is 33.8%. Using the previously collected data on the labor costs of identifying one patient with prostate cancer, we estimated the labor costs of identifying one patient who will survive without recurrence for five years after radical treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rate of administering radical treatment</td>
<td>92.0</td>
<td>89.0</td>
<td>28.0</td>
<td>8.0</td>
</tr>
<tr>
<td>The effectiveness of radical treatment (no recurrence for 5 years), %</td>
<td>86.7</td>
<td>72.7</td>
<td>54.0</td>
<td>40.0</td>
</tr>
<tr>
<td>CULCs per recurrence-free patient: physician</td>
<td>5,582.8</td>
<td>3,441.2</td>
<td>9,817.2</td>
<td>82,230.1</td>
</tr>
<tr>
<td>nurse</td>
<td>14,719.4</td>
<td>9,072.8</td>
<td>25,883.5</td>
<td>216,804.0</td>
</tr>
</tbody>
</table>

Fig. 2. Labor costs of identifying one patient with prostate cancer.
1 – CULCs per patient at a particular stage,
2 – CULCs per patient to whom radical treatment is indicated,
3 – CULCs per patient who undergoes radical treatment and survives without recurrence for 5 years.
This cost is 1712.7 CULCs for the physician and 4515.7 CULCs for the nurse.

**DISCUSSION**

It must be admitted that the labor costs of searching for target patients are rather high. They are comparable to, and in some cases higher than, the labor costs of the actual specialized urological care that is provided to these patients, including such complicated surgical interventions as radical prostatectomy or implantation of radioactive material in the prostate (brachytherapy).

In the light of this, it is desirable to find ways of optimizing the costs. The first method of cost optimization may be to adjust the scope of the initial examination. This would be the most effective solution to the problem, since any changes in the initial examination immediately become economically significant owing to the high frequency of its performance. However, as mentioned above, the scope of the initial examination (PSA levels, a visit to a urologist, etc.) in the framework of the Program is already extremely narrow. To restrict it even further is probably tantamount to sacrificing the diagnostic value of the entire procedure.

The only alternative is then to improve the likelihood of identifying target patients by means of setting more stringent inclusion criteria. The easiest to implement is the age criterion. The Program currently operates with only a lower age threshold (50 years), while the upper threshold is not set. However, very elderly patients seldom undergo radical treatment for prostate cancer. The main limiting factor is the presence of comorbidities, especially cardiovascular disorders. Moreover, there is a tendency in oncological practice to offer radical treatment of prostate cancer only to those patients whose expected survival is greater than 10 years. Therefore, it may be worth setting an upper age limit of 70 or 75 years. The precise number has to be calculated and justified in a separate study. The rights of the patients are not affected, since non-compromised senior and very elderly patients can still be examined outside the framework of the Program.

The objective of identifying patients with stage I prostate cancer is not at all expedient or cost-effective. The labor costs of their identification are unacceptably high, and the added effectiveness of treatment relative to stage II is minimal. If the stage of the disease is taken into account at all, the only economically justified formulation is to pool stages I and II. But then another question arises: what is to be done with the remaining patients? Naturally, they will also have to be examined and some of them will be operated on, so that future labor costs are not likely to become much lower.

There is also a fundamentally different strategy, which is essentially the reverse of that described above: instead of introducing further restrictions, the Program could be given a greater scope and implemented more vigorously. Since prostate cancer normally progresses at a relatively slow rate, the objective will then be to identify all the patients at late stages as soon as possible. After this, the number of such patients will inevitably drop, the proportion of patients with stage I or II prostate cancer will thus increase, and the majority of them will receive radical treatment and survive. The productivity and efficiency of the Program will then improve.

All the different ways of optimizing the costs of identifying patients with prostate cancer to whom radical treatment is indicated deserve consideration. The first method is technically straightforward, and its implementation does not entail significant expenses. The second method is costly, and it depends for its success on a particular organization of treatment and diagnostics in all medical centers of Moscow. However, if it succeeds, the problem of early diagnostics of prostate cancer may be considered to be solved.

It is up to the healthcare authorities of Moscow to choose one or the other way.

**REFERENCES**


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Advisory boards that bring together various experts in order to formulate and solve a particular problem in the format of a group discussion are now becoming an increasingly popular method, highly in demand in the context of decision making in various fields.

For example, a great number of various normative acts, which may be treated as compulsory or merely as recommendations, are produced in the modern healthcare system. The rapid development of the medical science, the appearance of a large number of new fields, medicines and medical technologies competing for a limited budget and, therefore, the escalation of ethical controversies emphasize the role of an objective interdisciplinary assessment involving an ever increasing number of specialists and experts in the process of decision making. Standardization in healthcare creates a situation in which the role of individual choice of a therapeutic alternative for the management of a patient is reduced, while the role of scientific guidelines, protocols and standards of treatment is becoming more prominent. In addition, there is a growing emphasis on the need for rational, justified group decisions and a consensus among physicians specializing in various fields, as well as healthcare managers, insurance companies, economists, lawyers, and patients. This calls for a considerable degree of expertise when organizing different events and meetings of working groups to settle a particular issue.

Reaching compromise solutions which can satisfy representatives of various schools and fields of medicine is a separate and often extremely challenging task. It is this task that is addressed by technologies of group decision making. In its essence, this method relies on using a “catalyst” to trigger the process of structured exchange of information to allow representatives of the expert community to reach a compromise solution. Moderators of such sessions are typically independent participants, who do not themselves have a profound knowledge of medicine and health care.

The healthcare sector, being the most public and sensitive sphere of our life, is particularly likely to encounter problems that call for consolidating the opinions of various parties, such as governmental authorities, medical experts, and representatives of the commercial sector. As a result of co-activity, several people may produce results that no one could ever achieve on their own, even through an outstanding effort [1].

Carl Marx claimed that simple social contact stimulates our instincts, increasing the effectiveness of each individual. Practicing psychologists have long been aware of the fact that some problems are solved more successfully through a group effort compared to individual solutions, that a person makes fewer mistakes when working in a group, and that the speed of problem-solving increases in a group. This fact was considered to be the result of higher sensory stimulation: the very fact that other people are working on the same problem in one’s vicinity stimulates the individual, improving their productivity. This effect is known in psychology as social facilitation. Its main principle is that the presence of other people facilitates individual activities and improves the performance.

Group decision making consists of four stages:
1) laying bare the facts (group interview);
2) evaluating the facts (opinions about these facts);
3) searching for solutions;
4) making the decision.

Once the problem has been formulated, the main task is to collect evidence related to this problem. This is stage one, which is primarily a factual and objective process. At this stage the facilitator (moderator) discourages the participants from evaluating the presented facts.

The second stage is the time to evaluate these facts. The participants are allowed to say what they think of the data without restraint. The moderator registers the expressed opinions.
At the third stage the search for decision commences. The participants reach the so-called “breakthrough point”, at which they “shed” their stereotypical views of the problem being discussed. This resembles brainstorming, which is discussed below, since at this stage the participants need as much imagination as possible in order to come up with diverse solutions to the problem.

The choice of the optimal action plan among all suggested solutions takes place at the fourth stage. The group compares the alternative solutions with the diagnosis (those opinions that were expressed at the second stage); some are rejected, and some are integrated and then elaborated until a solution is reached that satisfies all the participants [1].

**GROUP DISCUSSION AND ITS ROLE IN GROUP DECISION MAKING**

Most research has focused on the role of group discussion preceding group decision making. Experimental research of this issue, as well as other problems of group dynamics, was carried out by K. Lewin [2]. This experiment was conducted in the United States during World War II and had a practical application. In the time of economic troubles caused by the war, the availability of food products in the retail network dropped. Instead of meat, people were offered various types of offal, but housewives boycotted these substitutes. The purpose of Lewin’s experiment was to compare the effectiveness of molding the opinions of housewives through the traditional methods of advertising (lectures) or through the new method of reaching an independent group solution based on group discussion. Six groups of volunteers from the Red Cross were set up, each consisting of 13-17 participants. Some groups heard lectures about the advantages of offal and the desirability of buying it, while other groups participated in a discussion of the same issues. One week later the participants were interviewed in order to assess how far the housewives’ opinion had changed. The opinion was different in 3% of cases in the groups that heard a lecture and in 32% of cases in the groups that participated in group discussions.

Lewin suggested the following psychological interpretation of these results. During the lecture the housewives listened passively to a discussion, interpreting what they heard through the prism of their own previous experience. After the lecture they had two options: to buy or not to buy offal. This decision was not taken during the lecture, and thus they had no group support for their decision. The group did not establish a social norm that could then be accepted and followed by group members. Accordingly, any change in their opinion was based solely on the intrinsic power of persuasion, which in this case was rather poor. In contrast, every member who took part in a group discussion felt personally involved in the process of decision making, and this weakened their resistance to the innovation. It became clear in the course of discussion that other members were also moving towards a particular decision, and this fact could strengthen the individual’s own position. The participants were thus nudged towards the decision step by step, so that it was elevated to the status of a certain group norm, supported and accepted by those taking part in the discussion. This effect was made possible by the fact that this decision was not imposed on the group but taken freely.

There have been many other studies of the mechanism and effects of group decision making since Lewin’s experiment, and the role of group discussion in this process is now clear. Two important principles have been discovered:

1) Group discussion produces a clash between the opposite positions, thus allowing the participants to see different sides of the problem and reducing their resistance to new information.

2) If the decision is initiated by the group, it serves as a logical conclusion to the discussion supported by all participants, and its influence grows, since it becomes a group norm.

Furthermore, studies of group decision making have demonstrated new forms of group discussions. One such form, discovered by A. Osborn and called “brainstorming” [1], is an attempt to reach a collective solution in the following manner. The moderator divides the group into two parts: “generators of ideas” and “critics”. At the first stage of the discussion the “generators of ideas” are active, and their task is to produce as many solutions to the problem under discussion as they can. These suggestions can be completely unsupported by evidence or even fanciful, but no-one is allowed to criticize them at this stage. The objective is to collect the largest possible amount of very diverse proposals. This raises a very important question – the role of a critical personal approach in the course of decision making. Traditionally, a critical position is seen as a positive trait shielding the individual from the pressure of suggestion. However, it was shown experimentally that an excessively critical approach may be a negative rather than positive factor at certain stages of group decision making.

At the second stage, the “critics” become active and sort the generated ideas: some are rejected as totally useless, some are set aside as controversial, and some are accepted as obvious successes. Controversial solutions are discussed during a second round, and as much as possible of their substance is retained. Ultimately, the group is in possession of a fairly rich repertoire of alternative solutions to the problem.

**The principles of brainstorming** are [3]:

- a precise formulation of the objective and/or tasks and restrictions;
- maximal freedom of the participants (everyone should be allowed to speak, shy participants should be encouraged and the most active or authoritative ones re-
strained, freedom of opinion and “crazy” ideas should be encouraged, including analogies from literature, music, biology, etc);

- a careful selection of participants (the right number, different fields of specialization adequate to cover the entire relevant area and sometimes to go beyond it, potential for partial mutual substitution; psychological comfort of participants – no malignant conflicts or undisputed leaders; qualification – a high and comparable level of expertise);

- a hierarchical discussion: first it should be made as broad as possible, then the potential of different alternatives should be evaluated and the best ones selected, then once again the discussion is broadened;

- the importance of the moderator and a democratic leadership: a creative, goal-directed and non-conflictual milieu; skill at noticing proposals and steering the discussion (the Greek method).

Modifications of the method of brainstorming are presented in the Table.

The method of brainstorming was very popular some time ago, and it has won general recognition, especially for technical solutions. However, as is often the case with various innovations, some of its merits have probably been overestimated, and subsequently this spawned strong skepticism regarding its potential. Naturally, brainstorming cannot replace other approaches, and it should not be considered the ultimate solution. However, it may indeed be useful in some circumstances [4].

Another method of group discussion is synectics (literally “the joining together of different and apparently irrelevant elements”) developed by W. Gordon [5]. The signature features of this method are not dissimilar from brainstorming, since the central idea is the same – to begin by generating the greatest possible number of different and, in this case, directly clashing, mutually incompatible solutions. For this purpose, a number of “synectors” who will then trigger the discussion are chosen among group members. They are the ones who actually discuss the problem, even though the other members are also present. Synectors are group members who are particularly articulate about their position in the group. Experimental research demonstrated that their optimal number is between 5 and 7. They begin the discussion, and other group members join in later, but the task of synectors is to formulate as precisely as possible the opposing views: the group has to see two extreme approaches to the solution of the problem in order to be able to evaluate them comprehensively. These extreme positions are discarded in the course of group discussion, and a solution that all participants find satisfactory is then reached. The logical technique of analogical reasoning is widely applied within synectics. When discussing technical problems, it is even acceptable to use the following analogy: one of the synectors represents a particular technical process (water current, rotation of a shaft, etc) or a physical object. Less elaborate analogies are also common, such as solutions based on insights from other disciplines. Just like brainstorming, such discussions are very popular and rather effective for technical problems [5].

**METHODS OF COLLECTIVE DECISION MAKING**

The Delphi method, called after the Greek city of Delphi that became known for its wise men, provides an example of collective decision making. The Delphi method is a procedure based on multi-round surveying [6]. After each round the results of surveying are processed, and the outcome is communicated to the experts, including the distribution of opinions. The first round is done without argumentation, but in the second round any answer that diverges from others must be justified – alternatively, the expert may change their opinion. Once the opinions have stabilized, the surveys end and the solution suggested by the experts, or its modification, is adopted.

The morphological method and the method of analyzing the problem circle divide the original problem into several components or secondary problems, which are then sub-divided into alternative realization scenarios. Then all possible combinations of alternatives are considered, and a corresponding project is created for all of them (or only for the most promising alternatives).

The method of analogy consists in identifying the problem and attempting to find a solution with the help of ideas taken from other areas of life and science. At one point this method became so successful that an entire science was created on its basis – synectics. The branch of synectics that derives technical solutions from biology is called bionics.

In order to use the method of analogy, it is necessary to:

- identify the cause of difficulty;
- formalize it as far as possible, making it comprehensible to specialists from other fields;
- set the goals for the future solution and its objective limitations;
- identify an area of life or science that might harbor conceptually similar solutions;
- put together a team of specialists from this selected field;
- organize and conduct brainstorming;
- interpret the suggested solutions, adjusting them to the initial field;
- select feasible and most effective solutions.

The “635” method: six people generate three ideas each about the problem within five minutes. Then they pass on sheets of paper with their ideas, e.g. clockwise. Over the next five minutes each participant has to familiarize themselves with their neighbor’s ideas and make them more detailed. Then this procedure is repeated, until every participant has analyzed all the ideas generated by the group. Half an hour later there may be, at most, 18 different detailed
solutions. They are discussed and supplemented over the next 30 minutes, and then the best alternatives are chosen.

The method of moderation: participants fill in three cards each with a brief description of their problems (anonymously). The moderator shuffles the cards and reads them aloud one by one, suggesting which group should hear them. The moderators then discuss the problems in groups (clusters). Each cluster is given a name, and their relative importance is determined.

There is also a Japanese (circular) system of decision making called "ringi seido." First an innovative project is prepared for discussion and sent to several people listed by the leader. Every person on the list reviews the project and comments on it in writing. Then a meeting is held, usually involving those specialists whose opinions are not completely clear to the leader. The experts choose a decision in line with their individual preferences. If there is disagreement, a vector of preferences is determined with the help of one of the following principles:

- the majority of votes – the decision with the largest number of supporters is approved;
- Cournot’s principle – when there are no coalitions, i.e. the number of solutions is equal to the number of experts, the participants must find a solution that would meet the requirement of individual rationality without abridging the interests of each individual participant;
- Pareto’s principle – when there is a single coalition, i.e. all the experts are united, the optimal decision is such that it would be against all the participants’ interests to change it, since it unites them for a common goal;
- Edgeworth’s principle – this principle is used when the group consists of several coalitions, and it is against the interest of each coalition to abandon their decision [7]. Knowing the preferences of each coalition, the participants can make the optimal decision without infringing each others’ interests.

**MANAGEMENT OF THE PROCESS OF GROUP DECISION MAKING**

The structural organization of group decision making obeys a number of laws.

Specially designed studies have demonstrated that the process of group decision making is in general arranged in

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**Individual brainstorming**

One person plays all the roles (facilitator, scribe, generator, and evaluator). The duration of each sèance is 3 to 10 minutes. All ideas are recorded with pen and paper, a computer or (the most effective option) a dictaphone. The evaluation of ideas must be postponed. A warm-up may be helpful. The disadvantage of this method is the lack of synergistic effect. Its advantages include speed and saving human resources.

**Written brainstorming**

The task is formulated in writing. The fact that participants cannot influence one another has a positive effect at every stage of the brainstorm. Organizationally, the procedure is similar and may be used if the participants are dispersed geographically. Its disadvantages are the lack of synergistic effect and longer duration.

**Direct brainstorming**

In contrast to the classical method of brainstorming, the problem (goals, limitations, etc) is also formulated through brainstorming and by the same participants.

**Massive brainstorming**

This method is applied to global problems. First a competent group is set up, which divides the problem into several parts. Then brainstorming is performed separately for each block. At the final stage the leaders of different groups meet to discuss all the generated ideas.

**Double (paired) brainstorming**

Criticism of ideas is allowed. The stages are: direct brainstorming, discussion, back to generating suggestions.

**Reverse brainstorming**

Reverse brainstorming is applied when realizing projects that consist of many stages (elements). Failure at one stage undermines the entire project, and therefore the main goal is to ensure that each element is valid. The purpose of brainstorming is to think of every possible flaw. The stages are: compiling a list of existing, potential and possible future flaws through brainstorming; rank-ordering these problems.

**Brainstorm with evaluation of ideas**

This is a combination of double, individual and reverse brainstorming that is applied to extremely urgent problems. It demands a lot from participants: expertise, an ability to focus and some skill at brainstorming. The stages are: generating ideas, familiarizing all participants with alternative suggestions with an independent evaluation of the options, selecting a few (3-5) best alternatives and listing their pros and cons, discussing them with mini-brainstorms, narrowing down the list of most promising alternatives and re-evaluating their pros and cons, presenting the best alternatives individually and rank-ordering them collectively.

**The method of the ship council**

Suggestions are made in a hierarchical order. Disadvantages: if an idea occurs after one’s turn, it cannot be expressed.

**The method of “idea conference”**

This brainstorming takes place in a more relaxed atmosphere, e.g. a round-table discussion.
accordance with the principle of multi-level structure in the form of a hierarchy consisting of five principle levels [8]:
1) quasi-group,
2) aggregate group,
3) local group,
4) integrated group,
5) meta-group.

The differentiation into five levels mentioned above is based on such criteria as qualitative differences in the structure and extent of the “subjective basis” of decision making, i.e. in the characteristics of the group-level subject of decision making. As the level of group decision grows, the structuredness and extent of subjective basis, i.e. the organization of group-level, “collective” subject of choice, also increase.

The quasi-group level is a regular and necessary form of group functioning in all those cases when the group is either incapable of reaching a consensus decision or the majority of its members find this undesirable. Despite formal affiliation with the group, and sometimes even despite reaching a “common” but not formally binding decision, the actual individual activity directed towards finding some way out of this situation becomes more autonomous. In such cases the group no longer functions as a whole, losing the status of a collective subject of choice. If such decisions are made regularly, reduction of reference occurs, which means that individuals largely stop being actual carriers of the norms, values, rules and attitudes that are common to the group, while formal membership in the group is still preserved.

On the contrary, the aggregate group level preserves the presence of a collective (group) subject of choice, even though it is present in its simplest possible form – “summative”, aggregate. At this level by definition the group functions as a whole: it strives to find a common solution and preserve group identity. However, its structure as a subject of decision making turns out to be relatively primitive, since it consists of aggregated positions of its members “for” and “against”. Despite its obvious shortcomings, this method of group decision making is the most democratic, since it is based on the principle of equality of participation and takes the opinions of all group members into consideration at the stage of decision making.

The main salient feature of the local group level of the organization of the process of group decision making is that at this level the very principle of group structuring at the stage of decision making is regularly and quite considerably altered, and therefore this very structure changes as well. Aggregate structuring is replaced by integrative structuring: now decisions are not made based on the ratio of votes “for” and “against” but rather on the basis of more elaborate procedures and mechanisms. The main characteristics of this level are the following:

- specialization: in this decision making there is a clear mechanism for the differentiation of the roles of decision makers, who make and realize decisions in the course of decision making;
- selectivity: the sub-group of decision makers is differentiated from the general composition of the group under the influence of determinants shaping the decision making (i.e. instrumental rather than expressive determinants);
- a free, non-scripted nature of preparation and decision making.

Given these features, the final decision is reached primarily by means of integrating factual arguments and determinants.

At the next, integrated group level the subject basis of the decision once again undergoes a considerable transformation. Specifically, such decisions are made with the active participation of the entire group rather than its particular sub-structures. The extent of subject basis thus reaches its maximum: it becomes identical with the group as a whole. The choice is made through synthesis – discussion, deliberation, consideration of the alternatives – and it is primarily realized through the well-known phenomenon of consensus. There are four main types of consensus: partial, destructive, consensus-compromise, and integrated (or synergistic) consensus [8]. It may be said that the previous two levels are synthesized at this level.

The fifth, meta-group level occurs when the complexity of the objective situation of group choice exceeds the ability of the group to reach a decision. The natural reaction of the group is then to seek external help – from other groups and/or individuals, leading to logical changes in the structure and contents of the subject basis of the decision: either the group consciously and willingly goes beyond the original bounds of its subjectivity, or it becomes the object rather than subject of choice if the right of choice is delegated to another group or person.

The higher the level of group development, the more fully its chosen organizational structure is manifested in its functioning, and the more diverse methods and strategies are used by the group in the process of collective decision making [9].

As the complexity of the task of managing industrial systems grows, the search for solutions and decision making increasingly become the domain of group, collective effort. Decision making becomes collegial. Decisions that entail risk taking tend to involve a greater responsibility. However, the sense of responsibility is far from being the only reason that necessitates collective decision making. In some cases group decision making turns out to be less subjective, and it allows decision makers to identify more alternatives, evaluate numerous options comprehensively, select the best of them and sort out “weak” proposals [10].
CONCLUSION

The collective approach to decision making presumes that the top leader, who is ultimately responsible for decision making, delegates their authority (the responsibility and right of decision making) to the lowest management level. This approach prevents top managers from becoming “mired” in petty, everyday problems. Its main advantage is that giving members of the lower management an opportunity to take part in decision making improves its effectiveness, since the discussed issues are often of direct relevance to their interests.

Group decision making offers advantages when group members have no experience of making individual decisions. On the other hand, the experience of group decision making may improve the quality of decisions made individually. However, the advantages of group decisions are closely related to the type of task, and they can be particularly effective for those problems that are hard to formalize or that require a great deal of experience on the part of decision maker.

As a result, the methods of group decision making have stirred a lot of interest among both representatives of businesses and state authorities. Their implementation and application to the creation and development of compromise solutions in health care involving a multifarious expert community will improve the value and objectivity of proposals and engender a sense of engagement and cooperation among representatives of various subjects of the decision making process.

REFERENCES
5. Solov’eva T. Idu na “Vy”. Praktika mozgovogo shturma. Laboratoriya reklamy. 2007; No. 03 (46) iyun’. In Russian

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The creation of an original drug is a long process that may take over 10 years. Only one out of 5 to 10 thousand synthesized molecules reaches the market as a new medication. Upon the discovery of a new pharmaceutical substance its safety and biological activity are tested for several years in preclinical trials, followed by a few more years of clinical trials. After this the new drug is registered, but the research of various aspects of its safety and efficacy continues. The total expenditure related to the creation and synthesis of the molecule, as well as the prolonged stage of preclinical and clinical studies, determine the high price of a brand-name drug. Generics are quite different. The word “generic” refers to a drug that is a therapeutic equivalent of a brand drug and may be released only after the patent for the original drug has expired.

In accordance with the federal targeted program called “The development of the pharmaceutical and medical industry of the Russian Federation for the period until 2020 and future prospects”, the production of original drugs (including generic drugs) in our country should grow substantially.

The main advantage of generics is supposed to be their lower cost with the same therapeutic effectiveness as that of the original drug [1-4]. The price of generics is lower because it does not include the cost of synthesizing the original substance, developing a formulation and conducting preclinical and clinical studies. As a result, new companies are appearing and growing all around the world that specialize in the reproduction of original drugs after the patent protecting the brand has expired. The physician prescribing a generic must be certain of its therapeutic equivalence to the original drug. Generics are usually created for socially significant diseases with a high prevalence, such as hypertension, chronic heart failure, tuberculosis, diabetes mellitus, etc. Obviously, only relatively cheap and high-quality generics can produce a favorable effect on the progression and outcome of socially significant diseases. The European Community has set very strict standards for the quality and safety of generics. Their registration takes between 1 and 3 years. The rules for registering generics in the EU include compulsory disclosure of information about the complete composition of the drug (active substance and excipients), a description of production methods and their control by the manufacturer, the results of pharmacological tests of the active substance and the final product, as well as compliance with Good Manufacturing Practice (GMP) at every stage of the production process.

In order to be mutually replaceable as methods of pharmacotherapy, generics and the original drug or comparator drug must be fully equivalent in terms of their pharmaceutical, pharmacokinetic and therapeutic properties. Two pharmaceuticals are considered to be therapeutic equivalents if they contain the same amount of the same substance in the same formulation, meet the same or comparable quality standards, and are designed for the same administration route [5]. There are several methods of ensuring therapeutic equivalence. Large-scale, multi-center comparative clinical studies of the reproduced drug provide the most comprehensive data. However, this method has serious disadvantages related to the considerable duration and cost of such studies. As early as in the 1970s, pharmacokinetic approaches were suggested as one solution to this problem, giving rise to bioequivalence studies. Pharmacokinetics is a branch of clinical pharmacology concerned with absorption, distribution, biotransformation, and elimination of pharmaceutical drugs from the body. The basis of concrete data is to measure the actual concentration of the drug in various biological materials, usually in the blood. Pharmacokinetic approach is based on the following postulate: if pharmacokinetic parameters measured in a healthy volunteer who was given the original drug prove to be the same as for the reproduced drug (generic) taken by the same volunteer – in other words,
if the active component of one (innovative) drug is absorbed, distributed and metabolized at the same rate as the active component of another (generic) drug, we can assume that the therapeutic effect of the innovative drug and the generic should also be the same. However, this is far from always the case. The problem of the quality of reproduced drugs remains relevant, and many harbor doubts as to whether generics sold in drug stores have the same therapeutic effect as the original drugs [6]. In some cases these doubts may not be unfounded, and the reason may be that bioequivalence studies are not conducted correctly, which, in turn, is caused by the lack of strict regulations for the performance of such studies. Such regulations have been introduced in other countries [7-10]. At this point it is worth noting that certain regulations do exist in Russia, and they are constantly being perfected [11-12]. The problem is that the existence of regulations is not tantamount to them being followed closely. There are next to no professional centers whose main mission is to conduct comparative studies of pharmaceutical equivalence and bioequivalence, to check some selected drugs already sold in the pharmacies, etc. Furthermore, the publication of the results of such studies is still not compulsory. To clarify, the results of bioequivalence studies are the property of the sponsor of the study. Besides, all editions of Russian methodological guidelines fail to mention study monitoring with the requirement to provide a detailed description of the monitoring process and a list of responsible monitors. In my opinion, both clinical and analytical aspects of studies should be monitored. Finally, it is still not clear how much information has to be included in the reports. In my view, it is not enough to report only the final results presented as tables of the principal pharmacokinetic parameters, the results of a statistical analysis, and the conclusion that the tested drugs are bioequivalent. The reports should include all primary documentation detailing the procedure of working with volunteers, all inclusion, exclusion and non-inclusion criteria, the results of primary analyses, the reasons for withdrawal from the study, a randomization plan, adverse side effects, and many other aspects described in the study protocol. In addition, the study report should include all primary documentation pertaining to the analytical procedures: a description of the procedures for transporting and storing the samples, for their primary and final analysis, for measuring the concentrations (including a validation of the analytical method). Finally, the report should contain not only some typical chromatograms (when chromatographic methods are used) but all chromatograms from the study, including the necessary repetitions; modern equipment has the option of reporting the type of device, the conditions for separation, the properties of the chromatogram, the name of operator, etc. Since such primary documentation is rather bulky, it may be provided as appendices to the final report. Thus there should be the following appendices attached to the body of the report: a clinical part, an analytical part, and statistics. All analytical procedures have to comply with the modern requirements of Good Laboratory Practice (GLP). The section of the main report describing analytical procedures should provide a detailed description of the method, specifying the achieved sensitivity of detection, standard errors, working range, and a detailed description of validation procedures.

If analytical studies follow all these rules, we can count on obtaining correct data that may be used for future pharmacokinetic and statistical calculations.

Once this task is complete, its results have to be sorted through a very fine “filter”. Until recently, the function of this “filter” was performed by an expert pharmacological commission under the leadership of the prominent Russian pharmacologist, member of the Academy of Medical Sciences V. G. Kukes. Among the members of this commission there were several leading specialists in pharmacokinetics. At present no such commission exists. It remains unclear which body now performs this function and which specialists in this field are members of the expert group at the Ministry of Health of the Russian Federation.

As mentioned above, these problems can only be solved by pharmacokinetic centers, well equipped with modern analytical technology and staffed with highly trained professionals. At present these tasks are usually performed by departmental laboratories or laboratories set up in the best-known scientific centers (that have their own scientific goals). However, this handful of laboratories cannot completely solve the problem of controlling the quality of generics because they are few, lack the necessary equipment, and cannot offer high salaries to their staff. Moreover, to solve these problems in a satisfactory way, we need laboratories whose reports would be accepted by both Russian and international scientific community. However, the credentials of such laboratories remain doubtful. In fact, there is now an accepted procedure for the certification of analytical laboratories, such as laboratories of pharmaceutical surveillance, almost all the normative regulations are in place, and specific organizations are in charge of such certification. Pharmacokinetic laboratories largely need the same type of equipment and should be set up on the premises that meet well-known requirements. The only marked difference is that pharmacokinetic laboratories deal with biological objects (blood, tissue samples, etc), and therefore they have to meet the requirements that apply to such organizations. These requirements concern the receipt of biological samples, their initial and final processing, utilization of waste, data management, control of the quality of measurements, and some other important aspects. Certification of pharmacokinetic laboratories should take place both in Russia and in other countries, where there are relatively comprehensive and high-quality solutions to these problems. Ac-
Accordingly, the development of appropriate regulations for the certification of analytical laboratories and centers and the future implementation of these regulations should be the top priority for the competent authorities – either the Ministry of Health of the Russian Federation or the Russian Service for Surveillance in Health Care. The experience of establishing clinical pharmacokinetic laboratories shows that different approaches are possible, depending on the availability of analytical equipment. It is always a bonus if the laboratory has the most sophisticated equipment (for highly effective liquid and gas chromatography and chromatography-mass spectrometry, freezers with the appropriate range of temperatures, centrifuges, etc). However, the equipment intended for clinical and diagnostic laboratory tests can also be used – the question is how expensive the analyses will be. The equipment found today in most laboratories for clinical and diagnostic testing is designed primarily for immunoenzyme assays. To use these devices, it is necessary to buy appropriate reagent kits that have their own price and expiry date. There are now ready-made kits for the majority of drugs commonly used in the clinical practice. This means they are also available for most generics. All that remains is to estimate our need for such reagent kits. This problem is not simple, but it may be solved if we take a serious approach. Having estimated correctly the required number of analytical kits, we can calculate the cost of performing the analysis. However, it must be noted that modern chromatographic technology broadens the scope of therapeutic drug monitoring and any other pharmacokinetic studies considerably. The reason is that chromatographic methods of measuring concentrations are applicable to practically the whole gamut of pharmaceutical drugs, both original and reproduced. This is why such laboratories in other countries are equipped above all with chromatographs. Only well-trained professionals used to working with biological objects can operate this equipment. Chromatographic methods of measuring drug concentration are not only more universal than immunological methods – in many cases they also prove considerably cheaper. Besides, to switch from measuring the concentration of one drug to another, the researchers often do not need to buy any new kits: quite often it is enough to adjust slightly the settings and use a similar chromatographic column. Modern devices are equipped with a so-called “autosampler” that automatically introduces the sample and considerably speeds up the entire process. In all fairness, it must be noted that the volume of the sample often needs to be larger for chromatographic analysis compared to immunological analysis. But this shortcoming is not critical, since the sample still does not exceed 5 mL of whole blood.

In any case, a systemic approach is needed in order to meet the objectives set by the federal targeted program “The development of the pharmaceutical and medical industry of the Russian Federation for the period until 2020 and future prospects”. First of all, in my opinion, several federal pharmacokinetic centers must be established to ensure the quality of generics sold in Russia. What is the correct way to create a research center (laboratory) and what may be the cost? Several conditions must be met when such laboratories are established.

1. LOCALIZATION. A research center consisting of a clinical unit and an analytical unit should ideally be situated at a health center. This will make it possible to provide emergency care in case of adverse events and to deliver biological samples to the analytical unit without delay. The staff of this center should consist of two groups working in close cooperation with each other – a clinical and an analytical group. The clinical group will be working primarily at the clinical unit and should have at its disposal the following: wards for the volunteers, a cafeteria, recreational facilities, a treatment room, an emergency care unit, toilets, a room for preliminary processing of the samples, etc.

2. THE TASKS OF THE CLINICAL GROUP. The main tasks of this group include the following: selecting groups of volunteers, performing physical and instrumental examinations, performing all requisite tests (taking the original biological samples), organizing and conducting studies, taking blood samples, labeling samples, performing primary processing of samples, preparing samples for shipment, filling in the documentation, etc.

Members of the clinical group should include: 2-3 researchers / physicians (clinicians, pharmacologists who have experience conducting clinical trials), 2-3 nurses, 1-2 hospital attendants, a biochemist for preliminary processing of the samples.

3. EQUIPMENT FOR THE ANALYTICAL GROUP. This depends on the tasks facing the group. In my opinion, a laboratory designed to perform two bioequivalence studies per month should have more or less the following equipment: highly effective liquid chromatographs with the appropriate types of detectors; one highly effective liquid chromatograph with a mass spectrometry detector; one UV-spectrophotometer, dry boxes, laboratory utensils, closets for storing reagents, safes, etc.

4. PROJECT COSTS. The total cost of the project includes, first of all, the price of analytical equipment. According to my calculations, this will cost between 20 and 50 million roubles. Furthermore, the clinical unit needs to be equipped appropriately and provided with all the necessary materials for performing studies (wards for the volunteers, a treatment room, a cafeteria, a room for recreation, toilets, deposit boxes, etc). Last but not least, highly qualified professionals should be offered decent salaries. Obviously, a person controlling equipment that costs hundreds of thousands of dollars cannot receive a pauper’s salary.

Everything described above may be taken to be just another visionary’s pet project, but such centers have long
existed in the developed countries (Canada, Germany, the Netherlands, Great Britain, the United States); they have also been set up in countries where generics are produced (India, China, Slovenia, etc). Such centers are being established in Kazakhstan, Ukraine, and Belarus – they are only missing in the Russian Federation.

REFERENCES


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The last decades have witnessed ever more stringent requirements towards the evidence needed to justify large-scale implementation and public funding of medical technologies. At present health technology assessment (HTA) is accepted politically and integrated structurally in almost all economically developed and many developing countries. So far there is no institute for HTA in Russia, but the prerequisites for setting up a Russian system of clinical and economic evaluation in line with the best international examples have long been in place. International cooperation in HTA avoids duplication and promotes a mutually beneficial exchange of methodological innovations in order to improve the availability of highly effective pharmaceuticals, medical devices, and other technologies.

FEATURES OF HTA IN DIFFERENT COUNTRIES

The ongoing process of setting up HTA institutes and agencies began as early as the 1980s – 1990s in the majority of developed countries, but even today it is far from complete. New HTA agencies, institutes and organizations are created every year in Central and Eastern Europe, CIS countries, Latin America, Asia and Africa. In some countries HTA agencies are governmental structures affiliated with the Ministry of Health (e.g. in Poland). In other countries these are independent organizations funded from the national budget (as in Great Britain). Some HTA structures are funded from a combination of sources, from regional or private sources. In a number of countries there are several different agencies and structures involved in HTA (Germany, Sweden). Despite all this diversity of organizational forms, the goal is the same – to provide decision-makers with reliable clinical and economic data, allowing them to make informed decisions about re-allocating the limited resources of the public healthcare system. It is for a good reason that HTA is called “a bridge between politicians and experts”.

HTA programs have several functions, ranging from coordination of assessments and dissemination of expert reports (the Swedish Council for Health Technology Assessment, SBU) to consulting decision-makers on issues of market access and reimbursement of the cost of medical technologies (the German Institute for Quality and Efficiency in Health Care, IQWIG). In a number of countries HTA organizations participate in making decisions that concern pricing (France, Australia).

Overall, the growing role of HTA in healthcare policies is obvious. However, HTA is an independent process in every country, and its impact on decision making has its distinctive local features (Table 1). Key decisions about the market authorization of medical technologies, reimbursement of their cost and pricing are taken at the national and regional levels. Such decisions often vary across countries for one and the same technology.

There is a tendency for standardization and unification of the methods and instruments used in different countries to prepare expert reports on novel and already implemented technologies. A recent review of guidelines for economic assessment of health technologies performed for a sample of five countries (Canada, the Netherlands, Sweden, England, and Australia) demonstrated that HTA guidelines in these countries had similar approaches to most problems, including the choice of comparison tools, time horizons, the use of incremental cost-effectiveness, and the choice of the method of analysis. According to the authors, the dif-
ferences in the methods are not profound, and therefore we may conclude that these guidelines are harmonized across countries for the key aspects of HTA [3].

However, even though the methodological approaches and principles may be similar in different countries, the standards of HTA reports vary considerably, hindering exchange of information and delaying the implementation of new technologies [4].

In the practical policies of most developed countries these problems are solved by means of applying modern techniques for the transfer of factual pharmacoeconomic data obtained in one country to another country that needs this data to make an informed decision about the implementation of a new technology. Not only clinical and epidemiological data, which are relatively independent of the particular conditions in a given country, but even economic data can be transferred. These methods expedite the preparation of an adequate evidence base, providing new technologies with market access in good time.

**PREREQUISITES FOR INTERNATIONAL COOPERATION IN HTA**

As the functions and procedures of the systems in charge of assessment and authorization grew more similar in different countries, especially in Europe, it became possible to standardize clinical evaluation, leading to the establishment of the European Medicines Agency (EMA) in the mid-1990s. EMA is a transnational body authorized to perform pre-registration evaluation of pharmaceutical drugs based on a standard methodology (to assess their safety and clinical efficacy) and decide whether they should be granted marketing authorization in EU coun-

### Table 1. The role of HTA in the healthcare policies of different countries [5]

<table>
<thead>
<tr>
<th>Country</th>
<th>Name of the main national HTA agency</th>
<th>The goal of assessment</th>
<th>Status of the agency</th>
<th>Impact of HTA on decision making</th>
<th>The number of reports, 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>PBAC</td>
<td>+</td>
<td></td>
<td>Price and market access</td>
<td>228</td>
</tr>
<tr>
<td>Brazil</td>
<td>CITEC</td>
<td>+</td>
<td>+</td>
<td>Only market access</td>
<td>14</td>
</tr>
<tr>
<td>Canada</td>
<td>CADTH</td>
<td>+</td>
<td>+</td>
<td>Only market access</td>
<td>28</td>
</tr>
<tr>
<td>England</td>
<td>NICE</td>
<td>+</td>
<td></td>
<td>Only market access</td>
<td>17</td>
</tr>
<tr>
<td>France</td>
<td>HAS (Transparency Commission)</td>
<td>+</td>
<td>+</td>
<td>Price, reimbursement and market access</td>
<td>657</td>
</tr>
<tr>
<td>Germany</td>
<td>IQWIG</td>
<td>+</td>
<td>+</td>
<td>Reimbursement and market access</td>
<td>6</td>
</tr>
<tr>
<td>Italy</td>
<td>AIFA</td>
<td>+</td>
<td>+</td>
<td>Price and reimbursement (limited impact)</td>
<td>No data</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>CVZ</td>
<td>+</td>
<td>+</td>
<td>Price, reimbursement and market access</td>
<td>41</td>
</tr>
<tr>
<td>New Zealand</td>
<td>PHARMAC</td>
<td>+</td>
<td>+</td>
<td>Price and market access</td>
<td>58</td>
</tr>
<tr>
<td>Poland</td>
<td>AOTM</td>
<td>+</td>
<td>+</td>
<td>Price and market access</td>
<td>66</td>
</tr>
<tr>
<td>Scotland</td>
<td>SMC</td>
<td>+</td>
<td>+</td>
<td>Only market access</td>
<td>82</td>
</tr>
<tr>
<td>South Korea</td>
<td>HIRA</td>
<td>+</td>
<td>+</td>
<td>Price and market access</td>
<td>53</td>
</tr>
<tr>
<td>Spain</td>
<td>CAHIAQ (Catalan agency for HTA)</td>
<td>+</td>
<td>+</td>
<td>Only market access</td>
<td>6</td>
</tr>
<tr>
<td>Sweden</td>
<td>TVL</td>
<td>+</td>
<td>+</td>
<td>Price and market access</td>
<td>30</td>
</tr>
<tr>
<td>Turkey</td>
<td>SSK</td>
<td>+</td>
<td>+</td>
<td>Price and market access</td>
<td>No data</td>
</tr>
</tbody>
</table>
tries and other European countries. The main principles concerning the standardization of clinical evaluation as well as mutual acceptance of the results of clinical studies and licensing of pharmaceutical drugs are reflected in Directive 2001/83/EU of the European Parliament and the Council of the European Union of November 6, 2001: “On the community code relating to medicinal products for human use”, as well as other EU regulations. Thanks to this standardization of the rules of pre-registration evaluation, the time lag before a new drug could enter the market became much shorter, improving their availability in Europe and in the world.

However, pre-registration evaluation and licensing (granting a permit for marketing authorization), or the so-called “first stage” of the assessment, do not give the technology full market access or lead to its inclusion in programs funded by the public healthcare system. This is the object of the second stage of the assessment, which consists in the evaluation of the relative clinical efficacy and cost-effectiveness of the new medical technology compared to other alternatives used in the actual clinical practice, followed by a selection of the best alternative.

There is no transnational body comparable to EMA that could be put in charge of the second stage of assessment prior to the inclusion of the new technology in reimbursement schemes and decisions about pricing. Executive authorities in the EU are of the opinion that it is worth preserving the existing practice of regulating the market access of pharmaceuticals, namely that HTA and the final decision about adopting and launching new drugs on the market should occur at the national level. It is considered particularly important that the results of HTA should be independent in each country and should not prove an obstacle for making decisions about licensing. Regulatory authorities, HTA agencies and payers should be institutionally separated. The strategy of HTA development thus excludes any harmonization of decisions about market access, reimbursement of cost, and pricing [6].

However, we have to emphasize the immense importance of such achievements as the exchange of methodological approaches and the creation, through multinational efforts, of standardized models for the preparation and presentation of the results of the assessment of both pharmaceuticals and medical devices as well as the implementation of these models in order to improve the quality and reliability of HTA results in individual countries. Through this cooperation, small states, incapable of investing heavily in HTA systems, are given a unique opportunity to benefit from the achievements of the most developed countries in this field.

At present the unification of HTA methods and tools is taking place due to two factors. Firstly, “bottom-up” integration processes are becoming more prominent: more rational and effective HTA methods and forms of implementing its results in practice are becoming available, as well as cutting-edge methods for improving the organizational potential and staffing. Secondly, there is some support from the “top”, i.e. political good will. For example, the EU and the European Commission actively support integration processes, encourage lower post-registration barriers and prompt decision making about reimbursement and pricing[2]. The World Health Organization (WHO) and the World Bank, who interact with Ministries of Health and professional associations in this field in different countries, are also important actors in the promotion of HTA.

INTERNATIONAL HTA ASSOCIATIONS. EUROPEAN PROJECT “EUneHTA”

In the 1990s further integration of HTA led to the creation of international associations and networks of agencies for health technology assessment. Their members included governmental and non-governmental national agencies, universities, research organizations and centers, representatives of patient associations and the industry, i.e. all those who take part in performing HTA studies, prepare expert reports and can have an impact on the ultimate decisions. These international associations aim to improve the transparency, effectiveness and practical significance of HTA through the creation, implementation and perfection of standardized practical recommendations and guidelines reflecting the cutting-edge international experience.

The first HTA association was INAHTA (International Network of Agencies for Health Technology Assessment, www.inahta.org), which was established in 1993. Its membership consists mostly of formal (primarily governmental) agencies for HTA, with more than half the funding coming from the healthcare system. At present INAHTA has 53 members – agencies for HTA from 29 countries in North and South America, Europe, Asia, and Australia.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR, www.ispor.org) was created in 1995. Even though its main mission is to promote the development of pharmacoeconomics and outcomes research, ISPOR also emphasizes methodological development of health technology assessment as a tool of healthcare policies. ISPOR has over 11000 members and more than 60 chapters in different countries. ISPOR holds annual conferences of its members in the United States, Europe, Asia and Latin America, and it is a powerful platform for exchanging scientific innovations in pharmacoeconomics and HTA. It possesses immense educational resources and overall serves as a forum for pooling knowledge and making recommendations for healthcare

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[2] EU Directive 89/105 on transparency of pricing and reimbursement of pharmaceuticals obliges the competent authorities of member states to reach a decision on these issues within 180 days from the receipt of the license of a pharmaceutical drug, provided that there is evidence from clinical trials.
policies. ISPOR publishes a scientific and practical journal called “Value in health”.

HTAi (Health Technology Assessment International, www.htai.org) was set up in 2003 and includes organizations and individual representatives from 59 countries. The focus of attention for this association is the development of tools for performing HTA on the level of individual healthcare centers and the creation of models for the provision of integrated medical care and for improved access to health care. HTAi has signed memorandums of cooperation in promoting HTA with such organizations as the WHO and its regional branches, INAHTA, the European Commission, and the American Agency for Health Research and Quality (AHRQ). HTAi publishes the International Journal of Technology Assessment in Health Care.

The processes of integration in the area of HTA are particularly intense in Europe. Even at the initial stages of establishing HTA in European countries, the problems of cooperation and exchange of information were already at the forefront, and the need for formal collaboration between the increasing number of European organizations and institutes active in this field had become obvious. Starting from the 1990s, a number of HTA projects were successively realized: EUR-ASSESS (1994-1997), HTA-Europe (1997-1999), and ECHTA (1999-2001). In 2006 these projects led to the establishment of the European Network for Health Technology Assessment (EUnetHTA, www.eunethta.eu). This network was the result of a decision by the EU and European Commission to set up an official, constantly operating and effective organization uniting various HTA structures throughout Europe.

In addition to the leading HTA agencies, EUnetHTA unites departments of Ministries of Health and research groups specializing in health technology assessment from those countries which have no formal agencies for HTA. This network includes 64 organizations in 34 countries, and all members of the European Union are represented, as well as a number of other European Countries (Iceland, Norway, Serbia, Switzerland, Russia). Non-European members include the United States, Canada, Australia, and Israel. The main goal of EUnetHTA is to promote the influence of HTA on healthcare policies in Europe and its implementation in those countries that have a limited experience in this field.

The first project of EUnetHTA, realized in 2006-2008, was devoted to an analysis of HTA reports, prerequisites for cooperation in preparing these reports and for sharing the results of health technology assessment between European countries. The project currently being realized in this network is called “Joint Action 2010-2012”. It emphasizes three main directions:

1) the creation of unified methodological guidelines,
2) the performance of HTA by organizations – members of the network,
3) the dissemination of the results of HTA in Europe.

An important aspect of the work of EUnetHTA is the development of communication techniques in order to promote interaction among its members with the help of web technologies that make it possible to accumulate and store large amounts of information, while avoiding the drawbacks of ineffective and time-consuming communication methods thanks to electronic data transfer and direct communication.

Joint Action 2010-2012 consists of eight Work Packages. The results obtained by the team of Work Package 4, which is in charge of building an HTA Core Model, are of particular interest. Based on this model, the results of clinical and economic evaluation performed as a joint project by HTA agencies in different countries can be adapted to the situation in a particular country. With the Core Model it is possible to implement innovative approaches to preparing expert reports and considerably simplify their creation in Europe, while also improving their quality.

This model is a standardized, highly structured method for preparing and presenting the results of clinical and economic assessment that relies on web technologies. It consists of nine interdisciplinary domains, which are further divided into topics and issues. Various combinations of domains, topics and issues form elements of HTA, which are classified as either essential or non-essential, depending on their importance from the point of view of healthcare policies and on whether the results of assessment are transferable across countries. For each technology, the relevance of each element is assessed, and a concrete research question is formulated for each relevant element. Only essential aspects are considered in the core model. Based on a systematic review of published data and the model, reports containing the results of assessment in each domain are prepared for each core element of HTA.

Reports on the core elements of HTA or simplified (“liberal”) reports, which contain an assessment of only one or more (but not all nine) domains (the so-called “liberal use”), are written by teams of researchers in different countries, but their work is coordinated by a single center. A Finnish agency, FINOHTA, was the coordinator of the first two pilot projects for creating HTA core models – for surgical and diagnostic medical devices. However, the core model cannot replace HTA in an individual country or region. It does not provide recommendations for implementing particular technologies (Table 2).

Another important aspect of the work of EUnetHTA, carried out by the team of Work Package 7, is the creation and maintenance of a structured and standardized on-line database (EVIDENT) designed to promote an exchange of information about new technologies in order to fill in the gaps in the evidence base, suggest joint recommendations for further studies or obtain additional data on the new technology before its market launch. Internationalization of health technologies compels HTA
agencies to develop methods for exchanging evidence and results of the assessment. A major obstacle to the implementation of expensive new technologies and decisions about reimbursement is the lack of data on the clinical efficacy coming from the real-world clinical setting or pragmatic clinical studies. In a number of countries there are political mechanisms for granting temporary market access to promising technologies on the condition that additional data substantiating this decision will be provided in future (access with evidence generation, AEG). The mission of EVIDENT is to accumulate data about promising technologies and promote informed decision making for their timely implementation on an international scale.

A new field for EUnetHTA included in Work Package 5 is cooperation for the development and standardization of the methods for relative effectiveness assessment (REA). According to the definition by the Pharmaceutical Forum created on the initiative of the European Commission for promoting quality and innovation in healthcare through the development of HTA mechanisms, REA is the methodology for comparing (under the conditions of the real-world clinical practice) the safety and effectiveness of two or more alternative healthcare technologies that are used to achieve the same desirable treatment outcome [8]. In 2007 the Pharmaceutical Forum suggested that open and reliable exchange of data on relative clinical effectiveness should be ensured between regulatory authorities, HTA structures, and manufacturers throughout the life cycle of pharmaceuticals, including the period before the decision about market authorization is made and the postlicensing period. The main objective of this exchange of information is to minimize the barriers to market access for innovative drugs and to improve the control of prices [9].

Work Package 5 of EUnetHTA currently pursues two directions of research. Firstly, unified guidelines on the methodology of relative effectiveness assessment are being prepared based on an analysis of methods used in 29 countries, and these methods now have to be integrated into an HTA core model. Secondly, a simplified model for relative effectiveness assessment is being developed. This model will include the assessment of only a limited number of core HTA elements and is designed to expedite the process of decision making about reimbursement of the cost of pharmaceuticals to make them more widely available.

The methodology of relative effectiveness assessment (REA) is designed to streamline the bottlenecks in national HTA systems, to eliminate inconsistencies between the national standards of HTA reports in different countries, and to minimize its negative impact on the ultimate outcome of decision making about the implementation of innovative technologies. REA makes it possible to have control over the growing prices of medicines. This method eliminates duplication which takes place, for example, during the assessment of costly pharmaceuticals, such as anti-cancer drugs, when several separate national and regional HTA agencies may be involved in the process of assessment without appropriate exchange of information between them.

The European Network for HTA is a stable structure that provides a basis for ongoing international cooperation, coordination of joint HTA projects, facilitated exchange of standardized data between member organizations, transfer of knowledge and experience to new states, regions and organizations that wish to establish their own HTA systems in order to form the healthcare policies on a scientific basis. As far as its impact on healthcare policies is concerned, EUnetHTA is now among the most effective international HTA associations, and it may be seen as a model of cooperation in the area of standardization of clinical and economic evaluation for CIS countries.

The former Soviet republics are now taking steps to harmonize and unify the functions of control, access and surveillance. For instance, it has been suggested that the results of clinical trials and registration certificates of pharmaceuticals, medical devices and equipment should

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**Table 2. The structure of HTA reports based on HTA Core Model [7]**

<table>
<thead>
<tr>
<th>Domains of the model</th>
<th>Report for core HTA elements</th>
<th>Local HTA report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Health problem and current use of technology</td>
<td>Interdisciplinary assessment with HTA Core Model</td>
<td>Assessment of the technology for local use</td>
</tr>
<tr>
<td>2. Description and technical characteristics of technology</td>
<td>All core elements</td>
<td>Data from the report for core HTA elements and/or combined structured HTA data</td>
</tr>
<tr>
<td>3. Safety</td>
<td>Review of assessment outcomes</td>
<td>The possibility of a simplified HTA Core Model</td>
</tr>
<tr>
<td>4. Effectiveness (including accuracy)</td>
<td>No recommendations for using the technology</td>
<td>Local data and needs are taken into account</td>
</tr>
<tr>
<td>5. Costs and economic evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Ethical analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Organizational aspects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Social aspects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Legal analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The most important of the nine domains are shown in bold.*
be mutually accepted within the Customs Union and the United Economic Space of Russia, Belarus and Kazakhstan in order to improve their availability. These steps will lead to the desired outcomes only if one important condition is met – the regulatory practice of member states must be harmonized with the leading international examples, especially with European models. Another key prerequisite to improving the quality of health care and access to pharmaceuticals and other health technologies is harmonization of the methodological approaches and HTA guidelines.

CONCLUSION

Today HTA is an internationally recognized tool for improving the effectiveness of allocating limited resources and promoting transparent and evidence-based decision making about the inclusion of pharmaceutical drugs and other medical technologies in formulary lists and targeted programs funded from the healthcare budget. The impact of HTA on healthcare policies varies across countries. Each country decides independently how to fund or reimburse medicines and other medical technologies. International experience demonstrates that such key decisions should remain the exclusive prerogative of sovereign states. However, without stable and continuously evolving cooperation in HTA it is impossible to perfect its methodological principles, tools and standards of HTA guidelines and reports, to improve their quality and reliability, and to ensure that all promising new technologies have access to the market without delays and obstacles. International cooperation in HTA, which is developing so actively in Europe and in the world, and the establishment of international associations will undoubtedly prove to be important steps towards meeting these objectives. At the same time, those countries that are only beginning their journey to HTA, such as Russia, are given an excellent opportunity to use the combined results of international experimentation, thus avoiding the need to learn from their own mistakes.

REFERENCES
8. URL: http://ec.europa.eu/pharmaforum/docs/rea_principles_en.pdf

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Establishing Effective Communication with Decision-Makers

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Modern social psychology offers specially developed techniques and methods of exerting influence that can be used in preparation for important meetings with decision-makers. One of these methods is based on a typology of human temperaments, simplified in order to be of practical use in identifying the personality type in the course of direct interaction and choosing the behavior appropriate for this personality. The article contains practical recommendations for interaction with various personality types that take into account the particularities of each decision-maker.

KEYWORDS: temperament; decision-makers; melancholic, choleric, sanguine, phlegmatic.

Modern market access (MA) technologies are often used by pharmaceutical companies and manufacturers of medical equipment.

Attempts to define what Market Access is end up as descriptive constructions, each of which may be considered acceptable. According to one of these definitions, Market Access stands for an analysis of ways to implement a product with a limited budget – it is an assessment of the possible impact of the rapidly changing healthcare system on the promotion of a particular medical technology. It stands for the creation of a milieu for promoting a dialogue between the industry, authorities, insurance companies and other important actors in the context of decision making in the healthcare system.

This definition provides us with the most comprehensive and concrete description of this term. However, market access should not be regarded as merely a technology that allows a pharmaceutical company to put its product on the market throughout its life cycle. From the point of view of payers (decision-makers at various levels, budget holders, insurance companies), MA milieu provides them with the tools for a rational allocation of the national, regional or municipal budget, thus improving the healthcare system. Given the modern conditions, decision-makers choosing a particular technology have to consider not only the safety and clinical efficacy of each drug but also other arguments that are discussed in this article.

Traditionally, MA depends on how well the new drugs or technologies have been researched, the level of evidence for their clinical efficacy and cost-effectiveness. The creation of so-called “value dossiers”, which contain documents and materials proving the effectiveness and safety of new medications and medical technologies, epidemiological data, new diagnostic methods, standards of treatment of the disease, and data on the cost-effectiveness and impact of the drug or technology on the cost of illness, assumes that there is data on the comparative effectiveness of the new technologies, including their effectiveness in the real-life clinical setting, the social status of the illness, and the ability of the new technology to affect the progression of the illness and the cost of its treatment. Such arguments, prepared and adjusted for various target audiences (payers, other decision-makers, representatives of the legislative branch, insurance companies, medical community, and patients), determine how successful the market access strategy for the promotion of new products will be.

In addition to expert knowledge of the new technologies, MA strategy requires special skills in order to make various target audiences aware of the advantages of these technologies and liaise with decision-makers. These skills are particularly valuable in view of the Russian mentality when it comes to relations with officials and other powerful persons.

It is well known that the opportunities to meet decision-makers are typically limited. Accordingly, it is important to make communication more productive and take every possible measure to prepare for each visit as effectively as possible. It is thus important to plan and prepare for every meeting with a decision-maker, with due regard for the strong and weak points of this specific person, their professional and personal priorities, and the factors that are particularly relevant to their decision making.

Decision-makers are officials, holders and superintendents of budgetary and extra-budgetary funds, politicians, and top managers of large companies – authoritative, influential people who often do not take criticism well.

Modern social psychology offers specially developed techniques and methods of exerting influence that can be used in preparation for important meetings. For the very
reason that their number is limited, good preparation for such meeting becomes crucial, justifying the use of special techniques. From this point of view, it appears fruitful to simplify the main tenets of the theory of temperaments for its practical application: it can be used to determine the personality type, select the appropriate behavior style for this personality, and present the materials and arguments accordingly.

The classification of temperaments is based on the Ancient Greek human typology described by Hippocrates. According to Hippocrates, the human type is determined by the balance of four bodily fluids, which is unique to each person: blood dominates in the sanguine type, bile in the choleric type, black bile in the melancholic type, and mucus in the phlegmatic type [1]. His theoretical justification for this typology is no longer relevant, but the practical significance of the classification of people by their temperament suggested by Hippocrates has remained unchanged.

The method developed by Hans Jürgen Eysenck, the creator of the famous IQ test, turned out to be the most convenient one from the practical point of view.

To divide people into different temperament types, Eysenck suggested two bipolar traits:

1) A scale of emotional stability, which shows how emotionally labile and irritable a person is. On the behavioral level:
   - Low stability is manifested as increased frequency of somatic complaints (headaches, sleep disorders, a tendency to have mood swings, inner restlessness, anxiousness and fear), frequent changes of the emotional state, anxiety, and low self-esteem. Such people are anxious, worried, and prone to act impulsively.
   - High stability – no such signs are present.
2) A scale of extroversion – introversion.
   - A typical extrovert is open, optimistic, has a large circle of acquaintances, easily establishes contact with other people, and cannot do without interaction with others.
   - A typical introvert is calm, shy, withdrawn with all but the closest friends, plans all actions in advance, likes to have everything in order, and controls their feelings closely.

The combination of these extreme characteristics is what determines the personality type. Four combinations are possible:

1) Instability / introversion,
2) Instability / extroversion,
3) Stability / introversion,
4) Stability / extroversion.

To determine the individual type of temperament, Eysenck created a test that can be used to score a person on each scale and a coordinate system to present graphically the combination of traits on each scale and the corresponding scores (Fig. 1) [2].

Modern psychology thus offers the following typology of temperaments:

- melancholic – an unstable introvert,
- phlegmatic – a stable introvert,
- choleric – an unstable extrovert,
- sanguine – a stable extrovert.

The skill of diagnosing and identifying the dominant type allows one to prepare more effectively for the upcoming meeting: choose the right style of behavior, plan the arguments, and select the evidence to be presented.

The four personality types are described below, each with its salient traits [3].

1. The melancholic temperament is defined by low emotional stability and introversion. A melancholic person is usually very labile emotionally, prone to unfounded fears, hesitant and vindictive. They are excitable and often react strongly to an insignificant stimulus. They are also inconstant in everything except emotions, indecisive and easily fatigued. The nervous system of a melancholic person is extremely sensitive, but their nervous excitement is not manifested very vividly, even if inside there may be a veritable storm of emotions. When melancholic people are exposed to powerful stimuli, they often experience a prolonged inhibitory reaction and become disheartened. A typical feature of melancholic individuals is a low level of mental activity, slow movements, restrained motor activity and speech. Let us define the melancholic temperament as a weak, easily influenced type.

2. The phlegmatic temperament is defined by high emotional stability and introversion. A typical phlegmatic person is usually very labile emotionally, prone to unfounded fears, hesitant and vindictive. They are excitable and often react strongly to an insignificant stimulus. They are also inconstant in everything except emotions, indecisive and easily fatigued. The nervous system of a melancholic person is extremely sensitive, but their nervous excitement is not manifested very vividly, even if inside there may be a veritable storm of emotions. When melancholic people are exposed to powerful stimuli, they often experience a prolonged inhibitory reaction and become disheartened. A typical feature of melancholic individuals is a low level of mental activity, slow movements, restrained motor activity and speech. Let us define the melancholic temperament as a weak, easily influenced type.
deliberate and hesitate for a long time, but once a decision has been made, it is final. Phlegmatic people have a low level of mental activity, they are slow and do not use facial expressions much. They find it hard to switch to a new activity and adapt to a new situation. A calm, even mood is characteristic for phlegmatic individuals, and their feelings are constant. Another typical feature is that new styles of behavior develop slowly in phlegmatic people but then remain stable for a long time. Persistent and stubborn, phlegmatic people know their strength and finish what they have started; they are steady in their relations, moderately open but dislike idle talk and save their energy. Let us define the phlegmatic temperament as a strong, balanced, inert type.

3. The choleric temperament—high neuroticism and extroversion. Excitation in such people dominates over inhibition. The emotions of choleric people are extremely unstable, easily shifting from positive to negative and back again, often with no external reason—the moods come out of nowhere, and the choleric person him- or herself has a hard time explaining why they suddenly got all excited or, on the contrary, discouraged. A choleric temperament amplifies every manifestation of human activity. Choleric subjects have a high level of mental activity, act energetically, they are abrupt, fast, and impulsive, with powerful and fast movements. They are also easily irritated, impatient, prone to emotional explosions, sometimes aggressive. As a consequence of their instability, choleric people exert themselves to the utmost (and even more than necessary) when they are interested, but they may leave the task unfinished if they lose their interest. Let us define the choleric temperament as a strong, unbalanced, excitable type.

4. The sanguine temperament—low neuroticism and extroversion. They appear to be amiable, active and glad people who may look anxious but remain calm inside. They have powerful but balanced emotions, with positive emotions predominating. Sanguine subjects have a high level of mental activity, they are energetic, capable of sustained effort, have fast and lively movements, a rich and diverse gamut of facial expressions, and they speak fast. Sanguine people seek new impressions, respond quickly and easily to events in their environment, and adapt quickly to new conditions. They are open and quickly make new acquaintances. Their feelings arise and change easily, these people are expressive but sometimes also inconstant. They are somewhat restless, constantly need new impressions, do not control their impulses well enough, and find it hard to stick to the routine in their life and work. Let us define the sanguine temperament as a strong, balanced, “lively” type.

How can we distinguish these types based on external manifestations—appearance and behavior?

To know which type you are going to encounter at a business meeting, we suggest that you look at the following traits of appearance and behavior of an individual:

**Extroverts versus introverts**

1. **Personal energy.**

   An extrovert radiates powerful energy, and they “catch” this energy during a conversation; extroverts move and gesticulate a lot.

   An introvert has weak energy, and it dissipates during a conversation (if a person “droops” while talking to you, this is likely to be an introvert); introverts are quiet and calm.

2. **The style of interaction.**

   Extroverts take the initiative during interaction, do not consider their answers carefully, do not tolerate silence; they are noisy, usually talk a lot and talk fast, with a tendency to say “we”.

   Introverts speak in a calm voice, prefer to ponder the question, listen rather than talk. However, if the conversation has touched upon a crucial issue, they may take the initiative and “grind on”, ignoring their interlocutor. They are more self-centered and prefer to say “I”.

3. **Appearance, clothes.**

   There are no particular features in the appearance, but wearing glaring colors, flamboyant and glittering clothes, “showing off”, buying the latest accessories are all signs of extroversion.

   Introverts prefer to look more conservative and draw less attention to themselves.

4. **Openness.**

   Extroverts try to communicate more information, both useful and irrelevant; they are also more likely to enter a conversation.

   Introverts prefer to keep to the topic and have longer, more serious and profound conversations and relations; they try to minimize the number of their contacts.

**The level of emotional stability**

Emotional stability refers to the ability to preserve organized behavior and situational goal-directedness in both normal and stressful situations.

Emotional instability (neuroticism) is manifested as extreme nervousness, poor adaptability, mood swings (emotional lability), sense of guilt, anxiety and worry, depressive reactions, inattentiveness, instability under stress. Neuroticism corresponds to being emotional, impulsive, and uneven in one’s relations with other people, changing one’s interests often, lacking in self-confidence, being highly sensitive, impressionable, and irritable. A neurotic personality has strong reactions that are out of proportion to the stimuli that cause them.

As an auxiliary tool, the observer may note the characteristic bodily features of each personality type.

The first attempt to discover correlations between physique and temperament was made independently by E. Kretschmer and U. G. Sheldon, but the typologies they used differed from the conventional scheme discussed in this article. However, they found a certain correlation...
between the so-called “somatic types” they suggested and the typology described here [1].

As far as body build is concerned, there are two tendencies: unstable types tend to be slim (due to their fast metabolism), while stable types tend to be more solid (since their metabolism is, on the contrary, slow).

1) The unstable types. Melancholic and choleric individuals tend to be slim, sometimes skinny and brittle in their general physique; they have long bodies and limbs, poorly developed muscles and thin bones, “aristocratic” facial features with a large, pointy, long nose (choleric individuals often have a hooked nose). The cheekbones may be moderately or extremely prominent and sharp. The upper part of the skull is larger than the lower half, and the lower jaw often tapers up noticeably. The back of the head is often uneven, with bumps and an abrupt transition between the skull and the neck. The neck is long, so that the head appears to be clearly separated from the body.

2) The stable types. On the contrary, phlegmatic and sanguine types are prone to corpulence, and the most obvious feature of their figure is the chest and round stomach. They have a tendency to become obese, with a pronounced or moderate layer of fat. The musculature is well developed and massive, the limbs are short or moderately long and rotund, they have slow movements and a “swimming” gait. The facial features are soft, with a blunt or even meaty nose (typically more prominent in phlegmatic than in sanguine people). The cheekbones are not well developed, sometimes completely hidden in sanguine individuals and slightly protruding but not sharp in phlegmatic individuals. Both the phlegmatic and sanguine types have a ball-like head, without a marked transition between the skull and the neck, and a short, barely visible neck.

However, this method of distinguishing visually between the different temperament types is imprecise, and inconsistencies are common, especially with regard to the body build. Facial features offer a more reliable indication than the general physique, but they do not always correspond to the temperament perfectly, either.

Strategies for productive interaction with each personality type

When conversing with a decision-maker, it is important to take into account the personality type of your interlocutor; this will allow you to adjust to their needs and traits, avoiding an unconscious rejection and even invoking sympathy, which is always conducive to making a decision in favor of the applicant. Below you will find some practical advice for building interaction with different personality types.

Communicating with a melancholic person:
- be friendly but calm and restrained;
- never be hypocritical and do not try to appease them, since they are likely to notice this and become annoyed;
- do not provoke strong reactions in this person – be moderate;
- do not let a melancholic person see that you are irritated or displeased, do not show any negative emotions or excessive happiness;
- do not put pressure or persist;
- answer the questions calmly and in detail, make sure your formulations are comprehensive and unambiguous;
- try to take as little time as possible, since melancholic people are easily fatigued;
- melancholic people are quick to take offense, and therefore try to choose your words carefully, avoid negative judgments;
- a melancholic person needs appropriate motivation, since they may become disheartened at the slightest failure and say “I’ve told you”, or they may procrastinate and postpone the decision until the last moment;
- talk to a melancholic person tête-à-tête, without any third parties;
- remember that melancholic people are rather slow – make an appointment in advance and allow them to prepare for the meeting if they so desire.

Communicating with a phlegmatic person:
- make your arguments precise, well-founded and logical, keep to the point, avoid irrelevant details – phlegmatic people are not interested in those;
- do not rush them (even if there is time pressure) – they are going to do everything on time in any case, but probably not before then;
- do not show strong emotions during the conversation, avoid any casual manner, since this is unacceptable to a phlegmatic person in any conceivable situation;
- keep to the schedule and do not be late;
- provide them only with carefully selected facts that are not likely to change in future;
- despite appearing self-confident, phlegmatic people are easily wounded – keep that in mind and choose your wording carefully;
- keep the number of topics discussed at one meeting to a minimum, preferably to just one or two, since phlegmatic people find it hard to switch to a new subject, and they may lose the thread of the conversation or forget something afterwards;
- when summarizing, make sure that they have mentally “registered” the outcome of the meeting, e.g. have written down the date of the next meeting, noted what needs to be prepared for it, etc – otherwise they may simply forget;
- phlegmatic people may sometimes be vengeful, but it may be very hard to detect a shift in their attitude, therefore the main rule is to be restrained.

Communicating with a sanguine person:
- it is important to structure your demands / proposals, since a sanguine person may easily “slip away” from the topic;
• they may lose the thread of the conversation, therefore it may be worth returning them to the main problem, but not in a patronizing manner;
• stick to your objective as much as possible and keep in mind that sanguine people can be very persuasive and may make their interlocutor abandon a position that they find undesirable;
• since the emotional experience of sanguine people is rather shallow, you should try to appeal to their emotions, but without making it obvious to your interlocutor;
• use the love of novelty, new impressions that is so typical of sanguine individuals – explain that you are offering something new;
• you should not keep a “poker face” – it is essential to react appropriately to the gestures and facial expressions of your sanguine interlocutor; if they do not find an emotional response, their “fire” may go out – but this emotional response has to be fairly restrained;
• reciprocate their openness, avoid single-word answers;
• you do not have to offer a sanguine person distant headlines, since they are productive and may do a lot in a short time.

Communicating with a choleric person:
• a choleric person has to be encouraged in order to bring a task to its conclusion – tell them about the benefits and advantages (preferably for themselves personally) that will accrue as a result of your agreement, explain that this project is “the most important thing in the world” and therefore deserves attention; this approach to a meeting with a choleric person improves their productivity;
• choleric people like changes, and therefore you should explain that this issue is crucial for bringing about all the positive changes in the world;
• observe their facial expression, since it shows all the emotions of a choleric person; if they appear displeased, it may be worth changing the topic and finding a position that may be acceptable to them;
• if your choleric interlocutor loses interest, you may try to re-awaken it, but if that does not work, it may be better to return to the subject at a later meeting – choleric people are “fickle” and may react in a completely different way the next time;
• choleric people always encourage non-standard solutions;
• when talking to a choleric person, always appear calm and balanced – they will “catch” your calm mood.

It is worth paying particular attention to anything that may provoke the aggression of a decision-maker, since this reaction completely undermines the efforts of any meeting. Knowing how to avoid aggression in the person in whose hands the fate of the whole business rests, how to avoid all the pitfalls – this is an important skill for communicating with decision-makers, which is also based on a classification of decision-makers by their temperament type and, accordingly, their psychological stability.

1) Personality types that tend to be unstable are the types in which it is easy to provoke aggression.

The melancholic type: as a rule, these people tend to “get stuck” on a particular topic. Unfortunately, this trait is a serious obstacle: if something caused aggression in a melancholic person, they will remember it for a long time. Another problem is that they may forget WHAT EXACTLY it was that provoked their displeasure, so that their negative attitude may be generalized to their interlocutor as such and the problem that needs to be solved. To avoid aggression in a melancholic person (it is more easily avoided than suppressed afterwards), you have to act very carefully and accept the rules of the game suggested by your melancholic interlocutor. If they dislike something in your proposal, it is better to correct it immediately or suggest another alternative. If, in spite of all, a melancholic person does get angry, they need a long time to calm down – it is better not to disturb them.

The choleric type: these people tend to have an inflated self-perception, and therefore any criticism may provoke aggression. Furthermore, choleric individuals can easily break rules and agreements, while reprimands in this respect can also cause aggression. An everyday, bromidic, mediocre approach or lack of personal interest to the choleric person may also make them explode. The aggression of a choleric individual may reach serious proportions – all the reactions of this type are powerful. To overcome this aggression, remember that choleric people also calm down easily – simply let them “cool off”. Quite often this doesn’t take very long.

2) Personality types that are hard to throw off balance – the stable types.

The sanguine type: this is the easiest type to communicate with. However, a sanguine person’s aggression may be provoked by a very reserved interlocutor. If a sanguine person does become annoyed, remember that such people are rather “superfluous”, they calm down quickly, and therefore their aggression is not likely to be profound. In this case it is better to change the topic for a while or postpone the solution until the next meeting – the most likely outcome is that your sanguine interlocutor will simply have forgotten what it was that made them angry, or they may forget their anger altogether.

The phlegmatic type: the aggression of a phlegmatic person may be provoked by a rapidly changing situation (your suggestions, demands, etc), as well as extra workload, therefore do not pressure them, ask too much or provide too much information at a single meeting – give them time to consider the problem and make a decision before setting a new task. Besides, phlegmatic people may be annoyed by extremes, such as being too pushy or too flaccid. It is hard to say anything precise about how
easily phlegmatic people forget their anger, since they are
rather unpredictable in this respect. If their attitude to you
was positive before the incident, they are likely to forget
it soon, but if your relationship was purely formal, it is
likely to be very hard to restore a good impression.

Finally, it is worth emphasizing that any typology is
only a basis for making decisions about the actual situ-
ation. “Pure” types are practically non-existent, but there
is a tendency for one temperament type to predominate in
every person. In the case of communication with decision-
makers a further complication is the fact that the meeting
itself takes place in the context of formal relations and
a strict time frame. Even so, the recommendations sug-
gested above may prove useful and simplify the task of
establishing a good rapport with important interlocutors.
However, as mentioned above, these technologies are
only auxiliary – as a rule, it is impossible to achieve the
result without sound data and evidence that was correctly
collected and meets the requirements of decision-makers.

REFERENCES
1. Psihologiya individual’nyh razlichiy. Pod redaktsiei Yu. B. Gippen-
[The psychology of individual differences. Ed. by Yu. B. Gippen-
senck H. J. The structure of human personality. Moscow, KSP+, 1999.]
3. Laboratoriya gumanitarnyh tehnologii. URL: http://www.ht.ru. In
Russian [Laboratory of humanitarian technologies.]
4. Nikandrov V. V. Metodologicheskiye osnovy psihologii. Uchebnoye
posobiye. SPb.: Rech’, 2008. In Russian [Nikandrov V. V. Methodolog-

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Market Access Technology: the Main Features

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Healthcare reforms unfailingly entail a change in the “rules of the game” for all participants in the system. This article attempts to define, structure and analyze the mechanism of Market Access – a new technology for the Russian industry. This concept is presented from multiple perspectives, including a definition, the main principles on which it is based, its expert and communication components, while the application of this technology is described following the mandatory stages of its practical implementation. The main components and tools of Market Access and some examples of its application are presented in the context of international practice and Russian health care.

KEYWORDS: healthcare system, Market Access, health technology assessment, lobbying, decision makers, stakeholders.

THE CONCEPT OF MARKET ACCESS

At present any attempt to define the concept of market access is limited to descriptive approaches, each of which is justified and may be considered logical and well-grounded.

In terms of its contents, the term “Market Access” (MA) should include all issues pertaining to customs clearance, registration, licensing, distribution, pricing, inclusion in limited lists and national reimbursement schemes, as well as all the steps that determine the availability of the product to a particular patient.

The currently existing system of market access is such that every product has to pass a number of mandatory stages: the stage of development and manufacture, then the stage of clinical studies and pre-registration evaluation ensuring that the product can be registered at the national level [1]. After that the product may enter circulation and is launched on the market, where it competes for the resources of patients or individual healthcare centers. Already at this stage the manufacturer begins to campaign for the product to be included in limited lists (positive lists, reimbursement lists), which may give access to either state supply orders or reimbursement of the payer for the cost of this technology. The best scenario is the following: the first stage of evaluation leads to the registration of the new technology (market authorization), and the second stage, known as “medical technology assessment”, or “health technology assessment” (HTA), culminates in the creation of a systematic report and an economic model and the decision to adopt and fund the new technology. These two stages of expert evaluation are thus quite different both in terms of their timing relative to the life cycle of the drug and in terms of their goals, objectives and approaches.

In order to pass stage one, the pharmaceutical industry thus has to build and certify its manufacturing facilities in compliance with the requirements of Good Manufacture Practice (GMP), which is one of the responsibilities of manufacture departments. The next step is to initiate clinical studies to evaluate the safety and effectiveness of the new technology, and this is the main function of medical departments of pharmaceutical companies.

To prepare arguments and evidence (for a special dossier) required for the second stage of expert evaluation (HTA), pharmaceutical companies conduct additional studies, collect and analyze all available data about the tested product as well as the disease for which it is indicated. It is this stage of ensuring the availability of the product that is traditionally described as market access technology, or MA [2].

Therefore, the concept of market access, as it is at present generally understood in pharmaceutical industry, refers to a range of issues arising during the circulation of a medical technology (a pharmaceutical drug, medical device or another technology) after its market launch. In other words, it is the activity of the manufacturer that follows after the product has been registered and that aims to secure its funding from the state or from other financial sources, such as insurance companies. In this respect, we can say that the access of a new product to the market and the extent of its research are entirely determined by the “hurdles” – the requirements towards new medical technologies specified by the state. Therefore, market access may be seen as the response of the industry to the ever-increasing demands of regulatory authorities concerning both the results of clinical and pharmacoeconomic studies and their methodology.

The Western MA model is primarily designed to provide access to the market for original and innovative drugs and their inclusion in reimbursement lists.

In view of the current development of health care and its growing demands, no country in the world is capable of funding all technologies that could cater to the needs of all patients. This makes it necessary for the state to makes
distinctions when deciding which novel technologies should be funded, taking into account their advantages over the already established technologies and the competing innovative solutions. Over the last few decades this has become evident to all countries, including the United States, where national spending on health care has traditionally been immense. As a result, in 2010 the first organization for health technology assessment in American history was established – the Patient-Centered Outcomes Research Institute (PCORI) [3]. This measure illustrates the acknowledged necessity of creating and implementing instruments enabling the payers to make informed decisions in the context of reimbursing medication costs and funding particular medical technologies. Reductions and cuts in healthcare spending are thereby rendered more systematic and justified, dictating the implementation of modern approaches to expert evaluation.

The technology boom and advances made in many fields of medicine make a prompt and effortless entry of novel technologies into the market of medical services more doubtful. The time of “blockbusters” is gone. Modern health care is going through a stage at which a multitude of drugs with proven safety and efficacy already exist and are available on the market. The decision to reimburse the cost of new technologies from the national or insurance budget can only be made if they offer obvious advantages over the existing and already adopted technologies, i.e. such a decision necessitates comparative effectiveness research.

Modern market access technologies consist of two components, namely the expert and communication branches. The former appears to be crucial, since research and analysis of the new product provides the evidence and arguments needed for its promotion. International experience demonstrates that the main tasks of the expert branch throughout the entire life cycle of the new product include planning, collection and actualization of data on its effectiveness in terms of its clinical benefits, economic acceptability, therapeutic significance, social value, as well as its pros and cons from the payer’s point of view [4].

The communication component of the manufacturer’s market access serves the following objectives: to influence the payers and decision-makers, develop and encourage their expectations by means of using various communication channels and lobbying techniques. According to an expert survey performed among our international colleagues, these two branches are represented in the activity of market access departments in a 80% to 20% ratio in favor of the expert branch. As a result of the absence of a professional HTA service or transparent decision-making procedures, as well as the impact of corruption on decision making, in Russia this ratio is noticeably skewed towards lobbying.

The limitations of effective market access in Russia are also related to a number of other features of the Russian health care. For instance, the system of decision making about drug supply and standards of treatment has still not been finalized in Russia; the requirements towards evidence about new technologies (i.e. the data included in the dossier) are not clearly stated; expert evaluation of the documents submitted by the manufacturer has not been organized and its nature has not been regulated; the availability of data on the number of patients, their management and the proportion of various forms, types and severity of diseases remains limited. One of the most negative factors, still present today, is the lack of a clear understanding of the vectors of healthcare development and reform.

When discussing market access technologies, it is worth mentioning that this field has a lot in common with marketing – it is in fact a particular branch of marketing and is based on the same principles. For example, one of the key ingredients of success in the promotion of new products is the manufacturer’s focus on the target audience and an appropriate positioning of the product. Similarly, the activity related to market access must build on the product’s “packaging”, which is created at the evaluation stage to meet the demands of the target audience, or on measures taken to stimulate the expectations of decision-makers. In fact, it is the target audience that determines the main challenges that arise when marketing technologies are used to promote new products at the stage of their inclusion in the funding system, i.e. when the technology of market access is realized.

At present one of the most serious mistakes committed by pharmaceutical and medical companies is to neglect the interests of various target audiences when choosing the strategy for promoting a new product. Promotional and informational materials originally designed for patients and doctors are then used for the purpose of convincing the directors of healthcare centers, head physicians, head pharmacists, and officials at the Ministry of Health. However, these target audiences have different interests, different needs and thus different expectations from innovative products. Entirely different arguments may be relevant and valuable to different target audiences, and therefore the same materials cannot be used effectively to convince both physicians and decision-makers. This is why the efforts of pharmaceutical companies that do not target specifically the needs of decision-makers often remain futile. It is important to realize that the arguments must be tailored to suit the target audience that is of interest for promoting the products of the company.

Two scenarios of realizing market access technology, which are related to different attitudes of decision-makers to the illness targeted by the new technology, may be described.
The first and most favorable scenario occurs when the manufacturer originally intended to meet the demands of decision-makers or the so-called “unmet demand” of the medical community related to the treatment or management of a particular disease, provided that the decision-makers are well aware of the risk of mortality, disability or social significance of the targeted condition. In this case the main task of the department in charge is to provide evidence-based arguments in favor of the new product, the results of direct and indirect comparisons, and other data in accordance with the requirements of the competent authorities.

A different scenario arises when the product was not originally developed to meet a particular known demand, i.e. when the non-medical community is not well aware of the severity and social significance of the illness. In this case market access should primarily aim to educate the decision-makers and opinion leaders about the social significance of the condition and the associated hazards and costs. In such situations the need for GR (government relations – the establishment of constructive relations with governmental organizations) and PR (public relations) grows sharply at market access departments.

Therefore, market access technologies may now be seen as a separate field of activity of companies that manufacture pharmaceutical drugs and medical devices. They obey certain rules and are founded on scientific principles. This field includes the development of a new product, the search for evidence of its superiority, the presentation of this evidence, the assessment of its impact on clinical, economic and social outcomes, and an analysis of the social significance of the illness. Only an integrated, comprehensive and interdisciplinary approach to the presentation of evidence can help the decision-makers to analyze the current treatment of a particular disease, making this analysis both easier and more precise, as well as highlighting the advantages of the new product, its potential niche, prioritized indications and possible limitations. The more comprehensive and accessible this information, the more it corresponds to the needs and expectations of decision-makers, the more successfully and effectively the strategy for promoting the new product will be realized.

At the same time, we should remember that effective communication with decision-makers and with those who can affect decision making is also important [5]. Every contact or meeting should be planned on the basis of the other party’s needs, strong and weak points, priorities and primary interests that determine decision-making. Apart from explicit human needs – professional and personal – it is important to prepare for every meeting, since there are limited opportunities for organizing them. In this sense, we cannot ignore the advances made in modern social psychology, which offers technologies and methods specially designed for helping prepare for such meetings.

When promoting a new product among the medical community, the arguments relevant to this target audience may be limited to an assessment of the effects of the drug, its tolerability, convenience of use, and other surrogate outcomes. Practicing physicians are primarily concerned with providing a particular patient with the best possible care, and the patient is their main interest. In contrast to practicing physicians, leading specialists, who may be described as an intermediate link between physicians and decision-makers, formulate the task at hand in a slightly different way and serve as “therapeutic managers”. In other words, their task includes provision of optimal care not only to a single patient, but to all the patients in their therapeutic field, which may sometimes clash with the interests of an individual patient. The communication between leading specialists and decision-makers should employ the language of ultimate treatment outcomes, rather than a discussion of surrogate effects. This calls for some skill at adapting information, i.e. “translating” the expert jargon into the language of payers and decision-makers. Timely, correctly chosen and evidence-based arguments presented to leading specialists considerably raise the effectiveness of their communication and their influence on decision making. However, in real life the number of leading specialists who are trained and prepared for thinking in these terms is extremely limited. The reason is that leading specialists come from the ranks of practicing physicians, and at present no training is offered in this aspect of the organizational functions of leading specialists.

It must be noted that a somewhat similar situation has arisen among both pharmaceutical workers and in market access departments as such. The problem is that these workers usually transfer from other departments (medical, commercial, marketing) and are not trained well enough to prepare in a professional manner targeted and tailored arguments. Training in sales, communication techniques and marketing advantages of medications does not translate into an understanding of the needs and specific characteristics of decision-makers. This knowledge has be accumulated in the process of working, typically through learning from one’s own mistakes.

The skill of “translating” from the expert jargon into the language of decision-makers and payers is not only necessary for the representatives of a company endeavoring to promote its products effectively. Today these skills are also crucial for leading specialists and key opinion leaders (KOLs), enabling them to formulate appropriate arguments and a “platform” for decision making in order to promote new technologies and to establish targeted programs, e.g. for health care provision to patients suffering from a particular illness. At the same time, we must remember that leading specialists and KOLs compete against their colleagues for budgetary (and other) sources of funding for “their” therapeutic fields. In this situation appropriate arguments and evidence will go a long way...
towards making the communication with decision-makers more effective and convincing in the context of lobbying for particular therapeutic areas.

As mentioned above, a key factor in developing an evidence base is matching particular expectations, needs and “language” of decision-makers. Even so, professional experts, the medical community and medical advisers in the pharmaceutical industry often operate with arguments that hinge on surrogate (intermediate) treatment outcomes, such as laboratory test results or diagnostic criteria of the effectiveness of new products. Presenting efficacy data limited to surrogate measures in the process of promoting and launching new technologies on the market may be sufficient for their registration. However, this language is poorly understood by payers, who prefer the language of endpoints. Therefore, an assessment of the effectiveness and value of the new product for the purposes of adding it to limited lists or allocating funding will inevitably require some data on endpoints (mortality and survival rates, as well as the rate of hospitalization, exacerbations and complications, the impact on the patients’ capacity for work and quality of life, disability, etc). The inability of the industry and experts to interpret the advantages of the new product, translating from “insider’s” jargon into the language of payers and decision-makers, considerably reduces the effectiveness of market access strategy (Fig. 1).

The design of studies in which the new product was evaluated determines the strategy for its promotion and development of an evidence base. If the clinical trials were originally designed to study both intermediate and ultimate efficacy endpoints, formulating appropriate arguments should be straightforward. The task becomes more challenging if the clinical trials were not originally designed to study endpoints. In the latter case one alternative is to perform multi-staged modeling based on published data on the correlation between surrogate measures and clinical outcomes. Such results are less convincing and call for an additional search for scientific publications and their critical analysis. It follows that professionals from market access departments who are responsible for the inclusion of a new technology in limited lists should take part in the process of designing and planning clinical studies of this technology together with external experts and the staff from medical departments. Clinical outcomes should form the cornerstone of efficacy studies, and their choice should correspond to the requirements specified for the registration of a new product, as well as its inclusion in funding schemes.

All subjects of the decision-making process, albeit to a various extent, are interested in market access technologies, more specifically in making these technologies a standard tool for ethical and rational promotion of new medications and medical devices. However, at present the major principles of market access can hardly be considered to be generally accepted and understood by representatives of the pharmaceutical industry and other actors.

All participants in the process would benefit from understanding the main concepts, rules and stages of market access technologies. Below I suggest some basic principles on which market access may be built in an ethical and professional manner.

As mentioned above, market access technologies entail, firstly, research aiming to collect and develop expert, analytical and scientific evidence and economic arguments, and secondly, lobbying aiming to promote the awareness of new products.

The collection of data on new products and creation of an evidence base (as well as requirements towards such products) should be in line with the existing regulations approved by the competent national (regional) authorities or a competent HTA agency. However, at present the requirements of HTA agents vary considerably in different countries with respect both to the parameters that are included in the dossier and to the evaluation criteria [6].
This consideration was the reason for the establishment of international organizations (HTAi, EunetHTA, INAH- TA, etc), whose task is to harmonize HTA requirements and approaches to the assessment of new technologies [7].

Even so, when the global dossier (“Core”) is created, it seems reasonable to provide evidence in line with the requirements of HTA agents with the greatest “leverage” and the anticipated needs of the payers.

EVIDENCE-BASED ARGUMENTS AS A COMPONENT OF PRODUCT PROMOTION

To appreciate more fully what a decision-maker deliberating the question of funding a new technology ought to know, it is important to understand the actual goals and tasks they are facing, as well as their needs, priorities and the crucial factors influencing their decision (Fig. 2).

As mentioned above, pre-registration assessment is concerned primarily with the quality and safety of the new product, while its effectiveness is a low priority at this stage, and no comparison with the dominant, superior or cheaper alternatives is necessary.

This suggests that, from the point of view of the state, the registration of a new technology is meant to guarantee a certain level of quality and safety, allowing this product to enter the healthcare system and be administered to patients with particular conditions. Neither the desirability nor the necessity of including the registered product in the system of national or insurance funding is determined at this stage (Fig. 3 and 4).

The second stage of the assessment, performed after additional studies of the new technology have been completed, primarily aims to provide an informed answer to the following question: should this product be covered by the national or insurance funding?

An answer based on solid evidence clarifies whether the new technology offers any clinical advantages over the competing medical and non-medical approaches, what its economic acceptability is, and whether there are grounds for its funding in terms of its impact on the budget of the healthcare system as a whole.

If the results of this assessment are positive, the new technology is recommended for national or insurance funding. Unlike the first stage of the assessment, at which the selection criteria concern the quality and safety of medications and medical devices, the second stage corresponds to a selection of “the best among high-quality and safe products”.

Accordingly, it is at this second stage that evidence from additional studies is called for – evidence of the clinical efficacy and cost-effectiveness of the new product.

The following effectiveness criteria should be central to the dossier on a new medication:

- its effectiveness relative to other, competing medications (especially those already funded or included in limited lists);
- its effectiveness in real-life clinical practice;
- its effectiveness relative to other treatment options, including non-pharmaceutical approaches;
- an analysis of its effectiveness in patient subgroups;
- its long-term effectiveness;
- an analysis of the patients’ opinion of the treatment with this drug.

It should be noted that data pertaining only to the new medication itself, its safety and efficacy, is usually not sufficient at the second stage of assessment to satisfy the payers. New medications may be included in reimbursement lists and granted additional funding only after a thorough evaluation of the medical conditions that they

Fig. 2. Factors determining the value of innovations for different conditions.
are indicated for (it is only on very rare occasions that modern innovative medications demonstrably save resources and offer cost-saving outcomes). Many kinds of evidence must be provided: data on the epidemiology of these medical conditions, mortality or disability linked to them, real-life approaches to their diagnostics and management, hospitalization rates, sources of funding for this condition, its social and economic burden (cost of illness), the likelihood that the new technology will have an impact on the cost of illness and the performance of the healthcare system as a whole [8]. Besides, it is worth taking into account the guidelines of scientific associations and protocols of treatment, as well as their implementation (in Russia this includes standards of treatment). Furthermore, treatment strategies and the effectiveness of the new medication should be analyzed in different segments (subgroups) of the patient population, thus defining high-priority groups and suggesting possible future ways to segment the patient population by how much they are likely to benefit from the new treatment.

To summarize, the core dossier should include the following sections [9]:

- a description of the social significance of the illness;
- a description of the effectiveness of the new medical technology;
- comparative clinical efficacy and cost-effectiveness of the new medical technology:
  - compared to reimbursed alternatives,
  - given the current approaches to the management of this illness,
  - in real-life clinical setting,
  - for a particular illness,
  - for a particular patient group.

Choosing a market access strategy, the manufacturer has to identify the main segments of the patient population or forms of the illness (sometimes also its severity) for which the new medication / technology is likely to be most beneficial in terms of its clinical efficacy and possibly cost-effectiveness, analyzing for this purpose the results of clinical trials and pharmacoeconomic analyses, the existing treatment strategies, and data on resource consumption. Product promotion for this patient group should be aligned with the marketing strategy and supported by arguments stemming from the results of clinical and pharmacoeconomic analyses and an assessment of the existing approaches and the potential benefits of implementing the new technology. It is important to identify the segment of the patient population in which business expectations and the potential benefits of implementing the new technology are likely to be the highest both for these patients and for the healthcare system, i.e. in which a win-win situation is achievable.

The choice of patient group in accordance with the system of reimbursement or discounting may be based on both social and medical criteria.

Medical criteria include the type of disease, its progression or severity, comorbidities affecting the progression of the main condition, and a number of other factors. Social criteria may include age, social group (children, pensioners, working population), limited mental or physical capacity of patients (disability), in some countries also the patients’ income level, etc.

It is worth pointing out that there are examples of prioritized provision of medications in the Russian system of drug supply defined both by social criteria (subventions to people with limited abilities – the Program for the Provision of Essential Medicines, children, veterans; see Government Order 890) and medical criteria (the Seven Nosologies Program, the list of diseases in Government Order 890, the National Health Project, etc) [10, 11, 12].

The choice of the strategy of product promotion thus depends on an having an opportunity to identify the most promising segment of the patient population, in which the position of the new technology is particularly favorable with respect to its cost-effectiveness, provided that the amount of funding seems reasonable and that these patients have legal and normative rights for a discounted provision of medications (reimbursement of the cost of pharmacotherapy). This right can only be granted by federal or regional law, government order (including orders...
of regional governments), federal programs (in a particular region, branch or institution), and other programs approved by governors.

Cost-of-illness studies have recently excited a lot of interest, precisely because there is a need for data on funding, diagnostics and treatment of illnesses. These studies assess treatment strategies and the potential of the existing approaches to diagnostics; the “culture” of patient management as well as the conditions or “milieu” in which health care is provided; the overall cost of treatment of a particular disease and the cost of pharmacotherapy alone; the cost of treating all registered patients and the average cost per patient; the structure of prescriptions by physicians and their compliance with international and national recommendations. As mentioned above, studies of the real-life clinical practice and the effectiveness of new technologies under “imperfect” conditions in the actual healthcare system are of particular interest.

Market access technology includes an analysis of the burden of disease. It forms the basis for researching the market for the new product, its positioning and its likely “niche” in the system of national funding and supply orders. A good illustration of the importance of these parameters is the implementation of the programs for the treatment of acute coronary syndrome in different regions. The implementation of in-hospital or pre-hospital thrombolysis and PCI is possible only after a detailed study of the characteristics of each particular region, such as the availability of centers for emergency cardiology with the appropriate equipment and trained professionals, their accessibility in terms of logistics, the intensity of traffic, etc. All these parameters describing the conditions under which medical care is provided and the “culture” of patient management in real-life clinical practice determine the possibility of actually implementing new technologies. If these factors are ignored when new products are promoted, this may undermine all the “achievements” of research into new technologies.

The task of providing new technologies with market access includes the following:

I. A timely assessment of the needs of decision-makers and the factors that have a considerable impact on their opinions (at present and a forecast for the future); of the political climate, including formal requirements as well as informal expectations and preferences of the major participants in the decision-making process (employees of the competent ministries, leading specialists, etc).

II. The collection of all relevant data on the epidemiology of the disease, existing approaches to treatment, the “culture” of patient management in the real-life practice, and the cost of illness; an analysis of the actual medical costs of this illness in a particular region and of the market of pharmaceuticals, including programs for the Additional Provision of Medicines and Provision of Essential Medicines; the availability of protocols and/or standards of treatment, medical standards for this illness.

III. The creation and actualization of a patient registry, an analysis of disaggregated data on the prevalence of the illness in this particular region with respect to age, severity, comorbidities, and social factors.

IV. The creation of appropriate expectations of decision-makers at the earliest possible stage of promoting the new technologies.

V. The establishment and development of an evidence base, including data on the clinical efficacy and cost-effectiveness of the new technology, and an assessment of the advantages of the new drug based primarily on endpoints; the collection of pharmaco-economic data and the creation of a clinical and economic model that might be validated in a particular region; the creation of the “core” dossier or the adaptation of the global drug dossier.

VI. The identification of the most promising “niches” or segments of the patient population, considering the clinical and economic characteristics of the new technology and a limited budget.

VII. The creation and preparation of a body of arguments for different target audiences of decision-makers who participate in the decision-making process for the problem being discussed.

VIII. Training company employees and leading specialists in the methods of adapting the clinical and economic model and study results to match the characteristics of each particular region (morbidity, healthcare system, the cost of services, and other factors).

IX. Suggesting methods of funding the new technology within the framework of existing or additional resources (with the actual financial expectations).

X. Educating leading and regional specialists about the main advantages of the new technology and training them in the skill of presenting these advantages.

XI. Organizing educational programs dealing with the particularities of implementing the new technology.

XII. Pricing and negotiating the extent of reimbursement as the major issues of the general concept of market launch. This step is of less importance given the existing normative field in the Russian Federation, since the share of reimbursed cost of medications is fixed and at present cannot be negotiated when the decision to fund a technology is taken. Moreover, the question of implementing various risk-sharing agreements is not legally settled in the Russian Federation, even though such agreements are popular in other countries [13].

It should be noted that the modern expectations of increasing the effectiveness of health care are related to the implementation of health technology assessment and informed, evidence-based decision making. However, just as moving towards the horizon does not allow us to reach it, raising the plank dramatically for the requirements and quality of the assessment of submitted documents does not guarantee that the decisions will be completely transparent and objective – there will always be room left for
subjective opinion of the experts and decision-makers involved in this process. Similar laws have been described in mathematics: for any sequence there will always be a residual, so that the limit itself can never be reached (Cauchy’s criterion). Even so, from the point of view of practical implementation of HTA, a certain residual subjectivity in decision-making may reduce the resistance of authoritarian officials and improve the chances of establishing a system of HTA. On the other hand, subjectivity in decision-making encourages a better presentation of the new technology, making its value “contagious” among those who determine or affect its promotion.

Employees of market access departments should be able both to present the data related to the new product and to assess the chances of its adoption given a limited budget, taking into account the possible impact of the rapidly evolving healthcare system on this process. These efforts promote an environment that is conducive to a dialogue between the pharmaceutical and medical industry, the authorities, insurance companies, and other stakeholders, thus leading to more informed decision-making in health care.

From the position of classical market access technology, inclusion of new products in reimbursement schemes should begin with minimal indications and a narrow category of patients. This allows the company to avoid a refusal of funding if the costs are high and to ensure a “smooth” market entry, as the segment of patients entitled to reimbursement may be broadened in future.

I would like to highlight in particular the fact that the existing system of funding pharmaceutical drugs in Russia, which is based on medical criteria, sets various tasks when the strategy of product promotion is chosen, depending on the indications for the new technology. For instance, when there are legal (normative) requirements regulating the reimbursement of the cost of medications for a particular illness under the programs for the Additional Provision of Medicines and Provision of Essential Medicines, the objective of market access project is to have the new medications included in the limited lists at the federal or regional level (e.g. for oncological conditions, bronchial asthma, the Seven Nosologies, etc). To do this, it is necessary to collect data and compile a dossier on the effectiveness of the medication in accordance with the requirements of the competent authorities.

If the state does not reimburse the cost of pharmacotherapy of a particular illness or the allocated funds are grossly insufficient, the solution is to obtain additional funding under a regional, institutional or some other targeted program. The creation of a targeted program demands that the program itself be developed, written and, crucially, agreed upon in negotiation with healthcare authorities. Then the longest and most challenging stage of program promotion begins, namely its approval by legislative authorities and the government. This task calls for more in-depth research into the social and economic conditions in the region, the impact of the new technology on a particular medical condition and the healthcare system as a whole, as well as data about the number of organizational events and amount of financial resources required in accordance with the principles of target program approach.

The relevance of creating new regional programs depends on limited access to the market at the federal level and thus a shift of company activity from the central “platform” to the regional level. This is another salient feature of market access in Russia.

It is also worth pointing out that in Russia a popular method of “commercial promotion” of pharmaceutical drugs is to offer the distributors a higher discount or some other favorable contract conditions. The reason for this is that distributors wield more influence over decision-making compared to what is common internationally. This strategy remains fairly effective in Russia, but it has nothing to do with the ethics of market access – instead, it is linked to the corruption element in the existing healthcare system. This is another peculiar feature of market access in Russia, well understood and often used by Russian and foreign companies. However, with more stringent demands towards the submitted data on new technologies and the quality of assessment of this data, the role of “commercial promotion” as a tool is bound to decrease.

THE COMMUNICATIONAL COMPONENT OF TECHNOLOGY PROMOTION

We have seen that the second component of market access technology concerns the promotion of the new product among the target audience of decision-makers, which includes lobbying. This task consists of three obligatory stages: preparation, actualization, and decision (Fig. 5). Below are their brief descriptions with a list of the main measures taken at each stage [2].

![The obligatory stages of MA/GR](image)

Fig. 5. The obligatory stages of promoting new products.
At the preparatory stage the current situation in health care and in a particular therapeutic field is analyzed and evaluated, and arguments are formulated for various target audiences (medical, social, legal, psychological) to improve the effectiveness of negotiations and to increase the impact on decision-making about implementing the new product. Attempts are made at this stage to analyze the formal relations between the key decision-makers, their influence and their authority in a particular field. An analysis of internal, often purely psychological rather than professional relations at various levels may also be quite important.

The collection and analysis of “insider’s” information is to some extent an extension of monitoring the political situation. The identification of agents of influence at the federal and regional levels (so-called “mapping”) is a useful tool, but it may not always be able to reflect the actual situation in case of political volatility. As a rule, the creation of this tool begins with monitoring external, open sources and analyzing interconnections, i.e. the information that is purposefully released into the information space. This information may be supplied, verified or refuted by people who are familiar with the situation from within. At the regional level this person may be an assistant of a decision-maker, an official, a member of a legislative body or a local healthcare authority. Such people must be open, attentive to detail, and acquainted with decision-makers or those who can influence decision-makers.

The outcome of the preparation stage should be a plan of measures and initiatives necessary to achieve the final goal – launching a new national program, including the new medication in reimbursement lists, obtaining additional funding, etc. The creation of this plan (based on all possible tools for researching and developing an evidence base for the new product) goes hand in hand with its further adjustments reflecting the changing situation in health care and the political environment at large.

The second stage – actualization – consists in promoting the prepared arguments and “key messages” among the medical community, politicians and other decision-makers, depending on the task facing the manufacturer. Each target audience that controls or influences the promotion of the product on the market and its funding requires its own targeted approach and the preparation of specific arguments.

The task of translating from the expert jargon into the language of decision-making is fairly challenging, and sometimes it may be necessary to hire external specialists. The reason is that this task requires more than just familiarity with the features and advantages of the new technology and the pathological processes – one must also be familiar with the main principles of decision-making by national authorities.

The objectives at the actualization stage are to use as effectively as possible the “raw material” collected at the preparatory stage (arguments in favor of including the new technology in limited lists) and have them “flowing” out into the information space. This process should be active and continuous, i.e. directed at all the potential target audiences. The actualization stage calls for a coordinated effort of all the stakeholders interested in promoting the product. The name of this stage itself reflects its essence – to actualize the problem (on all possible levels) which the new product or technology addresses.

One of the most effective actualization methods is to host events and take part in the relevant events held by other organizations. It is important to keep in mind that the fight for the national budget takes place on the national stage. A gathering of the representatives of public associations may have a certain resonance, but it can never replace a presentation delivered directly at the Ministry of Health and legislative authorities.

This strategy may already bear fruit after a short period of time, provided that the topic has received extensive coverage. However, this cannot replace the creation of dedicated newsmakers and platforms for interaction with the state – in fact, such measures become crucial when there are no significant external coverage opportunities.

As a result, representatives of the industry or stakeholders should have a complete dossier of arguments directed at each target audience – physicians, health center directors, officials, and journalists. It is important to realize that this dossier is not put together a month ahead of a conference or a meeting with a leading specialist – it is compiled gradually, beginning practically from the first clinical trials of a new product.

It should be noted that market access technology cannot be reduced to preparing the evidence base, lobbying and using GR tools. PR (public relations) technologies are also important – a fact that is often underestimated when market access is organized. As a rule, PR department of the company or an external PR agency have “a life of their own” and have no direct contact with managers from the market access department. However, informational coverage at the stage of problem actualization is an effective instrument. The tasks performed by the PR service should be formulated by the manager of the market access department or the project leader, who is fully aware of all the subtle issues related to the product and its promotion. PR specialists tend to understand what emotions and reactions are desirable among the broad audience and which media and communication channels should be employed. A common mistake is to change the goals of actualizing the problem field, which defines the need for the new product, and instead to advertise the company, its social responsibilities and the medication itself. It is important to differentiate between marketing objectives of the company (to stimulate sales) and the objectives related to access to the market.

The next stage is decision making. It normally commences once a notion (amendment, concept, program) has officially been submitted to the competent legislative or
executive authorities. At this stage the path of the document is usually legally stipulated, but not uncommonly it becomes necessary to provide additional information and exert influence on those who determine the progress of the documents and the final decision.

Both local healthcare initiatives and events related to the political situation or changing priorities can affect decision-making. Business arguments must be comprehensible to the addressee, and therefore they should be presented not simply in an appropriate format but also in a language that is comprehensible to the authorities, public organizations, etc. This communicative principle must be taken into consideration by all participants in the process of providing market access for new products.

Under certain circumstances the anticipated scenario may change dramatically at the critical stage, after a huge amount of work has been performed. Even a slight change of priorities in the political sphere, in the opinions of key persons or in the company itself may require a drastic overhaul of the entire project and its adjustment to fit the changing political priorities.

Already at the preparatory stage it is important to choose the type of legal decision by means of analyzing the normative and legal base. Preferably, various solutions to the problem should be considered and an action plan formulated for each of them. Even so, these plans may be reviewed and updated at the critical stage, depending on the objective realities and the political situation. Healthcare programs that may have a significant impact on the feasibility of implementing new treatment and diagnostic technologies include, but are not limited to, the following: the funding of the National Health project, the allocation of financial resources for socially significant diseases, the modernization of health care, and medical insurance. Accordingly, it is important to possess a consolidated body of arguments for decision-makers, created and tested at earlier stages, in case new initiatives are put forward that may provide the framework for national funding of a new medication or medical technology.

To provide a product with market access in an ethical way, it is necessary to follow all the stages of this process. Skipping or completely ignoring some requisite steps on the way to realizing the project may jeopardize its success and undermine the entire effort.

Unfortunately, the “rules of the game” are not yet defined in the Russian sphere of lobbying and market access. “Lobbyist” is not a recognized occupation, and there is no law regulating their activities. Accordingly, those in charge of market access are forced to obey unofficial rules and take into account the mentality of Russian officials, i.e. to select such arguments that will be able to convince the experts, so that the experts might accept the argumentation, “digest” it and present it to decision-makers.

The next stage – monitoring the progress of decision-making and its outcome – is another essential component of any project that is arbitrated by national authorities.

Ethical market access stands not only for achieving a particular result favorable to the company, but also for an objective evaluation of the needs of health care and the demand for particular technologies, their creation and provision at an adequate price beneficial to the patients and the healthcare system as a whole.

CONCLUSION

Healthcare reforms inevitably change the “rules of the game” for all participants in this system. The mechanism of implementing market access technology, which is relatively new for the Russian pharmaceutical industry, has been regarded with a growing interest. The challenges of implementing this technology are primarily due to its novelty for the Russian health care and thus a lack of experience and professionals trained in this field. Another obstacle is the absence of such factors as a well-defined system of decision-making about the provision of medications and medical devices, standards of treatment, unambiguous vectors of healthcare development and reforms, and transparent requirements towards the evidence base, new pharmaceutical drugs and medical devices. The lack of transparent rules and procedures will inevitably shift market access technology from expert and evidence-based assessment towards approaches relying on lobbying and corruption. Such market access mechanisms cannot improve the transparency of decision-making, and neither can they promote a “healthy” healthcare system.

At the same time, it must be acknowledged that market access technology as a tool available to the pharmaceutical industry is equally beneficial to each subject of the healthcare system. The implementation of these technologies in parallel with the existing system of medical product assessment ought to be conducive to providing the patients with better treatments based on the latest scientific achievements. From the perspective of decision-makers, the implementation of market access technologies will provide a more objective and rational approach to making decisions and allocating healthcare resources. The manufacturers introducing and realizing these technologies will obtain data allowing them to identify the appropriate niche for their products on the market of medical services and to formulate arguments and reasons that will be convincing to decision-makers. To summarize, based on the experience of other countries, we can now state that a correctly structured healthcare system, with a civilized process of negotiating between the state, experts

1 As a reference: a draft of federal law “On the regulation of lobbying in national federal authorities” (the author is Lepehin Vladimir Anatolyevich, the director of EvrazES Institute (Eurasian Economic Community), member of the State Duma of the Federal Assembly of the Russian Federation of the first convocation) passed its first reading in 1995, but it was not approved because there was no quorum (less than half the delegates were present during the voting).
and representatives of the health industry that relies on the language of evidence and arguments, significantly improves the objectivity of healthcare authorities as well as the quality of medical care provided to citizens.

REFERENCES
3. URL: http://www.pcori.org/


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